

sort_order 2497
Pub # P3-428
Session Information POSTER SESSION: CLINICAL - Obesity: Causes & Consequences (1:30 PM-3:30 PM)
Title Higher Leptin Concentrations Suggestive of Leptin Resistance in Patients with Alstr[oum]m Syndrome as Compared to BMI-Z Matched Controls
Author String AE Huey, JD Marshall, P Maffei, MM Tsang, MG Wolde, SR Fuhr, EA Stern, SM Brady, JW Tsao, G Milan, J Naggert, JA Yanovski, JC Han
Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD; The Jackson Laboratory, Bar Harbor, ME; Padua University Hospital, Padua, Italy; Uniformed Services University of the Health Sciences, Bethesda, MD
Body
Background: Alstr[oum]m syndrome (AS) is an autosomal recessive disorder caused by mutations in *ALMS1*. AS is a disorder of primary cilia with multisystemic manifestations, including obesity. Genetic disruption of other genes involved in primary ciliary function in mice leads to hyperphagia and obesity [sup1] Mouse models of another ciliopathy, Bardet-Biedl syndrome, suggest that ciliary dysfunction leads to impaired leptin receptor trafficking and leptin resistance with impaired hypothalamic leptin signal transduction and increased leptin concentrations that precede the onset of obesity [sup2] We hypothesized that patients with AS would have higher serum leptin consistent with ciliopathy-induced leptin resistance.
Methods: Twenty-one patients with AS (100% met clinical diagnostic criteria, 71% had confirmed genetic diagnosis) were recruited and studied at the 6th Annual Alstr[oum]m Syndrome International Family and Medical Conference. Patients were matched 1:2 by age, sex, race and BMI-Z with 42 healthy controls who participated in metabolic studies at the National Institutes of Health. Leptin was measured by commercial ELISA from fasting serum and log-transformed for analysis. AS and control groups were compared using independent samples t-tests or Mann-Whitney U-tests (for skewed data) and by ANCOVA adjusting for age, sex and BMI-Z.
Results: Groups were comparable for age (mean \pm SD for AS vs. control: 19.3 ± 9.1 vs. 20.0 ± 10.6 y, $p=0.99$), sex (38% male in each group), race (100% Caucasian in each group), BMI (34.9 ± 11.2 vs. 33.1 ± 5.9 kg/m²), $p=0.59$) and BMI-Z (2.14 ± 0.59 vs. 2.12 ± 0.51 , $p=0.86$). The AS group had significantly higher serum leptin than controls (adjusted mean \pm SEM: 24.8 ± 1.1 vs. 17.0 ± 1.1 ng/mL, $p=0.02$).
Conclusions: Patients with AS have higher fasting serum leptin than expected for their body size, suggesting that they have leptin resistance. Peripheral leptin secretion by white adipose tissue is believed to be negatively regulated by leptin's actions within the central nervous system; hypothalamic brain-derived neurotrophic factor, a downstream mediator of the leptin-melanocortin pathway, has been shown to down-regulate leptin production in adipocytes via sympathoneural beta-adrenergic output [sup3] Our observation of higher serum leptin in patients with AS suggests that the pathophysiology of their obesity may be due to a primary defect in leptin signaling.

(1) Davenport JR et al., *Curr Biol* 2007; 17:1586.
(2) Seo S et al., *Hum Mol Genet* 2009; 18:1323.
(3) Cao L et al., *Cell* 2010; 142:52.

Sources of Research Support: Intramural Research Program of the National Institute of Child Health and Human Development, NIH.

Nothing to Disclose: AEH, JDM, PM, MMT, MGW, SRF, EAS, SMB, JWT, GM, JN, JAY, JCH

sort_order 2498
Pub # P3-429
Session Information POSTER SESSION: CLINICAL - Obesity: Causes & Consequences (1:30 PM-3:30 PM)
Title Leptin Is an Independent Correlate of Lean Body Mass in the Baltimore Longitudinal Study of Aging
Author String R Ramachandran, KS Gravenstein, EJ Metter, JM Egan, L Ferrucci, CW Chia
National Institute on Aging, National Institutes of Health, Baltimore, MD; National Institute on Aging, National Institutes of Health, Baltimore, MD
Body
Background: A decline in lean body mass is generally considered a constant feature of aging. In some individuals, an accelerated decline in muscle mass with age accompanies a substantial increase in fat mass. Since leptin receptors are present within muscle, it was hypothesized that excessive production of leptin from adipose tissue could be the mechanism for accelerated decline of lean body mass in these individuals. However, this hypothesis has not been formally tested in an epidemiological study. We therefore sought to characterize the relationship between lean body mass and circulating leptin levels in participants of the Baltimore Longitudinal Study of Aging (BLSA).
Methods: We performed a cross-sectional analysis of 1006 BLSA subjects (male =554, 50.1%) with complete data on total body fat (kg) and lean body mass (kg) measured by DXA scan, and fasting leptin levels (ng/mL). Independent associations of leptin with total lean mass, adjusted for age and total fat mass were then tested in linear models stratified by sex. Leptin had a skewed distribution and we therefore used log-transformed values for analyses. All data are presented as mean \pm SE except for leptin values which we present as median (interquartile range).
Results: The mean age of the population was 69.4 \pm 0.6 and 66.1 \pm 0.6 years for men and women respectively. As expected, leptin levels were significantly higher in women, 25.9 (14.0-43.6) ng/mL compared to men, 9.9 (5.3-17.8) ng/mL ($P < 0.001$). Women also had a higher total fat mass, 29.1 \pm 0.5 kg vs. 26.1 \pm 0.4 kg, $P < 0.001$. In contrast, men had a higher lean body mass compared to women, 55.8 \pm 0.3 kg vs. 39.6 \pm 0.2 kg, $P < 0.001$. Multiple linear regression analysis revealed a strong negative, independent relationship between leptin and total lean mass after adjusting for age and total fat mass: men ($\beta = -0.29$, $P < 0.001$) and women ($\beta = -0.18$, $P < 0.001$).
Conclusion: These results support the hypothesis that leptin plays a role in the accelerated decline of lean body mass with aging, especially in obese individuals. One possible explanation of our findings is that leptin may stimulate the adipogenic conversion of satellite cells, ultimately leading to decreased muscle mass with increasing intramuscular adipose tissue.

Sources of Research Support: Intramural Research Program of the NIH and National Institute on Aging.

Nothing to Disclose: RR, KSG, EJM, JME, LF, CWC

sort_order

2499

Pub #

P3-430

Session Information

POSTER SESSION: CLINICAL - Obesity: Causes & Consequences (1:30 PM-3:30 PM)

Title

Circulating Estrogen and Physical Activity Are Associated with Ectopic Thigh Adipose Tissue Deposition in Healthy Postmenopausal Women

Author String

AM Goss, BA Gower
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Body

Background: Intermuscular adipose tissue (IMAT) has been identified as an independent risk factor for type 2 diabetes and muscle weakness. Changing hormonal parameters and decreased physical activity are thought to contribute to the accrual of IMAT in an aging population. However, no studies have examined the potential role of declining estrogen in distribution of adipose tissue to intermuscular spaces of the thigh. The objective of this cross-sectional and longitudinal study was to determine independent associations among estrogen, physical activity, and thigh adipose tissue distribution. **Methods:** 95 healthy, early postmenopausal women were evaluated at baseline and 2 yrs; 52% were using hormone replacement therapy (HRT). Serum analysis of estradiol and estrone were conducted in all women. Cross-sectional areas of skeletal muscle, IMAT, thigh subcutaneous adipose tissue (SAT), and perimuscular adipose tissue (PMAT) were determined by single-slice computed tomography (CT) scan at the mid-thigh. Total body adipose tissue (TAT) was determined by DXA. All measures of thigh adipose tissue were adjusted for TAT; IMAT and PMAT were also adjusted for thigh muscle area. Baseline physical activity was self-reported as light and moderate hours per week. **Results:** At baseline, estradiol and estrone were positively associated with thigh SAT (partial $r=0.26$, $P=0.03$ and partial $r=0.21$, $P=0.08$, respectively) and PMAT (partial $r=0.30$, $P=0.015$ and partial $r=0.36$, $P=0.003$, respectively) and were inversely associated with IMAT (partial $r=-0.45$, $P<0.001$ and partial $r=-0.42$, $P<0.001$, respectively). Baseline moderate physical activity was associated with less gain in IMAT over 2 yrs ($P<0.01$), while baseline light physical activity was associated with greater gain in IMAT over 2 yrs ($P<0.01$). **Conclusion:** In postmenopausal women, greater estradiol and estrone concentration may facilitate greater fat deposition to thigh SAT and PMAT and lesser accumulation of IMAT. Also, more hours of moderate physical activity may reduce IMAT accumulation, whereas a sedentary lifestyle, represented by increased hours of light physical activity, may have the opposite effect. These findings suggest that maintenance of relatively higher estrogen concentrations and relatively higher levels of physical activity with aging may limit accrual of IMAT, which in turn may be beneficial for maintenance of physical function and independence, and reduction in risk for type 2 diabetes.

Nothing to Disclose: AMG, BAG

sort_order 2500
Pub # P3-431
Session Information POSTER SESSION: CLINICAL - Obesity: Causes & Consequences (1:30 PM-3:30 PM)
Title Decreases in the Testosterone-to-Estradiol Ratio Contribute to Increased Levels of Pro-Inflammatory Adipokines in Males
Author String DM Ouwens, B Lapauw, H Sell, S Lehr, Y VanNieuwenhove, C Cuvelier, P Pattyn, JM Kaufman, J Eckel, JB Ruige
German Diabetes Center, Duesseldorf, Germany; University Hospital Ghent, Ghent, Belgium; University Hospital Ghent, Ghent, Belgium
Body Low testosterone (T) levels in obese males associate with insulin resistance. This study aimed to evaluate changes in adipokine levels that can potentially be ascribed to alterations in sex steroid metabolism in obese man. Therefore, plasma levels of sex steroids and 30 adipokines were determined in morbidly obese males, as well as in healthy young males before and after treatment with an aromatase inhibitor (letrozole) plus E2 patches to lower T and raise E2, thus mimicking obesity-related changes in sex steroid levels. Morbidly obese males had lower T and higher E2 levels compared to lean controls. While adiponectin and omentin levels were decreased, circulating levels of chemerin, GCSF, IFN γ , interleukins (IL) 1b, IL11Ra, IL4, IL6, IL9, IL10, IL12-p70, IL13 and IL17, IP10, leptin, PAI1 and VEGF were increased in obesity (all $P < 0.05$). Correlation studies identified a positive relation between the free T-to-E2 ratio (FT/FE2) and adiponectin ($P < 0.001$) and omentin ($P < 0.05$). Inverse correlations were found between the FT/FE2-ratio and chemerin, GCSF, IFN γ , IL1Ra, IL6, IL9, IL10, IL12p70, IL13, and IL17, IP10, leptin, MCP1, MIP1a and MIP1b (all $P < 0.05$). All correlations remained significant after adjusting for age. Only the relation between the FT/FE2-ratio and MCP1 remained significant after adjustment for body fat percentage. Accordingly, treating healthy young males with letrozole+E2 patches increased MCP1 levels. Treatment with letrozole (control group) alone had no significant effect on circulating adipokine levels in healthy young males. Collectively, these results suggests that the association between a low FT/FE2-ratio and decreased insulin sensitivity is related to decreased levels of omentin and adiponectin, and increased levels of pro-inflammatory adipokines. Furthermore, an increase in levels of MCP1, an important mediator of insulin resistance, might directly result from obesity-related changes in sex steroids.
Nothing to Disclose: DMO, BL, HS, SL, YV, CC, PP, JMK, JE, JBR

sort_order

2501

Pub #

P3-432

Session Information

POSTER SESSION: CLINICAL - Obesity: Causes & Consequences (1:30 PM-3:30 PM)

Title

Increased Sedentary Time Is Associated with Greater Weight Gain during Short-Term (3-Day) Overfeeding

Author String

J He, S Votruba, J Pomeroy, S Bonfiglio, J Krakoff
NIDDK/NIH, Phoenix, AZ

Body

Objective: Given the wide availability of highly palatable foods, overeating is common. Changes in physical activity have been proposed as a mechanism to maintain weight in response to overeating. Methods: In a monitored inpatient clinical research unit using a cross over study design, we investigated sedentary time and non-exercise activity following a short term (3-day) weight maintaining (WM) vs. overfeeding (OF, 150% of WM calories) diet in healthy volunteers (n=21; BMI=33.2±8.6 kg/m² (mean ± SD), 74% male). During each diet, sedentary time and non-exercise activity were measured with an omnidirectional, uni-axial accelerometer. Sedentary time was calculated as the percentage of wear time where activity counts were less than 10 per minute. Volunteers spent the last 24 hours of each diet period in a metabolic chamber to measure energy expenditure. Results: Mean weight change during WM and OF was -0.1±0.7 (kg) and 0.7±1.0 (kg), respectively. Overall, sedentary time, as calculated from the waist measurement, was not different between WM and OF while living on the inpatient unit (70.9±12.9 vs. 72.0±7.4%, p=0.8) or in the metabolic chamber (74.6±10.6 vs. 78.4±6.6%, p=0.5) but was negatively associated with age during OF (r=-0.48, p=0.05). However, sedentary time was positively associated with weight gain during OF (r=0.51, p=0.03) but not during WM (r=0.02, p=0.6). The association during OF was still significant after adjustment for age, sex and initial body weight, (r=0.45, p=0.05). During WM, there was no difference in sedentary time when measured on inpatient unit vs. metabolic chamber (p=0.6), however, during OF, sedentary time was significantly higher while subjects were in the metabolic chamber (inpatient unit vs. chamber: 72.0±7.4% and 78.4±6.6%, p=0.0005). There were no associations of non-exercise activity as measured from waist, wrists and ankles with weight change during OF (p=0.5, p=0.8, p=0.7, respectively), nor during WM. Fasting insulin, leptin, active ghrelin, total ghrelin, PYY, or GLP-1 concentrations measured prior to each diet were not associated with sedentary time. Conclusions: We demonstrated that in humans, short term (3 day) overfeeding weight gain was positively associated with sedentary time. This indicates that during positive energy balance, adaptive changes in sedentary behavior may avert weight gain.

Sources of Research Support: Intramural Research Program of the NIH, NIDDK.

Nothing to Disclose: JH, SV, JP, SB, JK

sort_order 2502
Pub # P3-433
Session Information POSTER SESSION: CLINICAL - Obesity: Causes & Consequences (1:30 PM-3:30 PM)
Title No Influence of Intravenously Infused Carbohydrates and Fat on Hunger and Spontaneous Food Intake
Author String SM Schmid, K Jauch-Chara, W Britta, H Manfred, L Hendrik, S Bernd
University of Luebeck, Luebeck, Germany; University of Luebeck, Luebeck, Germany; University of Luebeck, Luebeck, Germany; Kanton Hospital St Gallen, St Gallen, Switzerland
Body
Objective:
Regulation of appetite and food intake is a major focus of endocrine metabolic research since obesity has become epidemic in western society. Here, we investigated the influence of equicaloric amounts of continuously infused glucose and fat, and pulsatile infused glucose, respectively, on glucose metabolism as well as feelings of hunger and spontaneous food intake.
Methods:
We studied 15 healthy, young (mean \pm SEM: 25.1 \pm 0.6 years), normal weight (22.8 \pm 0.4 kg/m²) men in a single-blinded, randomized, four condition cross-over design. Blood glucose and insulin and free fatty acids (FFA), feelings of appetite/hunger, and spontaneous ad libitum food intake were assessed during a 14h period with equicaloric (600 kcal) intravenous infusion of (i) glucose continuously, (ii) glucose pulsatile, and (iii) fat continuously. A session with infusion of non-caloric NaCl 0.9% served as control.
Results:
As expected, the dynamics of blood glucose and circulating concentrations of insulin and FFA significantly differed between conditions ($P < 0.01$). Feelings of hunger/appetite as well as oral energy uptake were comparable between all conditions. However, due to the amount of infused calories, total energy intake was lowest within the placebo condition ($P < 0.05$).
Conclusion:
Different profiles of blood glucose, insulin and FFA during a 14h period of equicaloric, pulsatile as well as continuous glucose or fat infusion did not result in a compensatory modulation of perceived feelings of hunger/appetite and spontaneous food intake. Moreover, oral energy intake was not decreased as compared to the non-caloric placebo infusion condition, thereby resulting in a ~600 kcal higher total energy intake. A possible reason for the lack of a compensating modulation of oral energy intake might be the absence of fast acting gastrointestinal signals, as e.g. GLP-1 and ghrelin, due to the intravenous application of macronutrients. Our findings add to the scientific knowledge of nutritional modulation of human hunger/appetite and eating behavior. On the background of total parenteral nutrition in clinical practise, our findings are furthermore of clinical and ethical relevance.
Sources of Research Support: Deutsche Forschungsgemeinschaft (DFG).
Nothing to Disclose: SMS, KJ-C, WB, HM, LH, SB

sort_order 2503
Pub # P3-434
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Insulin Action & Glucose Homeostasis in Model Systems (1:30 PM-3:30 PM)
Title Circadian Clock Gene, Bmal1, Regulates Skeletal Muscle Metabolism and Development
Author String S Chatterjee, NP Barquero, L Li, K Ma
The Methodist Hospital Research Institute, Houston, TX
Body Tissues that play central roles in regulation of whole body metabolism such as the skeletal muscle and adipose tissue have functional circadian clocks that drive cyclic expression of key enzymes involved in glucose and fatty acids metabolism. But the physiological function of circadian clock genes in muscle and adipose tissue is largely unknown. Here we report Bmal1 protein is expressed in a circadian fashion in skeletal muscle and white adipose tissue. NMR analysis revealed that the Bmal1 global knockout mice (Bmal1^{-/-}) exhibit significantly increased fat (11%) and similarly reduced total lean mass, which was confirmed by direct measurement of epididymal fat pad and muscle. Despite lower muscle mass in the Bmal1^{-/-} mice oxygen consumption was significantly higher compared to the wild-type controls with similar activity level and food intake. We hypothesized that Bmal1 plays a direct role in the regulation of muscle metabolism and development. Bmal1^{-/-} skeletal muscle gene expression analysis revealed fiber type switching from type II to type I with ~5 fold induction of slow myosin heavy chain beta (Myh7) and a ~40% reduction of IIf (Myh4). Consistent with this, there was a concerted shift of fuel utilization from glucose to fatty acids as indicated by up-regulation of genes involved in lipid oxidation, including LPL, CD36, FABP4, MCAD and lower GLUT4 as well as higher PDK4 level. Stable shRNA knockdown of Bmal1 in C2C12 myoblasts also led to significant up-regulation of PDK4. Strikingly, Bmal1 knockdown resulted in a substantial suppression of myogenic differentiation (~10% of control) with markedly lower expression of Myf5, MyoD, myogenin and muscle-specific markers, which were confirmed by immunostaining. The ID proteins (ID1 and 3), known inhibitors of myogenesis and well-characterized circadian genes, were consistently induced in shRNA knockdown cells and Bmal1^{-/-} skeletal muscle. On the other hand, overexpression of Bmal1 resulted in spontaneous differentiation and accelerated myotube formation. Furthermore, in C3H10T1/2 mesenchymal stem cell line, Bmal1 knockdown completely blocked myogenic lineage commitment and differentiation while promoted expression of adipocyte-specific markers, suggesting that Bmal1 is a lineage commitment determination factor. Thus, our study demonstrates that the core clock gene, Bmal1, plays an important role in metabolic regulation in skeletal muscle and promotes myogenesis through inhibition of the ID proteins.

Nothing to Disclose: SC, NPB, LL, KM

sort_order 2504
Pub # P3-435
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Insulin Action & Glucose Homeostasis in Model Systems (1:30 PM-3:30 PM)
Title TXNIP in Bone as a Potential Regulator of Glucose and Energy Homeostasis in Endogenous Cushing Syndrome Involving the Bone-Specific Protein Osteocalcin
Author String T Lekva, T Ueland, H Boyum, H Scholz, A Sahraoui, JA Evang, K Godang, J Bollerslev
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Body Context: Recent evidence has described bone as an endocrine organ regulating glucose metabolism. Insulin receptor signaling in osteoblasts may control osteoblast differentiation and osteocalcin expression.
Objectives: To investigate the functional role of TXNIP in bone with special focus on insulin signaling and osteocalcin synthesis in osteoblasts and further its action on islets and osteoclasts through osteoblast signaling. Moreover, to examine the associations between bone turnover, fat mass and glucose metabolism *in vivo* in these patients.
Patients: 33 patients with endogenous Cushing's syndrome (CS).
Research Design and Methods: We analyzed bone biopsies from CS, before and after treatment, to screen for expression candidate genes. Microarray analysis combined with real-time RT-PCR revealed that the gene encoding TXNIP ranked among the most regulated genes, and was selected for further characterization *in vitro*.
Results: We found that TXNIP gene in bone is down-regulated in CS following surgical treatment. Furthermore, our *in vivo* data indicate novel associations between thioredoxin/TXNIP and bone turnover with potential effects on glucose metabolism. Our *in vitro* studies showed that silencing TXNIP in osteoblasts was followed by increased differentiation, augmented insulin receptor and osteocalcin expression, and increased secretion of intact and undercarboxylated osteocalcin. Treating islets and osteoclasts with silenced TXNIP osteoblast media, showed an increased islets function and osteoclast activity.
Conclusions: TXNIP expression in bone is regulated by glucocorticoids and may, in part, explain the decreased osteoblast function in CS with effects on secretion and carboxylation status of osteocalcin, and further link bone and glucose homeostasis together in these patients.
Nothing to Disclose: TL, TU, HB, HS, AS, JAE, KG, JB

sort_order 2505
Pub # P3-436
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Insulin Action & Glucose Homeostasis in Model Systems (1:30 PM-3:30 PM)
Title Altering AP-1 Transcription via [Delta]FosB Delays Age-Related Skeletal and Metabolic Changes in Mice
Author String K Sato, GC Rowe, S Lotinun, H Saito, M Yin, R Baron
Harvard School of Dental Medicine, Boston, MA; Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; Harvard Medical School, Boston, MA; Massachusetts General Hospital, Boston, MA
Body Aging is associated with a high risk of developing osteoporosis, impaired glucose tolerance and type 2 diabetes due to a reduction in insulin sensitivity. [Delta]FosB is a naturally truncated form of the AP-1 transcription factor FosB. Overexpression of [Delta]FosB under the control of the enolase 2 promoter (ENO2), which drives expression in several tissues including bone, white and brown fat, and the brain, results in increased bone mass, decreased adipose mass, increased insulin sensitivity and glucose tolerance, and increased energy expenditure (1,2). To examine whether [Delta]FosB is implicated in the development of age-related skeletal and metabolic changes, we analyzed the bone and metabolic phenotype of ENO2-[Delta]FosB mice at 4, 12 and 50 weeks of age. In ENO2-[Delta]FosB mice, trabecular bone density of the distal femur showed a 37% and 56% increase versus control littermates at 12 and 50 wks, respectively. Cortical bone density in the midshaft of the femur increased prominently with age in ENO2-[Delta]FosB mice compared to control mice (12 wks, 43%; 50 wks, 187%). Although control mice had a progressive increase in abdominal fat mass, ENO2-[Delta]FosB mice didn't develop abdominal adiposity and had smaller white and brown adipocytes compared to control mice at 12 and 50 wks. Consistent with this, energy expenditure in ENO2-[Delta]FosB mice increased at 12 and 50 wks, by 12 % and 86 %, respectively, with identical food consumption compared to control mice at same ages. During intraperitoneal insulin (IPITT) and glucose tolerance testing (IPGTT), ENO2-[Delta]FosB mice were more insulin sensitive and glucose tolerant at 12 and 50 wks than control mice. IPGTT revealed that ENO2-[Delta]FosB had markedly improved insulin response to IP glucose bolus at 50 wks while control mice exhibited severe hyperinsulinemia and exacerbated insulin response. Pancreatic islets in ENO2-[Delta]FosB mice were smaller and had denser insulin immunostaining than those in control mice at 12 and 50 wks. Islets isolated from old ENO2-[Delta]FosB mice had a 35-fold increase in [Delta]FosB expression. Furthermore, ENO2-[Delta]FosB islets were more glucose sensitive and had significantly increased glucose-stimulated insulin secretion concomitantly with increased *Ins1* and *Glut2* and decreased *Ucp2* mRNA expression. Taken together, our results demonstrate that signaling downstream of [Delta]FosB has protective effects against age-related skeletal and metabolic changes, including the preservation of β -cell function which attenuates with age.

(1) Sabatakos et al., Nat Med 2000; 6(9):985
(2) Rowe et al., Endocrinology 2009; 150(1):135

Nothing to Disclose: KS, GCR, SL, HS, MY, RB

sort_order 2506
Pub # P3-437
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Insulin Action & Glucose Homeostasis in Model Systems (1:30 PM-3:30 PM)
Title Maternal and Paternal Metabolic Milieus Are Important Determinants of Adult Skeletal Phenotypes: Evidence from a Murine Model of Fetal Programming Due to Parental Hyperglycemia
Author String C Grasemann, MJ Devlin, P Rzezczkowska, ML Bouxsein, MR Palmert
Hospital for Sick Children and The University of Toronto, Toronto, Canada; Kinderklinik UK-Essen and The University of Duisburg-Essen, Essen, Germany; Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA
Body In utero exposure to maternal diabetes has been associated with later-in-life phenotypes, such as cardiovascular disease and diabetes, in offspring.
Methods: To investigate the effects of *maternal* hyperglycemia more fully, we utilized an autosomal dominant model of murine diabetes [C57BL/6J-Ins2Akita (Akita mice)], which allowed for characterization of wildtype offspring of diabetic mothers and WT fathers. To examine the effects of *paternal* diabetes, WT offspring of Akita fathers and WT mothers were also assessed. Offspring of WT breedings served as controls.
At 14 and 26 wks of age intraperitoneal (ip) glucose tolerance tests were performed and fasted leptin, insulin and serum IGF1 levels were measured. Whole body bone mineral density (WBBMD, g/cm²) and whole body bone mineral content (WBBMC, g) were obtained via pDXA, and trabecular (Tb) bone architecture at the distal femur via [micro]CT.
Results: At 14 wks, male WT offspring of *Akita mothers* weighed less than controls (p<0.0001). Fasted glucose was elevated (p<0.001), and glucose clearance after ip challenge was significantly impaired at all time points (p<0.001). IGF-1 levels were unchanged, but fasted leptin and insulin were slightly decreased (p=ns). At 26 wks, the impairment after glucose challenge was even more pronounced and significant hypoinsulinemia and hypoleptinemia developed (p<0.01 for both).
Male offspring also showed a skeletal phenotype at 14 wks with reduced WBBMD and WBBMC compared to controls (p<0.01 for both). Distal femur Tb. bone volume fraction (BV/TV, %) and Tb. thickness (Tb.Th) were normal at 14 weeks but reduced by 29% and 12% at 26 wks (p<0.03 for both).
Male offspring of *Akita fathers* also had a mild metabolic phenotype but developed a severe skeletal phenotype, with decreased WBBMD (p<0.002) and WBBMC (p<0.01) at 14 wks, and lower distal femoral BV/TV (-39% and -47%) and TbTh (-12 and -11%) at 14 and 26 wks (p<0.04 for all).
Conclusion: The Akita mouse is a good model for investigating the effects of maternal diabetes on metabolic outcome of adult offspring. Strikingly, not only maternal but also paternal hyperglycemia negatively impacts offspring skeletal phenotype, and paternal hyperglycemia appears to be more deleterious. The mechanism of this effect is not known, but must involve mechanisms beyond the in utero metabolic environment. Further study should expand our understanding of the paternal influence on fetal programming.

Sources of Research Support: HSC Research Institute and Department of Pediatrics (MP); Restrcomp Program Sick Kids Research Institute (CG); NIH Grant F32HD060419, T32DK007028, and RC1AR058389 (MB and MD).

Nothing to Disclose: CG, MJD, PR, MLB, MRP

sort_order 2507
Pub # P3-438
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Insulin Action & Glucose Homeostasis in Model Systems (1:30 PM-3:30 PM)
Title The Effect of Nutrient Excess and Resveratrol as Nutriceutical on NAMPT Activity
Author String S Schuster, S Petzold-Quinque, A Garten, A Bamikol-Oettler, S Laue, R Gebhardt, W Kiess
Pediatric Research Center, Leipzig, Germany; Institute of Biochemistry, Leipzig, Germany
Body
Aim: Nicotinamide phosphoribosyltransferase (NAMPT) is a key enzyme of the NAD- biosynthesis and regulates the activity of the NAD- dependent deacetylase sirtuin 1 (SIRT1). Overexpression of NAMPT and SIRT1 improves insulin sensitivity and glucose metabolism. Similarly, resveratrol, a potent activator of SIRT1, improves insulin sensitivity in a diet-induced obesity model. We aimed to establish a NAMPT enzymatic assay and asked whether nutrient excess and resveratrol, a plant derived polyphenol, are able to modulate NAMPT activity and alter intracellular NAD levels.
Methods: HepG2 cells, primary human and rat hepatocytes were cultured. NAMPT and SIRT1 protein expression was quantified by Western blotting. NAMPT mRNA expression was measured by real-time PCR. NAD concentrations were quantified using a commercially available fluorimetric NAD assay. By using Nile red staining and flow cytometry, intracellular lipid accumulation was analyzed. NAMPT enzymatic activity was measured using a radioactive filter disc assay.
Results: We established a radioactive NAMPT enzymatic assay with optimal parameters. Resveratrol increased NAMPT activity in HepG2 cells by 50.2± 2.6%, in primary rat hepatocytes by 262.1± 9.5% and in human hepatocytes by 112.0± 13% and raised the intracellular NAD level (3.5 fold). High glucose levels [30mM] decreased NAMPT activity by 51.3± 9.0% without influencing NAMPT protein level in HepG2 cells. Upon addition of insulin [100nM], NAMPT activity was restored (101.6± 25.3%). Overload of HepG2 cells with oleate or an oleate/palmitate combination induced lipid accumulation but did not affect NAMPT protein expression nor enzymatic activity. Palmitate significantly induced cell death (0.5mM: 53.1± 18.9%), elevated NAMPT release by 201.1± 12.9% and NAMPT mRNA expression (1.2 fold) in HepG2 cells.
Conclusion: We demonstrated that NAMPT activity was increased by the SIRT1 activator resveratrol without influencing NAMPT protein level. Resveratrol might exert beneficial effects by up-regulation of the intracellular NAD levels via elevated NAMPT activity. High glucose levels decreased NAMPT activity. The negative effects of glucose on hepatocellular metabolism might be mediated through reduced NAMPT activity. The addition of insulin restored NAMPT activity, potentially due to the metabolization of glucose.

Sources of Research Support: The Deutsche Forschungsgemeinschaft (German Research Foundation): KFO 152 ; The Deutsche Diabetes Gesellschaft (German Diabetes Association).

Nothing to Disclose: SS, SP-Q, AG, AB-O, SL, RG, WK

sort_order 2508
Pub # P3-439
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Insulin Action & Glucose Homeostasis in Model Systems (1:30 PM-3:30 PM)
Title Catalase Overexpression on Redox Balance and Insulin Resistance in Skeletal Muscle Cells
Author String LR Silveira, MR Barbosa, VC Figueiredo, IH Sampaio, RI Reis, LT Parreira-e-Silva, IC Kettelhut, EM Carneiro, R Curi
Faculty of Medicine, University of São Paulo, Ribeirão Preto, Brazil; UNICAMP, Campinas, Brazil; University of São Paulo, São Paulo, Brazil
Body Reactive oxygen species (ROS) are known to be involved in several physiological processes in skeletal muscle. However, abnormal availability of fatty acids (FA) induces insulin resistance and its complications. The pathogenesis of insulin resistance involves disordered lipid metabolism. Although the mechanism is not completely understood, elevated levels of reactive oxygen (ROS) are involved in the establishment of insulin resistance conditions. We, therefore, investigated the effects of overexpression of catalase (CAT), a H₂O₂ scavenger, in rat skeletal muscle cell exposed to elevated concentration of FA. The skeletal muscle cells were isolated from quadriceps muscle from Wistar rats and cultured in DMEM medium. The cells were transfected with pcDNA3 plasmid in medium containing Lipofectamine (1:4). After differentiation, the cells were exposed to the palmitic acid (700[μM]) during 72h. After this period, the cells were collected and the catalase content and mRNA were determined as a control experiment. In addition, the citrate synthase activity (CS) and the mRNA level of PGC1α and Sirt1 were examined as mitochondrial biogenesis factors. The extracellular ROS production were determined by Amplex fluorescent probe. Whereas the oxygen consumption was measured at presence of glucose with or without insulin 0.1U (5.6 mM) using a Clark-type electrode (Hansatech Instruments). The CAT encode plasmid was successfully transfected as indicated by CAT mRNA and content (p<0.05). The palmitic acid treatment markedly reduced the CS activity as well as the mRNA levels of PGC1α and SIRT1 (p< 0.05). This effect was accompanied by a significantly reduction of oxygen consumption in the presence of palmitic acid (p<0.05). However, the CAT transfection was observed to attenuate this effect (p<0.05). The H₂O₂ production was increased at 24 h after palmitic acid treatment (p<0.05), whereas it was markedly reduced at 72h (p<0.05). Transfection was able to prevent this effect compared to control (p>0.05). Our results showed that elevated nutrient availability reduces mitochondrial oxygen consumption favoring ROS production and insulin resistance. The effect of CAT overexpression improving mitochondrial biogenesis and oxygen uptake suggesting that ROS is an important regulator of glucose metabolism in skeletal muscle cells.

Sources of Research Support: FAPESP, CNPq, and CAPES.

Nothing to Disclose: LRS, MRB, VCF, IHS, RIR, LTP-e-S, ICK, EMC, RC

sort_order 2509
Pub # P3-440
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Insulin Action & Glucose Homeostasis in Model Systems (1:30 PM-3:30 PM)
Title Mineralocorticoid Receptor Blockade Improves Diastolic Function Independent of Blood Pressure Reduction in Transgenic Model of RAAS Overexpression
Author String J Habibi, VG DeMarco, L Ma, L Pulakat, N Rehmer, WE Rainey, AT Whaley-Connell, JR Sowers
University of Missouri, Columbia, MO; University of Missouri, Columbia, MO; University of Missouri, Columbia, MO; University of Missouri, Columbia, MO; Harry S Truman VA Medical Center, Columbia, MO; Medical College of Georgia, Augusta, GA
Body **Rational:** There is increasing evidence that aldosterone can promote diastolic dysfunction and cardiac fibrosis independent of blood pressure effects, perhaps through increased oxidative stress and inflammation. Accordingly, this investigation was designed to ascertain if mineralocorticoid receptor blockade improves diastolic dysfunction independent of changes in blood pressure.
Experimental Design: Male TG(mRen2)27 and age-matched Sprague-Dawley rats were treated with either low dose ($-1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) or a vasodilatory, conventional dose ($-30 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) of spironolactone or placebo for three weeks.
Results: TG(mRen2)27 rats displayed increases in systolic blood pressure, plasma aldosterone levels as well as impairments in left ventricle diastolic relaxation without changes in systolic function on cine-MRI. The TG(mRen2)27 hearts also displayed hypertrophy (left ventricle weight, cardiomyocyte hypertrophy and septal wall thickness), as well as fibrosis (interstitial and perivascular). There were increases in oxidative stress in TG(mRen2)27 hearts as evidenced by increases in NADPH oxidase activity and subunits as well as reactive oxygen species formation. Low dose spironolactone had no effect on systolic blood pressure but improved diastolic dysfunction comparable to a conventional dose. Both doses of spironolactone caused comparable reductions in reactive oxygen species, 3-nitrotyrosine immunostaining, perivascular and interstitial fibrosis. These data support the notion mineralocorticoid receptor blockade improves diastolic dysfunction through improvements in oxidative stress and fibrosis independent of changes in systolic blood pressure.
Nothing to Disclose: JH, VGD, LM, LP, NR, WER, ATW-C, JRS

sort_order 2510
Pub # P3-441
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Insulin Action & Glucose Homeostasis in Model Systems (1:30 PM-3:30 PM)
Title Mitochondrial Function and Protein Expression in CSL2KO Mouse Skeletal Muscle after 10 Weeks of High-Fat Diet Intake
Author String C Roy, S Paglialunga, J Hoeks, K Cianflone, P Schrauwen
IUCPQ Research Centre, Québec, Canada; Maastricht University, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht, Netherlands
Body
Introduction: Understanding the mechanisms regulating food intake and energy expenditure are important for the treatment of obesity. Acylation stimulating protein (ASP, C3adesArg) is an adipokine which stimulates triglyceride synthesis and glucose transport via interaction with its receptor CSL2. The receptor is expressed both peripherally (adipose tissue, muscle) and centrally. Previous studies have shown that ASP-deficient mice (C3KO) and CSL2-deficient mice (CSL2KO) are hyperphagic (59% and 229% increase, $P < 0.0001$) yet this is counter-balanced by increased oxygen consumption (VO₂) and a lower RQ suggesting a physiological role for ASP-CSL2 in regulation of energy metabolism.
Objectives: To elucidate the impact of lack of ASP signaling on muscle metabolism and insulin sensitivity.
Methods: Male mice WT (n=14) and CSL2KO (n=17) were fed a chow diet or a high fat diet (60% fat) for 10 weeks. Body weight was measured 3 times per week. At week 8, after a 4 hr fast, insulin sensitivity was assessed by an insulin tolerance test. Mitochondria were isolated from hindleg skeletal muscle and used in an OROBOROS Oxygraph-2k, for high-resolution respirometry (HRR). Meanwhile, the tibialis anterior muscles were harvested for histology, enzyme activity and protein measurement.
Results: Body weight measurement showed no differences in weight gained between WT and CSL2KO on either diet, although the mice on high fat diet gained more weight than chow fed mice. We observed no differences in non-fasted glucose levels between all four groups, but glucose levels after a 4 hours fast were higher in the HF mice compared to chow fed WT mice. High-resolution respirometry showed a substrate specific increased in (ADP stimulated) state 3 respiration with palmitoyl-CoA plus carnitine as a substrate, but not in the presence of pyruvate, in the KO mice when compared to WT on HF.
Conclusion: We previously showed that mice lacking the ASP signaling had an increased capacity for fat oxidation in the muscle. The results in this study showed that mitochondria from CSL2KO mice on HF have an increased in (ADP stimulated) state 3 respiration, when given a fatty acid substrate. Leading us to believe that interfering with the ASP-CSL2 receptor pathway is a metabolic target in skeletal muscle metabolism.

Sources of Research Support: The Canadian Institutes of Health Research (Doctoral research grant) and the Fonds de la recherche en santé du Québec (Training award).

Nothing to Disclose: CR, SP, JH, KC, PS

sort_order 2511
Pub # P3-442
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Insulin Action & Glucose Homeostasis in Model Systems (1:30 PM-3:30 PM)
Title Mesangium Proliferation in Obese Zucker Rats: Effect of Gender, Age and Antioxidant Diet
Author String Y Slyvka, R Malgor, SR Inman, J Ding, FV Nowak
Ohio University, Athens, OH; University of Texas at Austin, Austin, TX
Body A major structural sign of diabetic nephropathy (DN) is mesangial matrix (MM) expansion. The aim of this study was to observe the status of MM in the obese Zucker rat (fa/fa) model of DN related to gender, age and the effect of an antioxidant-fortified (AO) diet. Obese Zucker rats were studied at 6 and 20 weeks of age, males and females on a regular (REG) or AO diet. MM was assessed by PAS-staining with subsequent estimation of glomerular tuft area (GTA) and PAS positive stained area (PSA). Increasing age resulted in larger GTA and PSA on both REG and AO diets in both males and females. However the PSA/GTA ratio was higher only on REG diet in both males and females. Males on the REG diet had larger GTA than females at both 6 and 20 weeks. In comparison to the males PSA/GTA ratio was higher in females on REG diet at both ages and on the AO diet at 20 weeks. Compared to the age and gender matched animals on the REG diet, males on the AO diet had smaller GTA at 6 and 20 weeks, and both males and females on the AO diet had smaller PSA at 20 weeks. Conclusion: MM expansion in an obese Zucker rat model is greater with age, more severe in females and is ameliorated by AO diet in both genders at 20 weeks.

Sources of Research Support: NIH R15 DK073066 to SRI and FVN.

Nothing to Disclose: YS, RM, SRI, JD, FVN

sort_order 2512
Pub # P3-443
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Insulin Action & Glucose Homeostasis in Model Systems (1:30 PM-3:30 PM)
Title Preptin, a ProIGF2-Derived Peptide, Is a Novel Regulator of Hepatic Glucose Homeostasis
Author String L Whiting, DL Hay, CM Buchanan, GJS Cooper
Auckland University, Auckland, New Zealand; Auckland University, Auckland, New Zealand; University of Manchester, Manchester, UK; University of Auckland, Auckland, New Zealand
Body Preptin is a 34-amino-acid peptide discovered during our systematic analysis of hormone granules isolated from pancreatic β TC6-F7 cells (a continuous murine beta cell line). The rat preptin sequence corresponds to Asp(69)-Leu(102) of the proinsulin-like growth factor-2 (proIGF2) E-peptide region of IGF2. In both *in vitro* cell systems and *ex vivo* perfused pancreas, exogenous preptin increases glucose-mediated insulin secretion suggesting preptin may be a novel regulator of glucose homeostasis and an incretin-like hormone (1). The liver plays a key role in glucose regulation through hormone-mediated regulation of hepatic glucose production. We sought to determine the role of preptin in this tissue using an isolated perfused liver model. Livers from male Wistar rats (220-250g) were isolated and perfused in a non re-circulating manner and organ effluent collected for glucose and lactate measurements. Livers were stabilised for 40 minutes before preptin (71nM) or vehicle were delivered via a side arm infusion ($t = 0$). At 30 minutes, epinephrine (50nM) was infused through a second side arm for 30 minutes. After 60 minutes, the infusion of preptin/vehicle and epinephrine was stopped and glucagon (1.15nM) infused for 15 minutes to confirm liver viability. Small sequential biopsies of liver tissue were taken during the perfusion and snap frozen in liquid nitrogen for subsequent glycogen measurements and western blotting. Preptin decreased hepatic glucose production, an effect that was maintained in the presence of epinephrine, a powerful stimulator of hepatic glycogenolysis. These data indicate that preptin influences glucose regulation in the liver independently from insulin and contributes to our understanding of how glucose homeostasis is controlled.

(1) Buchanan, C.M., Phillips, A.R. and Cooper, G.J., *Biochem J* 2001; 360:431
Nothing to Disclose: LW, DLH, CMB, GJSC

sort_order 2513
Pub # P3-444
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Insulin Action & Glucose Homeostasis in Model Systems (1:30 PM-3:30 PM)
Title Berberine Regulates Glucocorticoid Receptor and 11 β -Hydroxysteroid Dehydrogenase Type 1 Expression in Murine Adipose Tissue and 3T3-L1 Adipocytes
Author String H Du, W Wang, Y Nakagawa, TC Friedman, Y Liu
Charles Drew University of Medicine & Science, Los Angeles, CA; School of Basic Medical Sciences, Jilin University, Changchun, China; Hamamatsu University School of Medicine, Hamamatsu, Japan
Body The glucocorticoid receptors (GR) are nuclear receptors that play an important role in the regulation of glucocorticoid-induced insulin resistance and hepatic gluconeogenesis linked to the development of type 2 diabetes and obesity. 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1) mediates intracellular steroids exposure to mouse adipose GR by regeneration of active corticosterone from inactive 11-dehydrocorticosterone. Hexose-6-phosphate dehydrogenase (H6PDH) mediates intracellular NADPH availability to mouse 11 β -HSD1 and thus ensures 11 β -HSD1 driving tissue GC production linked to the development of type 2 diabetes and obesity. Berberine (BBR) is an anti-inflammatory drug and has recently shown to improve obesity and insulin resistance. Here, we evaluated the potential beneficial effects of BBR in type 2 diabetic mice by examining the possible influence of BBR on the expression of GR, 11 β -HSD1, and H6PDH in vivo and in vitro in adipocytes. Chronic treatment of db/db mice with BBR markedly decreased the increased expression of both GR mRNA and its protein in adipose tissue and increased the insulin sensitivity with reduction of fasting blood glucose levels and body weight. This inhibition of GR expression in responded to the significant reduction of both 11 β -HSD1 and H6PDH mRNA expression within adipose tissue. Addition of BBR to mouse adipocytes led to a significant down-regulation of GR mRNA levels and was corrected with the suppression of 11 β -HSD1 and H6PDH expression. These findings indicate that BBR could exert beneficial metabolic effects in insulin resistance and obesity by interfering with adipose 11 β -HSD1 driving tissue GC action.
Nothing to Disclose: HD, WW, YN, TCF, YL

sort_order

2514

Pub #

P3-445

Session Information

POSTER SESSION: BASIC/TRANSLATIONAL - Insulin Action & Glucose Homeostasis in Model Systems (1:30 PM-3:30 PM)

Title

Maternal Fructose Intake during Pregnancy and Lactation Alters Placental Growth and Leads to Sex-Specific Changes in Fetal and Neonatal Endocrine Function

Author String

ZE Clayton, C Yap, DM Sloboda, MH Vickers
University of Auckland, Auckland, New Zealand

Body

There is growing interest in the effects of maternal obesity and inappropriate maternal nutrition on the risk of childhood and adult disease in the offspring. In this context, the effects of maternal fructose intake on offspring health remain largely unknown, despite the marked increase in consumption of sweetened beverages that has paralleled the obesity epidemic. The present study investigated the impact of maternal fructose intake on placental, fetal and neonatal development. Female Wistar rats were time-mated and allocated to receive either water (CONT) or fructose solution designed to provide 20% of caloric intake from fructose (FR). FR was administered from day 1 of pregnancy until postnatal day (P)10. All dams had ad-libitum access to standard laboratory chow and water. Dams and offspring were killed at embryonic day (E)21 and P10. FR dams demonstrated increased total caloric intake and maternal hyperinsulinemia at E21 as well as increased maternal plasma fructose levels at E21 and P10. FR intake did not alter maternal blood glucose, β -hydroxybutyrate (BHB) or electrolyte levels at either timepoint. Fetal weights at E21 were unchanged, although placental weights were reduced in FR female but not FR male fetuses. Plasma leptin, fructose and blood glucose levels were increased and BHB levels decreased in FR female but not male fetuses. Although unchanged in FR dams and female fetuses, levels of the non-essential amino acid taurine ($p < 0.05$) were increased in male FR fetuses. Plasma insulin levels were not different between groups. Male and female FR neonates had higher plasma fructose levels and were hypoinsulinemic but euglycemic at P10 compared to CONT. Blood BHB levels were increased in FR male neonates but not females at P10. P10 plasma leptin levels were not different between groups. Stomach content leptin levels were increased in all FR offspring at P10 but no differences in stomach content insulin or fructose levels were observed. This study reports for the first time that maternal FR intake resulted in sex-specific changes in offspring development, whereby females appear more vulnerable to metabolic compromise during neonatal life. Further studies are now critical to establish the long term effects of maternal FR intake on the health and well-being of offspring and whether our observed sex differences elicit different risk profiles for metabolic disease into the post-weaning period.

Sources of Research Support: The National Research Centre for Growth and Development.

Nothing to Disclose: ZEC, CY, DMS, MHV

sort_order 2515
Pub # P3-446
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Insulin Action & Glucose Homeostasis in Model Systems (1:30 PM-3:30 PM)
Title Effects of Dietary [omega]3 and [omega]6 Fatty Acids in Rats Exposed to a Fructose-Rich Diet
Author String WJ Malaisse, Z Mellouk, T Hachimi Idrissi, K Louchami, E Hupkens, Y Zhang, N Bular, D Ait Yahia, A Sener
Université Libre de Bruxelles, Brussels, Belgium; Es-Sénia Univ, Oran, Algeria
Body A metabolic syndrome prevails in rats exposed to either a fructose-rich diet or a diet deprived of long-chain polyunsaturated [omega]3 fatty acids. The present study concerns the possible metabolic and hormonal effects of dietary [omega]3 and [omega]6 fatty acids in rats exposed to a fructose-rich diet. Two groups of 6 female rats each were exposed from the 8th week after birth and for the ensuing 8 weeks to diets containing 5% (w/w) [omega]3-deprived sunflower oil and 64% either starch (S[omega]3D rats) or D-fructose (F[omega]3D). In the 3th and 4th group, respectively, a third of the sunflower oil in the fructose-rich diet was replaced by an equal amount (1.6%) of either [omega]3-rich salmon oil (F+[omega]3) or C18:2[omega]6-rich safflower oil (F+[omega]6). As judged by the ratio between the relative gain in body weight and food intake over the 8 weeks experimental period, the estimated caloric efficiency was much lower in the (S[omega]3D) rats (1.25±0.02) than in the 3 groups of fructose-fed rats (2.54±0.13). At time zero of an IPGTT conducted on day 50 after overnight starvation, the HOMA index of insulin resistance was inversely related to the [omega]3/[omega]6 dietary ratio in the 3 groups of fructose-fed rats. The time zero insulinogetic index was much lower in the (F+[omega]6) rats than in the other 3 groups, such being also the case for the ratio between the total AUC for insulin/glucose during the IPGTT. This coincided with selected perturbations of both D-glucose metabolism and insulin secretion in isolated pancreatic islets. For instance, at 3 D-glucose concentrations (2.8, 8.3 and 16.7 mM), the utilization of D-[5-³H]glucose, but not the oxidation of D-[U-¹⁴C]glucose, only represented in the (F+[omega]6) rats 52±4% of the mean corresponding values found in (F+[omega]3) rats. Likewise, despite a comparable insulin content of the islets, the ratio for the increment in insulin output above basal value recorded at 8.3/16.7 mM D-glucose was about twice lower in (F+[omega]6) rats (13±4%) than in (F+[omega]3) rats (23±3%). Such a difference contrasted with a comparable secretory response to 2-ketoisocaproate (10 mM) in the 4 groups of rats. In conclusion, the dietary supply of [omega]3 and/or [omega]6 fatty acids affects several metabolic and hormonal variables in rats exposed to a fructose-rich diet.

Nothing to Disclose: WJM, ZM, THI, KL, EH, YZ, NB, DAY, AS

sort_order

2516

Pub #

P3-447

Session Information

POSTER SESSION: BASIC/TRANSLATIONAL - Insulin Action & Glucose Homeostasis in Model Systems (1:30 PM-3:30 PM)

Title

The Peculiarities of NOS Isoform Expression in Obese Zucker Rat Kidney: Effect of Gender, Age and Antioxidant Diet

Author String

FV Nowak, Y Slyvka, R Malgor, SR Inman
Ohio University, Athens, OH

Body

Development of diabetic nephropathy (DN) is associated with impairment of nitric oxide (NO) synthesis and increased oxidative stress. The aim of this study was to observe the expression of three NO synthase (NOS) isoforms and test the effect of an antioxidant-fortified (AO) diet during the progression of DN based on obese (fa/fa) Zucker rat model. NOS isoforms (n-neuronal, e-endothelial and i-inducible) kidney immunohistochemistry and kidney function assessment based on glomerular filtration rate (GFR) were performed at 6 and 20 weeks of age in male and female animals fed a regular (REG) or antioxidant-fortified (AO) diet. At 20 weeks, eNOS expression in cortex was higher in females on the AO diet but lower in males on the AO diet, compared to age and gender matched animals on the REG diet. This was associated with more preserved GFR in females on AO than REG diet at 20 weeks. With age eNOS expression in cortex decreased in females on REG diet and male on AO diet, associated with decrease of GFR adjusted to kidney weight. Males on the AO diet exhibited higher levels in cortex of nNOS at 20 weeks and iNOS at 6 weeks than males on the REG diet but these differences did not correspond to GFR. Although age and gender related changes were seen in expression of nNOS and iNOS, there were no associated differences in renal function. Conclusion: Increased levels of eNOS expression associated with factors of diet and age correspond to kidney function preservation in obese Zucker rats.

Sources of Research Support: Supported by NIH R15 DK073066 to SRI and FVN.

Nothing to Disclose: FVN, YS, RM, SRI

sort_order

2517

Pub #

P3-448

Session Information

POSTER SESSION: BASIC/TRANSLATIONAL - Insulin Action & Glucose Homeostasis in Model Systems (1:30 PM-3:30 PM)

Title

Establishment of Overexpression Cell Line for Inducible Cyclic AMP Early Repressor Gene in Porcine Fibroblast

Author String

Y-K Kim, E-B Jeung

College of Veterinary Medicine, Chungbuk National University, Cheongju, Republic of Korea

Body

Diabetes Mellitus is a metabolic disease caused by impaired insulin secretion of pancreatic beta cells and increased insulin resistance of peripheral tissues. Recently, it was reported that inducible cyclic AMP early repressor (ICER) *Iy* expression in pancreatic beta cells was strongly induced by glucagon and increased in diabetes. In this study, the role of ICER was examined as an important factor for diabetes. First, we measured the human insulin promoter activity. The various regions of the human insulin promoter region were prepared by a long-range PCR using genomic DNA from human as a template. Amplified fragments were ligated with the promoterless pGL3-Basic vector and ICER *Iy* was prepared by a PCR using cDNA from pig pancreas as a template. MIN6 mouse beta cells were transfected with a luciferase reporter plasmid containing human insulin promoter. The human insulin-luciferase reporter plasmid is 0.5kb or 1.5kb size. ICER *Iy* gene expression is controlled by human insulin promoter 1.5kb for selectively expressed in MIN6 mouse beta cells. The human insulin promoter was strongest to the luciferase activity. Transfected into primary porcine fibroblast cells and then the previous media were replaced by selective media containing G-418. The resistant cells to neomycin were further selected by EGFP expression under fluorescent microscopy. After several passages, continuous EGFP expressing cells were confirmed by PCR.

Nothing to Disclose: Y-KK, E-BJ

sort_order

2518

Pub #

P3-449

Session Information

POSTER SESSION: BASIC/TRANSLATIONAL - Insulin Action & Glucose Homeostasis in Model Systems (1:30 PM-3:30 PM)

Title

Generation of Transgenic Dogs Overexpressing *Phosphoenolpyruvate carboxykinase* for Type II Diabetes Mellitus Model

Author String

S-H Hyun, Y-K Kim, E-M Jung, E-B Jeung
Chungbuk National University, Cheongju, Republic of Korea

Body

Type II diabetes mellitus (T2DM), a non-insulin-dependent diabetes mellitus's disease (NIDDM), is one of the most common complex metabolic disorders and is characterized by hyperglycemia and metabolic alterations. In T2DM, fasting hyperglycemia is attributed to excessive hepatic glucose production, and increased gluconeogenesis has been ascribed to increased transcriptional expression of phosphoenolpyruvate carboxykinase (PEPCK). A primary cell line was established from pig fetal fibroblast by transfected with PEPCK containing the enhanced green fluorescent protein (EGFP) gene. In the present study, each 9 piglets were born and 4 (female 2 and male 2) of them were confirmed as positive transgenic piglets. Positive piglets significantly expressed EGFP in the hoof and skin. PCR analysis determined that contained the PEPCK transgene in the cloned offspring. The female and male piglet body weights were increased by approximately 2-folds at the age of 4 weeks.

Nothing to Disclose: S-HH, Y-KK, E-MJ, E-BJ

sort_order 2519
Pub # P3-450
Session Information POSTER SESSION: CLINICAL - Inpatient Diabetes Management Issues (1:30 PM-3:30 PM)
Title Risk Factors for Inpatient Hypoglycemia in a Tertiary Care Medical Center
Author String JR Grogg, P Singal, A Jarori, JP Walsh
Indiana University School of Medicine, Indianapolis, IN; Richard L Roudebush VA Medical Center, Indianapolis, IN
Body
Objective: Hypoglycemia in hospitalized patients is associated with adverse outcomes, and is a significant barrier to optimal glycemic control. To better understand the causes of inpatient hypoglycemia, we conducted a historical cohort study of severe hypoglycemia (≤ 50 mg/dl) in patients hospitalized at a large, tertiary care teaching hospital.
Methods: We reviewed the medical records of all admissions over a three month period with any inpatient blood glucose ≤ 50 mg/dl. For a comparison group, we also reviewed 105 inpatients who received scheduled insulin during their admission, but did not experience hypoglycemia.
Results: There were 146 episodes of blood glucose ≤ 50 mg/dl in 71 patients. The normoglycemic and hypoglycemic groups were similar in age, diabetes prevalence, outpatient insulin use, oral hypoglycemic agent use, hemoglobin A1c, admission glucose, and Charlson co-morbidity index. Patients experiencing hypoglycemia had a lower BMI (28.7 vs. 33.0, $p < 0.001$), and higher 90 day mortality (18.3% vs. 4.8%, $p = 0.005$) than the normoglycemic group. There were 116 hypoglycemic events in patients receiving subcutaneous insulin. Of these, 53.4% were due to basal insulin, 25.0% to nutritional insulin, 6.9% to an insulin correction dose, and 14.7% to multiple insulin types. Of the 116 events due to subcutaneous insulin 58 (50.0%) were preceded by a blood glucose measurement < 80 mg/dl in the 12 to 36 hours prior to the event. Of those, 53.4% had no change made to their insulin regimen. Co-morbid conditions significantly associated with hypoglycemia included stage 5 chronic kidney disease, infections, malignancies, dysphagia, and malnutrition. One or more of these conditions was present in 55 (77.5%) of the patients experiencing hypoglycemia and 123 (84.2%) of the 146 hypoglycemic events.
Conclusions: Severe hypoglycemia at this medical center was associated with significantly higher 90 day mortality. The majority of events occurred in patients with one or more risk factors for low glucose. Many events were preceded by milder hypoglycemia. Interventions targeted at reducing insulin doses and setting higher glucose targets in patients with hypoglycemia risk factors, as well as encouraging timely insulin adjustment after mildly reduced glucoses have the potential to dramatically reduce iatrogenic hypoglycemia in hospitalized patients.

Nothing to Disclose: JRG, PS, AJ, JPW

sort_order 2520
Pub # P3-451
Session Information POSTER SESSION: CLINICAL - Inpatient Diabetes Management Issues (1:30 PM-3:30 PM)
Title Effect of Hospital Admission on Glycemic Control One Year after Discharge
Author String NJ Wei, RW Grant, DM Nathan, DJ Wexler
Massachusetts General Hospital, Boston, MA; Massachusetts General Hospital, Boston, MA; Harvard Medical School, Boston, MA
Body
Objective: To determine the effect of hospital admission on subsequent glycemic control in patients with diabetes and hemoglobin A1C (A1C) [ge]7%.
Background: Hospital admission has been called an opportunity to improve diabetes management. We hypothesized that patients with glycemia above goal (A1C [ge]7%) would benefit from hospitalization with a sustained improvement in A1C at 1 year.
Methods: We retrospectively studied 470 medical and surgical adults with diabetes and baseline A1C [ge]7% admitted to a tertiary care hospital. Each patient had A1C measured within 6 months before admission (baseline) and twice within 12 months of discharge (1/2002-6/2006) in the same laboratory. We excluded patients with conditions likely to affect hemoglobin kinetics. We determined change and correlates of change in A1C relative to the baseline A1C.
Results: Patients with baseline A1C [ge]7% (mean \pm SD, 8.53% \pm 1.66), had a significant A1C decline within three months of discharge (7.89% \pm 1.48, p <0.01; mean 2.73 \pm 1.86 mo) that was sustained over 1 year (A1C 7.98% \pm 1.54, p <0.01; 9.57 \pm 1.6 mo). Variables associated with greater post-discharge A1C decline included: baseline A1C [ge]9% (27% of cohort; A1C change -1.88% \pm 2.5, p <0.01), diabetes as the admission diagnosis (3% of cohort; A1C change -2.6% \pm 4.2, p <0.01), and longer length of stay. Diabetes as primary admission diagnosis predicted achieving goal A1C <7% at 1 year (OR 4.96 [95% C.I. 1.7, 14.9], p <0.01), whereas higher baseline A1C was associated with lower odds of obtaining this goal (OR 0.82 [0.69, 0.96], p 0.01), after adjusting for age, gender, race, duration between A1C measurements, admitting service, and type of insurance.
Conclusions: In this observational study of diabetes patients with A1C [ge]7%, hospital admission is associated with sustained reductions in A1C. The finding that patients admitted primarily for diabetes, who may undergo more intensive inpatient diabetes-specific management and follow-up, were more likely to reach goal A1C with a large decline in A1C at 1 year than patients admitted for other reasons suggests that the inpatient setting can provide an opportunity to optimize long-term diabetes care in high-risk populations. Future study designs and quality assurance evaluations of inpatient interventions on glycemic control post-discharge will need to account for tendency for slight A1C improvement in all hospitalized patients.
Nothing to Disclose: NJW, RWG, DMN, DJW

sort_order

2521

Pub #

P3-452

Session Information

POSTER SESSION: CLINICAL - Inpatient Diabetes Management Issues (1:30 PM-3:30 PM)

Title

Glycemic Variability as a Predictor of Hospital Mortality and Complications in General Surgery Patients

Author String

D Smiley, OI Klindukhova, P Chandra, F Farrokhi, L Peng, C Newton, ME Ferreira, S Jacobs, G Umpierrez
Emory University, Atlanta, GA; Emory University, Atlanta, GA

Body

Glycemic variability (GV) is a predictor of mortality in critically ill patients; however, the impact of GV on clinical outcome in general surgery is unknown. Accordingly, we determined the impact of GV in predicting hospital complications in 2 different studies: a randomized trial of SQ insulin treatment (Rabbit Surgery) and a large, observational study in general non-cardiac surgery patients. Rabbit Surgery included 211 patients with T2DM (58±11 yrs, admission blood glucose (BG): 190±92 mg/dl, mean±SD) with an admission BG between 140-400 mg/dl randomized to glargine once daily and glulisine before meals (post-op daily BG 145±32 mg/dL) or sliding scale insulin (BG 172±47 mg/dl). There were no differences in mortality; but, basal bolus significantly reduced the frequency of a composite of post-op complications including wound infection, pneumonia, respiratory failure, acute renal failure, and bacteremia (24.3% and 8.6%, p=0.003). The observational study included 3,184 patients (56±16 yrs, post-op BG 123±28[non-DM 118±22 mg/dl, DM 139±39 mg/dl]). Post-op complications were seen in 20.9%; and the inhospital and 30-day mortality were 1.8% and 2.3%, respectively (p=NS). GV was calculated in separate analyses from inpatient daily BG values using mean standard deviation. The mean GV was positively associated with post-op mean daily BG levels (p<0.01) and with higher rate of hypoglycemic events (p<0.01). In multivariate analysis adjusted for age, gender, history of DM, severity of surgery and hypoglycemia, GV was associated with increased mortality in non-DM patients (p<0.01), but not in DM patients. A similar association was observed between GV and hospital complications in non-DM, but not in DM patients. In summary, the results of these prospective and observational studies indicate that glucose variability is associated with post-op mortality and hospital complications in non-diabetic patients, but not in diabetic subjects undergoing non-cardiac, general surgery. Randomized clinical trials are needed to determine the role of glucose variability as a clinical tool in predicting outcomes in noncritically ill patients in general surgery settings.

Sources of Research Support: Sanofi-Aventis.

Disclosures: GU: Researcher, Sanofi-Aventis; Researcher, Takeda. Nothing to Disclose: DS, OIK, PC, FF, LP, CN, MEF, SJ

sort_order 2522
Pub # P3-453
Session Information POSTER SESSION: CLINICAL - Inpatient Diabetes Management Issues (1:30 PM-3:30 PM)
Title Outcomes Associated with Insulin Therapy Discontinuation after Hospital Discharge in Patients with Type 2 Diabetes (T2D) Initiated on Insulin during Hospitalization
Author String E Wu, S Zhou, AP Yu, M Lu, TR Graf
Analysis Group, Boston, MA; sanofi-aventis US, Bridgewater, NJ; Geisinger Health System, Danville, PA
Body **Objectives:** To investigate clinical outcomes and risk of hospital re-admission associated with disruption of insulin therapy (INS) after hospital discharge among T2D patients who initiated INS during hospitalization.
Methods: Adult T2D patients newly initiated on INS during a hospitalization were identified in MedMining Electronic Health Record data (01/2004-04/2010). Patients with a last recorded A1C [ge] 8% within 3 months of (or during) the hospital stay were included. Outcomes were compared between patients with INS continuation after the hospitalization (defined as an outpatient INS order within 60 days post-discharge) vs. patients with INS disruption. During the 12-month post-discharge, changes in A1C were compared using t-tests and regression models. A1C goal achievement (<7%) and hypoglycemia were evaluated using chi-square tests and logistic regression models. Time to re-admission was compared using Cox proportional hazard models. All regression models controlled for patient characteristics prior to and during hospitalization and medications post-discharge. A subgroup analysis was performed in patients with baseline A1C [ge]9%.
Results: 180 patients with continued INS and 552 patients with INS disruption were included (baseline A1C 11.1% vs. 9.5%, respectively). During the 12-months post-discharge, patients continuing INS had greater A1C reduction (3.4% vs. 1.5%, $P<0.01$), higher A1C goal achievement (41% vs. 31%, $P=0.02$), and comparable hypoglycemia (8% vs. 5%, $P=0.25$) vs. those with INS disruption. In the A1C [ge]9% subgroup similar patterns were observed for INS continuation (N=146) vs. disruption (N=277) (baseline A1C: 11.8% vs. 10.6%; A1C reduction: 4.1% vs. 2.3%, $P<0.01$; A1C goal achievement: 44% vs. 30%, $P=0.02$; hypoglycemia: 6% vs. 5%, $P=0.75$). Multivariate analysis were generally consistent with descriptive findings for both the A1C [ge]8% and [ge]9% groups (A1C reduction: adjusted difference=-1.68% and 1.53%, both $P<0.01$; A1C goal achievement: odds ratio [OR] = 1.66 and 2.18, $P=0.06$ and $P=0.03$; hypoglycemia: OR=1.04 and 0.68, $P=0.93$ and 0.58; respectively). Among the A1C [ge]9% subgroup, INS continuation was associated with lower risks of all-cause and diabetes-related hospitalizations (hazard ratio: 0.59 and 0.46 respectively; both $P<0.05$).
Conclusions: T2D patients who continued INS after hospital discharge had a greater A1C reduction, a greater A1C goal achievement, and a lower risk of hospital re-admission compared with patients with disrupted INS.
Sources of Research Support: sanofi-aventis US.
Disclosures: EW: Researcher, Sanofi-Aventis. SZ: Employee, Sanofi-Aventis. APY: Researcher, Sanofi-Aventis. ML: Researcher, Sanofi-Aventis. TRG: Speaker Bureau Member, Merck & Co.

sort_order 2523
Pub # P3-454
Session Information POSTER SESSION: CLINICAL - Inpatient Diabetes Management Issues (1:30 PM-3:30 PM)
Title Pediatric Diabetes Outpatient Center at Rhode Island Hospital: The Impact of Changing Initial Diabetes Education from Inpatient to Outpatient
Author String MM Pingul, SE Reinert, G Gopalakrishnan, W Plante, CM Boney, JQ Quintos
Rhode Island Hospital/The Warren Alpert Medical School of Brown University, Providence, RI; Lifespan Corporation, Providence, RI; Rhode Island Hospital/The Warren Alpert Medical School of Brown University, Providence, RI
Body **Background:** New-onset Type 1 diabetes mellitus (T1DM) patients are usually admitted for inpatient diabetes education. Few studies have suggested that outpatient diabetes education could be provided to new onset T1DM in the outpatient setting at lesser cost without compromising metabolic control. In September 2007, we established the Pediatric Diabetes Outpatient Center (PDOC) to educate families with new onset T1DM who meet our inclusion criteria. The objective of this study was to compare outcomes and costs of new-onset T1DM patients educated at the outpatient center with those educated in the inpatient setting.
Methods/Design: Retrospective chart review comparing the outcome of patients diagnosed with new onset T1DM prior to and after establishment of the PDOC in terms of: 1) hemoglobin A1c (HbA1c) in the first 3 years after diagnosis, 2) frequency of severe hypoglycemia, 3) admissions for DKA (pH < 7.3) or ER visits, and 4) healthcare cost.
Results: One-hundred-fifty-two patients were diagnosed with new onset T1DM from September 2007- August 2009. Thirty-three (22 %) subjects met our inclusion criteria for outpatient group (OG). Twenty-three subjects spent one night in the hospital and received the majority of their education at the PDOC and 10 subjects comprised the [pure outpatient] group (pure OG), receiving all of their education at the PDOC. Each of these 33 patients was matched to subjects in the inpatient group (IG, historical control) who received their education entirely as inpatients. Baseline characteristics of the 2 groups revealed no statistically significant differences in gender and age (OG: 10.5 years vs. IG 10.6 years, p= 0.16). There were no significant differences between OG and IG in mean HbA1c levels at 1, 2 and 3 years post-diagnosis (OG 8%, 8.5%, 9.3%; IG 8.3%, 8.9%, 9%, p= 0.51). Episodes of severe hypoglycemia, DKA, and ER visits, were not significantly different between the two groups (p>0.05). Mean total hospital cost for OG was significantly less than IG (OG: \$2886 vs. IG: \$4925, p<0.001); this difference was more pronounced when pure OG was compared to IG (pure OG: \$1044 vs. IG: \$4925, p<0.0001).
Conclusions: Our preliminary data demonstrates a positive impact of the outpatient-based pediatric diabetes center in lowering healthcare cost without compromising medical outcomes. The results of this study justify the need to increase reimbursement from third party payers for outpatient pediatric diabetes education programs.
Nothing to Disclose: MMP, SER, GG, WP, CMB, JBQQ

sort_order 2524
Pub # P3-455
Session Information POSTER SESSION: CLINICAL - Inpatient Diabetes Management Issues (1:30 PM-3:30 PM)
Title Glycemic Variability Is a Predictor of Hospital Mortality during Parenteral Nutrition
Author String P Chandra, D Smiley, L Peng, F Pasquel, G Umpierrez
Emory University School of Medicine, Atlanta, GA; Emory University, Atlanta, GA

Body Glycemic variability (GV) has been reported to be independent predictors of mortality in critically ill patients in the ICU, but the impact of GV on mortality in patients receiving parenteral nutrition (PN) is not known. Methods: We analyzed the impact of GV as measured by the standard deviation (SD) of BG values and by mean daily delta change ([Delta] daily max - daily minimum) during hospital stay on mortality in patients receiving PN. Results: A total of 276 patients on PN were included in the study (Age 51±18 yr [mean ± SD], known DM 19.2 %, ICU 74.3 %, non-ICU 25.7 %). PN was started 12±13 days after admission and was given for duration of 15±24 days. The hospital mortality was 27.2%. We found a strong association between BG pre- and during-PN (days 2-11) and hospital mortality, p<0.01. The mean GV by SD was 38±21mg/dL and [Delta] change was 51±29 mg/dL. GV was significantly larger in deceased compared to non-deceased patients (SD 48±25 vs 34±18 mg/dL, [Delta] change 75±39 vs 58±34 mg/dl, both p<0.01). In univariate analysis when data on GV by SD was divided into quartiles (<22.7 mg/dL, 22.7-31.7 mg/dL, 31.7-45.8 mg/dL and >45.8 mg/dL), patients in 3rd and 4th quartile had higher risk of mortality (OR=4.6, 95% CI: 1.6-13.2; OR=4.1, 95% CI: 1.4-12.0) compared to those in the lowest quartile. Similarly, GV as divided by [Delta] change into quartiles (<33.7 mg/dL, 33.7-47.6 mg/dL, 47.6-75.2 mg/dL and >75.2 mg/dL), patients in 3rd and 4th quartile had higher risk of mortality (OR=3.1, 95% CI: 1.2-7.7; OR=6.7, 95% CI: 2.7-16.6) compared to those in the lowest quartile. However, in multivariate analysis adjusted for age, diabetes status, gender, BG levels and hypoglycemia, GV was found to be a predictor of mortality only in non diabetics, but not in patients with DM (p<0.05). Hypoglycemia (BG < 70 mg/dl and < 40 mg/dl were reported in 41% and 3% of patients during PN, respectively. Excluding these patients, GV remained to show a significant association with mortality. Conclusions: Glycemic variability correlates with mortality independently of severity of hyperglycemia or the presence of hypoglycemia in patients receiving PN. This association is more pronounced in patients without DM compared to DM subjects. Prospective randomized control trials are needed to investigate the use of glycemic variability as a tool to improve mortality in critically-ill patients treated with PN.

Nothing to Disclose: PC, DS, LP, FP, GU

sort_order 2525
Pub # P3-456
Session Information POSTER SESSION: CLINICAL - Inpatient Diabetes Management Issues (1:30 PM-3:30 PM)
Title Admission Serum Blood Glucose and Hemoglobin A1c Levels Strongly Correlate with the Need for Insulin Treatment in Patients Receiving High Dose (HD) of Methylprednisolone (MP) Treatment for Multiple Sclerosis Exacerbation
Author String A Mallisho, F Elkhatib, N Saadeh, W Taha, A Alkhatib, A Abou-Samra
Wayne State University, Detroit, MI; Utah University, Salt Lake, UT
Body **Background:** Patients (pt) with multiple sclerosis (MS) often require HD-MP (>500 mg/d), some may require insulin treatment (Rx) for steroid induced hyperglycemia. There is no study that explored the impact of systematic (HD-MP) Rx on glycemic control in pts with MS **Aim:** Identify factors that could predict pts requiring insulin RX during HD-MP.
Method:
This is a retrospective study. We reviewed 4103 charts of MS pts admitted to Detroit Medical Center during the period of 1998 to 2009. We selected those who received HD-MP during admission & were not on steroid previously and for whom blood glucose levels (BG) were measured during hospitalization. Out of the 4103 pts, 1398 pts (34%) received HD-MP. Among these, 427 pts had electronic records. We collected demographic data, use of oral hypoglycemic agents, the frequency and the dose of HD MP, BG readings starting from the day of the first HD-MP dose and up to seven days, complete blood count, creatinine level & the insulin doses given before each BG reading. We calculated the total dose of insulin given for each day. We evaluated insulin requirement on 2nd day as we observed that pts who did not require insulin by the 2nd day, were unlikely to require insulin at all. Multiple regression analysis (MRA) was used to analyze the data.
Results:
A total of 269 pts met the analysis criteria; 85% of them received 1 g MP IV qd, and 15% received 0.5 g MP IV bid. Their mean age was 45±11 y. BMI was (28.5±6.6). Over 21.1% of pts had a history of DM. Mean serum BG at admission was 111.8±56 mg/dL, creatinine level was 0.86±0.3 mg/dL, WBC 7.7±2.9 & hemoglobin 12.7±1.6 g/dL. Mean daily insulin dose on 2nd day of HD-MP was 12.6±26 units. Only 1.8% of all patients with admission BG<100 required more than 10 units of insulin on day 2 of MP injections.
Using MRA, we found that BMI, MP Dose regimen, prior oral hypoglycemic agents use & gender were not significantly associated with need for insulin RX. BG at admission (P<0.00001) and age (p<0.03) associated with and predicted the use of insulin during the 2nd day of MP RX.
In the subgroup (41 patients) who had HbA1c measured within 1 month of admission, an abnormal value (defined as >5.7%) was also strongly associated with the requirement for insulin treatment (p<0.00001).
Conclusion: Older age, high serum BG at admission and abnormal HbA1c in pts presenting with MS exacerbation are highly correlated with the use of insulin to control steroid induced hyperglycemia in day 2 of HD-MP RX.

Sources of Research Support: F Elkhatib and A Mallisho qualify as first author.

Nothing to Disclose: AM, FE, NS, WT, AA, AA-S

sort_order 2526
Pub # P3-457
Session Information POSTER SESSION: CLINICAL - Inpatient Diabetes Management Issues (1:30 PM-3:30 PM)
Title Risk Factors for Severe Hypoglycemia among Hospital Patients
Author String ML Griffith, ME Matheny, JB Boord
Vanderbilt University School of Medicine, Nashville, TN; Vanderbilt University School of Medicine, Nashville, TN; Veterans Administration Tennessee Valley Health System, Nashville, TN; Vanderbilt University School of Medicine, Nashville, TN
Body **Background:** Hypoglycemia among hospitalized patients has been associated with increased mortality and increased length of hospital stay. While some physiologic risk factors for hypoglycemia are known, no risk prediction tools exist to identify inpatients at greatest risk for hypoglycemia. **Methods:** We conducted a retrospective cohort study of admissions to Vanderbilt University Hospital from 4/1/2008 to 10/31/2009 to elucidate risk factors for hypoglycemia occurring >24 hours (hr) into admission. Adult inpatient admissions with length of stay [ge]24 hr were eligible for inclusion. Exclusion criteria included age <18 years (yr), pregnancy or palliative care. Demographics, initial vital sign and laboratory data, diagnosis codes, glucocorticoid and diabetes (DM) medication use, and use of enteral/parenteral nutrition were collected. Primary outcome was defined as laboratory or bedside glucose <50 mg/dL occurring after the first 24 hr of admission. **Results:** 23,741 unique patients were represented in the cohort of 33,011 admissions. Median age was 55 yr (interquartile range (IQR) 42-66 yr); 51.9% were male. 22.7% had a diagnosis of DM. Patients with admission glucose <50 mg/dL (n=94) were excluded from this analysis. 919 of the remaining 32,917 admissions (2.8%) had a hypoglycemia event at a median of 4.2 days (d) after admission (IQR 2.1-8.4 d). In a multivariate logistic regression model adjusted for age, decreasing estimated glomerular filtration rate (GFR)(OR 1.37 for GFR 60-89 mL/min, P=0.008; OR 1.62 for GFR 30-59, P<0.001; OR 2.31 for GFR <30 or stage 4 or 5 CKD, P<0.001), increasing Charlson Comorbidity Index (CCI) score (OR 2.30 for highest quartile of CCI, P<0.001), diagnosis of DM (OR 2.26, P<0.001), pre-admission insulin prescription (OR 2.39, P<0.001), order for enteral formula feeding (OR 2.0, P<0.001) or nothing-by-mouth status (OR 1.75, P<0.001) in the first 24 hours of admission were all independently associated with risk of subsequent hypoglycemia. Model intercept was -4.94 (β -coefficient). Area under the ROC curve was 0.77, and Hosmer-Lemeshow goodness of fit test yielded $[\text{Chi}]^2=14.56$ and P=0.07 for the model. **Conclusions:** Several clinical factors that can be easily identified on hospital admission are associated with increased risk of hypoglycemia after the first 24 hr of hospital admission. A prediction model using this information may guide clinical interventions to reduce the risk of severe hypoglycemia in hospital patients.

Sources of Research Support: Veterans Health Administration HSR&D Career Development Award CDA-08-020 (M.E. Matheny).

Nothing to Disclose: MLG, MEM, JBB

sort_order 2527
Pub # P3-458
Session Information POSTER SESSION: CLINICAL - Inpatient Diabetes Management Issues (1:30 PM-3:30 PM)
Title Factors Associated with Insulin Therapy Discontinuation after Hospital Discharge in Patients with Type 2 Diabetes Initiated on Insulin during a Hospitalization
Author String E Wu, S Zhou, AP Yu, M Lu, TR Graf
Analysis Group, Boston, MA; sanofi-aventis US, Bridgewater, NJ; Geisinger Health System, Danville, PA
Body **Objectives:** This study examined factors associated with the discontinuation of insulin therapies post-discharge among patients with type 2 diabetes (T2D) naive to insulin prior to hospital admission, who initiated insulin therapy during their hospitalization.
Methods: Adult patients with T2D with a hospital discharge were identified in MedMining Electronic Health Record data from 01/2001 to 04/2010. The patients included in this study were newly initiated on insulin during the hospitalization, had a last recorded HbA1C value [ge]8% within 3 months of (or during) the hospitalization, and had [ge]1 glucose measurement in the hospital. A logistic regression model was used to identify predictors of insulin therapy discontinuation, defined as having no outpatient orders for insulin within 60 days of discharge from hospital. The potential predictors of discontinuation evaluated included demographics, comorbidities, prior drug use and health care resource use, baseline HbA1C and glucose values, and inpatient characteristics (e.g. type of in-hospital insulin use, length of hospital stay, and ICU stay).
Results: Within the study sample of 698 patients initiated on insulin in hospital, 520 patients (75%) did not receive insulin orders within 60 days of their discharge. In the logistic regression analysis, factors predicting a significantly lower risk of insulin therapy discontinuation post-discharge included in-hospital use of short-acting or long-acting insulin (odds ratio [OR], 95% confidence interval [CI]: 0.30 [0.16, 0.56] and 0.16 [0.09, 0.28], respectively), receiving an insulin order upon discharge (OR, 95% CI: 0.16 [0.07, 0.33]), baseline HbA1C levels [ge]9% (OR, 95% CI: 0.27, [0.16, 0.44]), and longer length of inpatient stay (OR, 95% CI: 0.93, [0.89, 0.98]).
Conclusions: Use of short-acting and long-acting insulin in the hospital, uncontrolled HbA1C level, and longer length of inpatient stay were associated with significantly lower risks of insulin therapy discontinuation after discharge in patients initiating insulin therapy during their hospitalization.

Sources of Research Support: sanofi-aventis US.

Disclosures: EW: Researcher, Sanofi-Aventis. SZ: Employee, Sanofi-Aventis. APY: Researcher, Sanofi-Aventis. ML: Researcher, Sanofi-Aventis. TRG: Speaker Bureau Member, Merck & Co.

sort_order 2528
Pub # P3-459
Session Information POSTER SESSION: CLINICAL - Inpatient Diabetes Management Issues (1:30 PM-3:30 PM)
Title Risk Factors for Hyperglycemia among Hospitalized Patients without Established Diabetes Mellitus
Author String ML Griffith, ME Matheny, JB Boord
Vanderbilt University School of Medicine, Nashville, TN; Vanderbilt University School of Medicine, Nashville, TN; Veterans Administration Tennessee Valley Health System, Nashville, TN; Vanderbilt University Medical Center, Nashville, TN
Body **Background:** Hyperglycemia among hospitalized patients, including those without recognized diabetes (DM), has been associated with increased morbidity and mortality in a variety of clinical conditions. While some risk factors for hyperglycemia in hospital patients are known, no risk prediction tools exist to identify non-diabetic inpatients at greatest risk for hyperglycemia after hospital admission. **Methods:** We conducted a retrospective cohort study of admissions to Vanderbilt University Hospital from 4/1/2008 to 10/31/2009 to elucidate risk factors for persistent hyperglycemia occurring >24 hours (hr) after admission in patients without established DM. Adult inpatient admissions with length of stay [ge]24 hr were eligible for inclusion. Exclusion criteria included age <18 years (yr), pregnancy, or palliative care. Demographics, initial laboratory data, diagnosis codes, glucocorticoid and DM medication use, and enteral/parenteral nutrition were collected. The primary outcome of hyperglycemia was defined as two laboratory or bedside glucose values >200 mg/dL occurring within a 48-hr period, after the first 24 hr of admission. **Results:** 23,741 patients were represented in the cohort of 33,011 admissions. Median age was 55 yr (interquartile range (IQR) 42-66) and 51.9% were male. Patients with a coded diagnosis of DM (22.7%) or admission glucose > 200 mg/dL (4.6% of non-DM patients) were excluded from this analysis. 1,229 of the 24,336 remaining admissions (5.1%) had hyperglycemia at a median of 3.1 days (IQR 1.9-6.1) after admission. In a multivariate logistic regression model, decreased estimated glomerular filtration rate (GFR)(OR 1.35 for GFR 60-89 mL/min; OR 1.61 for GFR 30-59; OR 1.52 for GFR <30 or stage 4 or 5 CKD, all P<0.001), admission to intensive care (OR 2.27, P<0.001), inpatient glucocorticoid treatment (OR 2.82, P<0.001), nothing-by-mouth status (OR 1.74, P<0.001) within first 24 hr of admission, and increasing age (OR 1.01, P<0.001) were all independently associated with subsequent hyperglycemia. Model intercept was -4.37 (β -coefficient). Area under the ROC curve was 0.70 and Hosmer-Lemeshow goodness of fit test was well-calibrated with $[\text{Chi}]^2=8.95$ and $P=0.35$ for the model. **Conclusions:** Several factors that are identifiable early in hospital admission can predict risk for subsequent hyperglycemia in patients without established DM. This prediction model has potential use for identifying patients at risk for adverse outcomes during hospital admission.

Sources of Research Support: Veterans Health Administration HSR&D Career Development Award CDA-08-020 (M.E. Matheny).

Nothing to Disclose: MLG, MEM, JBB

sort_order 2529
Pub # P3-460
Session Information POSTER SESSION: CLINICAL - Inpatient Diabetes Management Issues (1:30 PM-3:30 PM)
Title Insulin Dose-Related Hypoglycemia in Hospitalized Patients with Diabetes
Author String DJ Rubin, D Rybin, G Doros, ME McDonnell
Temple University School of Medicine, Philadelphia, PA; Boston University School of Public Health, Boston, MA; Boston University School of Medicine, Boston, MA
Body We performed a retrospective, case-control study of 1990 non-critically ill inpatients with diabetes to determine the association of weight-based insulin dose with hypoglycemia. Patients with a glucose <70 mg/dl (cases) were matched 1-to-1 to non-hypoglycemic controls on the hospital day of hypoglycemia, age, sex, and BMI. Relative to 24-hour insulin doses <0.2 units/kg, the unadjusted odds of hypoglycemia significantly increased with increasing insulin dose. Adjusted for insulin type, SSI use, albumin, creatinine, and hematocrit levels, the higher odds of hypoglycemia with increasing insulin doses remained. Compared to patients who received <0.2 units/kg, the adjusted odds of hypoglycemia were not significantly greater in patients who received 0.2-0.4 units/kg (OR 1.08, 95%CI 0.64-1.81, p=0.78) or 0.4-0.6 units/kg (OR 1.60, 95%CI 0.90-2.86, p=0.11). At insulin doses >0.6 units/kg, patients had significantly increased odds of hypoglycemia relative to <0.2 units/kg (0.6-0.8 units/kg: OR 2.10, 95%CI 1.08-4.09, p=0.028; >0.8 units/kg: OR 2.95, 95%CI 1.54-5.65, p=0.001). Although the relationship between insulin dose and hypoglycemia did not vary by insulin type (p=0.524 for interaction), patients who received NPH trended towards greater odds of hypoglycemia compared to those given glargine or short-acting insulin (p=0.062). Higher weight-based insulin doses are associated with greater odds of hypoglycemia independent of insulin type. However, 0.6 units/kg appears to be a threshold below which the odds of hypoglycemia are relatively low. These data suggest that 0.4-0.6 units/kg, a dose range tested in randomized controlled trials and recommended by professional organizations, may be the highest dose at which the risk of hypoglycemia remains low. Such findings may help clinicians use insulin more safely.
Nothing to Disclose: DJR, DR, GD, MEM

sort_order 2530
Pub # P3-461
Session Information POSTER SESSION: CLINICAL - Inpatient Diabetes Management Issues (1:30 PM-3:30 PM)
Title Implementation of a Diabetes Management Protocol as Compared to Conventional Management in a Heart Hospital's Non-Intensive Care Unit: Randomized Clinical Trial
Author String B Schaun, MA Moraes, J Rodrigues, M Cremonesi
Instituto de Cardiologia do Rio Grande do Sul/Funda[ccedi]ão Universitária de Cardiologia, Porto Alegre, Brazil; Hospital de Clínicas de Porto Alegre/UFRGS, Porto Alegre, Brazil
Body Introduction: Although guidelines are clear as to the advantages of glycemic control in hospitalized diabetic patients by giving priority to early insulinization and preventing the use of sliding-scale insulin (SSI), this type of approach often fails. Aim: To assess the effectiveness of implementing a diabetes management protocol (early insulinization, avoiding use of SSI) in a heart hospital's non-intensive care unit. Methods: Randomized clinical trial (number clinical trial 01154413) conducted from December 2007 to May 2009. Randomization (computerized process to generate random numbers) was made of 9 months of intervention (IG = intensive education of the health care team on the protocol) and 9 months of control (CG = without intervention in the team), in blocks of 3 months. The primary outcome was reduction in hypo (<70 mg/dL) and hyperglycemia (> 250 mg/dL) episodes and the secondary outcomes were lower mean glycemia, reduced time of stay in hospital and reduced frequency of events potentially related to diabetes. Results: The trial included 182 type 2 diabetes patients (IG n = 95, CG n = 87), 61% women, 61.7 ± 10 years old, HbA1c 8.7 ± 2.1%, glycemia 169.6 ± 48.3 mg/dl, similar baseline characteristics among groups, who stayed in hospital for 6.0 (4.0-10.0) days. Glycemia at admission was 163.6 ± 43 (IG) and 176.2 ± 53 mg/dl (CG), p = 0.07. Hypoglycemia episodes were 17 (17.9%) and 18 (20.7%) (IG and CG, respectively, p = 0.77) and hyperglycemia episodes were 47 (49.5%) and 50 (57.5%) (IG and CG, respectively, p = 0.35). Average capillary glycemia during hospitalization was 163.6 ± 43.0 (IG) and 176.2 ± 53.0 mg/dL (C), similar between groups (p=0.078). Time of stay in hospital was 7.0 days (5.0-10.0) for IG versus 6.0 (4.0-10.0) days for CG, p = 0.64. IG patients were administered 0 (0-10) IU of regular insulin and CG patients were administered 28 (7-56) IU of regular insulin (p < 0.001), while NPH insulin was 0 (0-114) vs. 0 (0-52), p = 0.16. The CG was administered 73 (83.9) doses of regular insulin vs. 40 (42.1) doses in the IG (p < 0.001). Number of patients who presented any infection, coma or cardiovascular event was similar between groups. Conclusions: Intervention based on education of health care professionals on the use of hospitalized diabetic patient management protocol can modify their conduct without, however, altering patients' mean glycemia, time of stay in hospital and number of hypoglycemia and hyperglycemia episodes.
Nothing to Disclose: BS, MAM, JR, MC

sort_order 2531
Pub # P3-462
Session Information POSTER SESSION: CLINICAL - Inpatient Diabetes Management Issues (1:30 PM-3:30 PM)
Title Comparison of Outcomes of Different Insulin Regimens in Type 2 Diabetics during the Perioperative Period: A Single-Blind Multi-Center Study
Author String M Ahemad, SK Mathur, S Lodha, ZY Khan, DP Bansal, S Lalwani, ZA Wafai
MG Medical College & Hospital, Jaipur, India; SMS Medical College, Jaipur, India; Sher- I- Kashmir Institute of Medical Sciences, Srinagar, India; MG Medical College & Hospital, Jaipur, India; Fortis Escort Hospital, Jaipur, India; Birla Institute of Scientific Research, Jaipur, India
Body
Aims & Objectives: To compare the outcomes of different subcutaneous insulin regimens in type 2 diabetics during peri-operative period.
Subjects & Methods: 289 type 2 diabetes mellitus patients admitted for major elective surgery were enrolled and randomly allocated to four treatment groups of different insulin regimens viz. regime A (regular:NPH 30/70) premixed, regime B (regular+NPH) split-mixed, regime C (glargine+lispro) split-mixed and regime D (detemir+aspart) split-mixed respectively. The incidence of complications attributable to postoperative outcome of specific treatment was recorded.
Results: The patients who received treatment regime A, C and D have shown significant difference ($p<0.01$, $p<0.05$, $p<0.001$) in incidence of complications of hypoglycaemic episodes ($BG<60\text{mg/dl}$), infection rate and mortality scores recorded during peri-operative period. However, the least number of complications at low dose were recorded in patients who received treatment regime D (detemir+aspart).
Conclusion: Treatment with basal/bolus regime with detemir once daily and aspart before meals resulted in minimum number of complications at comparatively low dose with less mean hospital length stay during peri-operative period in type 2 diabetics.

Disclosures: SL: Speaker, Novo Nordisk; Sanofi-Aventis. Nothing to Disclose: MA, SKM, ZYK, DPB, SL, ZAW

sort_order 2532
Pub # P3-463
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title Transcriptome Metanalysis of Peripheral Blood Mononuclear Cells of Type 1, Type 2 and Gestational Diabetes Mellitus Patients Features Modulated Immune System and Metabolism Genes
Author String CVA Collares, AF Evangelista, DJ Xavier, FN Navarro, C Macedo, F Manoel-Caetano, DM Rassi, MC Foss-Freitas, MC Foss, ET Sakamoto-Hojo, GA Passos, EA Donadi
Faculty of Medicine of Ribeirao Preto, Ribeirao Preto, Brazil; Faculty of Medicine of Ribeirao Preto, Ribeirao Preto, Brazil
Body **Background:** Type 1 diabetes (T1D) is an autoimmune disease caused by the selective destruction of the pancreatic beta cells, which are responsible for insulin-producing. Type 2 diabetes (T2D) is a phenotypic and genetically heterogeneous chronic disease characterized by insulin resistance and deficient beta-cell function, being the most prevalent type of diabetes, accounts for 90% of all cases of diabetes. The standard definition of gestational diabetes mellitus (GDM) is the abnormal glucose metabolism diagnosed during pregnancy. Although these three types of diabetes are clinically well defined and T1D is the type more associated to the genetic background, little is known on the genetic contribution to T2D or GDM. **Objectives:** To compare/contrast the transcriptome profiling of peripheral blood mononuclear cells (PBMC) from patients presenting T1D, T2D or GDM by using the microarray technology allowing identifying the common or the exclusive differentially expressed genes, which characterize the three types of DM. **Methods:** One-color Agilent 4x44K whole functional genome microarray hybridizations of samples from T1D (n=19), T2D (n=20) or GDM (n=17) patients were quantified and data analyzed using bioinformatics pipeline included in the GeneSpring GX1.1 pack (Agilent). Cluster-TreeView algorithm was used to average hierarchical clustering of genes using Pearson uncentered metrics. Finally, DAVID functional analysis tool was used to analyze the functional clusters of interest. **Results:** Differentially expressed genes between patients of three types of diabetes were identified and classified according to: (i) association with biological regulation, immune response and insulin gene cluster (Venn diagram); (ii) DAVID functional clusters categories: T1D (INS, IGF2, HLA-G, HLA-E and GAD1), T2D (SOCS1, SOCS2, SOCS3, SOCS4, IGF2 and INS) and a third cluster identified by GOTERM_BP_FATIGO: response to corticosteroid stimulus and GO:0051384-response to glucocorticoid stimulus (GHR, TRH, FOS, CCND1 and HSD11B2). **Conclusion:** i) PBMC were adequate for the use as reporter cells to analyze the transcriptome profiling in DM, ii) although the three types of DM may present distinct etiopathogenic mechanisms, they exhibit shared modulated immune response and metabolism response genes, suggesting common pathways in the pathophysiology.

Sources of Research Support: FAPESP; CNPq; CAPES.

Nothing to Disclose: CVAC, AFE, DJX, FNN, CM, FM-C, DMR, MCF-F, MCF, ETS-H, GAP, EAD

sort_order

2533

Pub #

P3-464

Session Information

POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)

Title

Carbohydrate-Modified Diet and Insulin-Sensitizing Medications Reduce Body Weight and Fasting Insulin in the Empowir (Enhance the Metabolic Profile of Women with Insulin Resistance) Trial

Author String

HR Mogul, R Freeman, M Frey, R Greenbaum, S Jozak, L Klein, K Tanenbaum
New York Medical College, Valhalla, NY; Einstein, Bronx, NY; Westchester Medical Center, Valhalla, NY

Body

BACKGROUND Despite an explosion in diabetes prevention research, new cases of diabetes continue to rise at alarming rates. Safe, effective, preventive interventions for high risk populations are critically needed. EMPOWIR (NCT00618071) is a double blind, placebo controlled, randomized clinical trial to evaluate a unique carbohydrate diet, alone and in combination with metformin (MF) 2000mg & MF plus rosiglitazone (RSG) 4mg in Syndrome W - normoglycemic, hyperinsulinemic Women with Weight gain (>20 lbs after the 20's), Waist gain, and White Coat hypertension.¹ The **primary study hypothesis** is that insulin sensitizing medications, in combination with alterations in carbohydrate intake will reduce insulin levels and improve established Metabolic Syndrome risk factors, as previously reported.²⁻³ The primary outcome variable is change in FIn at 6 months. Inclusion criteria: age 35-55; 20 lb weight gain; normal GTT and increased insulin response curves. **METHODS** We compared fasting insulin (FIn), BW, and relevant covariates at screening and 6-months post randomization using paired t-tests and multivariate models (SPSS 13.0). Participants attended 4 weekly nutrition workshops (lead-in phase) at 2 study sites to introduce the EMPOWIR dietary intervention: a food exchange program (40% carbohydrates-40% protein-20% fat) promoting increased intake of vegetables, low-glycemic index fruits, low-fat protein and dairy products, elimination of free sugars, and notable restriction of 3 allowable additional carbohydrates (starches) to after 4PM. Anthropometric measures and adverse events (AE's) were monitored at 1, 2, 3, and 6 months. **RESULTS** 46 subjects (mean age 46.6±1.0, BMI 30.5±.04kg/m²; 54.3% white), enrolled from Feb, 2008-Dec, 2009 were randomized; 37 completed >6 months. Significant BW reductions were observed at 6 months in placebo, MF, and MF-RSG arms, respectively 4.7, 4.7, and 6.0% (P=.049, .005, .0170); significant FIn reductions were noted in the placebo and MF-RSG arm (P's=.043, .011); % change in BW correlated with % change in FIn (r_{xy}=.550, P=.007); but not with age, race, baseline BW, insulin, or menopausal status. MF was well tolerated in a gradually escalating dose and no AE's were reported. **CONCLUSIONS** The EMPOWIR study diet independently, and in combination with insulin sensitizing medications, reduced BW in a diverse sample of normoglycemic, hyperinsulinemic midlife women. These findings are consistent with other research⁴⁻⁶ and merit additional study.

1. Mogul HR, Weinstein BI, Mogul DB et al. Syndrome W: a new model of hyperinsulinemia, hypertension and midlife weight gain in healthy women with normal glucose tolerance. *Heart Dis* 2002; 4(2):78-85.

2. Mogul HR, Peterson SJ, Weinstein BI, Zhang S, Southren AL. Metformin and carbohydrate-modified diet: a novel obesity treatment protocol: preliminary findings from a case series of nondiabetic women with midlife weight gain and hyperinsulinemia. *Heart Dis* 2001; 3(5):285-292.

3. Mogul HR, Peterson SJ, Weinstein BI, Li J, Southren AL. Long-term (2-4 year) weight reduction with metformin plus carbohydrate-modified diet in euglycemic, hyperinsulinemic, midlife women (Syndrome W). *Heart Dis* 2003; 5(6):384-392.

4. Ludwig DS, Majzoub JA, Al-Zahrani A, Dallal GE, Blanco I, Roberts SB. High glycemic index foods, overeating, and obesity. *Pediatrics* 1999; 103(3):E26.

5. Foster-Schubert KE, Overduin J, Prudom CE et al. Acyl and total ghrelin are suppressed strongly by ingested proteins, weakly by lipids, and biphasically by carbohydrates. *J Clin Endocrinol Metab* 2008; 93(5):1971-1979.

6. Salas-Salvado J, Bullo M, Babio N et al. Reduction in the incidence of type 2 diabetes with the Mediterranean diet: results of the PREDIMED-Reus nutrition intervention randomized trial. *Diabetes Care* 2011; 34(1):14-19.

Sources of Research Support: EMPOWIR (ClinicalTrials.gov:NCT00618071) is an unsolicited, investigator-initiated study supported by Glaxo Smith Kline with additional support from a Clinical and Translational Science Award (CTSA) from the National Institutes of Health (UL11RR025740) awarded to the GCRC at Einstein of Yeshiva University.

Disclosures: HRM: Principal Investigator, GlaxoSmithKline; Study Investigator, Lilly USA, LLC; Consultant, Pfizer, Inc. Nothing to Disclose: RF, MF, RG, SJ, LK, KT

sort_order

2534

Pub #

P3-465

Session Information

POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)

Title

Effects of Four-Day Fast on Gut-Derived Hormones and Inflammatory Markers in Healthy, Normal-Weight Women

Author String

MV Zanni, B Canavan, J Wei, SK Grinspoon
Massachusetts General Hospital, Boston, MA; Children's Hospital, Boston, MA

Body

Background: Gut-derived hormones GLP-1, oxyntomodulin, PYY, and ghrelin participate in energy metabolism and glucose homeostasis. The way in which these hormones and related inflammatory markers change in response to prolonged fasting remains unclear.

Methods: 20 female subjects had participated in a prior randomized study examining effects of leptin vs. placebo over a four-day fast (1). Using data from the placebo group alone, we assessed fasting effects on gut-hormone and cytokine secretion. Subjects were healthy, normal-weight (BMI 20-26 kg/m²), eumenorrheic women ages 18-35. Gut-hormones and cytokines measured at baseline and end-of-fast were quantified using commercial assays.

Results: With extended fasting, GLP-1 significantly increased (2.82 ± 0.11 to 3.58 ± 0.39 pmol/liter, mean \pm SEM, baseline vs. end of fast, p for change from baseline = 0.043) and ghrelin significantly decreased (646.4 ± 60.0 to 366.3 ± 29.9 pg/ml, $p = 0.0001$). No significant changes in oxyntomodulin or PYY were seen. TNF- α significantly decreased (0.9 ± 0.1 to 0.7 ± 0.1 ng/liter, $p = 0.012$), while IL-6 and CRP significantly increased (1.1 ± 0.1 to 4.5 ± 0.9 ng/liter, $p = 0.006$; and 0.5 ± 0.1 to 1.2 ± 0.3 mg/liter, $p = 0.049$, respectively). Inverse relationships between changes GLP-1 and TNF- α ($r = -0.79$, $p = 0.003$) and between changes in ghrelin and IL-6 ($r = -0.69$, $p = 0.011$) were seen.

Discussion: While states of chronic energy deprivation are associated with lower levels of inflammatory cytokines, our data demonstrate that prolonged fasting lowered TNF- α , while raising IL-6 and CRP. Strong, inverse correlations were noted between the fasting-induced changes in GLP-1 and TNF- α and between those in ghrelin and IL-6. *In vitro*, GLP-1 can suppress TNF- α and ghrelin can suppress IL-6 (2,3). Thus, a fasting-induced rise in GLP-1 and fall in ghrelin could theoretically influence levels of inflammatory markers in the pattern seen here. Alternately, fasting-induced changes in inflammatory or other markers could be driving discordant changes in GLP-1 and ghrelin.

Conclusions: In healthy, normal-weight women, a four-day fast paradoxically alters the gut-hormone profile by increasing anorexigenic GLP-1 and decreasing orexigenic ghrelin. Fasting also decreases TNF- α , while increasing IL-6 and CRP. These data are the first to our knowledge to show strong inverse correlations between the observed changes in gut-hormones and in inflammatory markers during prolonged fasting.

1. Schurgin S et al. J Clin Endocrinol Metab 2004; 89:5402-5409
2. Dixit VD et al., J Clin Invest 2004; 114:57-66
3. Hahm E et al. J Endocrinol Invest 2008; 31:334-340.

Sources of Research Support: NIH K24 DK064545 to S.G; NIH F32 DK 085969-01 to M.Z.

Disclosures: SKG: Investigator, Theratechnologies; Consultant, Sero, Theratechnologies. Nothing to Disclose: MVZ, BC, JW

sort_order 2535
Pub # P3-466
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title Efficacy of Basal-Bolus Insulin vs. Sliding Scale Insulin for Inpatient Glycemic Management of Type 2 Diabetes -- A Clinical Practice-Based Audit
Author String GW Roberts, NR Aguilar-Loza, A Esterman, SN Stranks, MG Burt
Repatriation General Hospital, Adelaide, Australia; Flinders University, Adelaide, Australia; Repatriation General Hospital, Adelaide, Australia; University of South Australia, Adelaide, Australia
Body
Randomized-controlled trials have reported that basal-bolus insulin (BBI) produces better inpatient glycemic control than sliding scale insulin (SSI) in subjects with type 2 diabetes¹. However, it is not known if these findings can be replicated in routine clinical practice by junior medical staff. In November 2008 Repatriation General Hospital introduced a new protocol for management of inpatient hyperglycemia using BBI. We have compared glycemic control using this protocol to patients previously treated with SSI to assess the efficacy of BBI and SSI in the hospital setting under non-study conditions.
Finger prick capillary blood glucose levels (BGL) were prospectively collected 4 times daily for up to 8 days in 124 patients with type 2 diabetes admitted to hospital and treated with BBI (age = 74±11 years, BMI = 30±8 kg/m², HbA1c = 8.0±1.9%) and compared to retrospective data from 96 inpatients with type 2 diabetes treated with SSI alone or in combination with their usual hypoglycemic therapy (age = 76±10 years, BMI = 28±6 kg/m², HbA1c = 7.9±1.8%). The primary endpoint was the independent effect of insulin regimen on mean daily BGL, which was assessed using a cross-sectional random effects regression model after adjustment for admission BGL.
Mean ± SD admission BGL was not significantly different in subjects on BBI and SSI (204±74 vs 191±77 mg/dL, p=0.23). Mean daily BGL in subjects on BBI was 29±7 mg/dL lower than at admission by the second day in hospital (p<0.001) and remained 44±11 mg/dL lower than admission by day 7 (p<0.001). In contrast, there was no statistically significant change in mean BGL in patients administered SSI. In the random effects regression analysis, BBI resulted in a significantly lower mean daily BGL than SSI (p[le]0.001). A lower admission BGL (p<0.001), surgical rather than medical management (p=0.016) and a longer duration of hospital admission (p<0.001) were the other variables independently associated with a lower mean daily BGL. The prevalence of a BGL<72 mg/dL was significantly greater in patients receiving BBI than those administered SSI (3.3 vs 1.4%, p<0.001), while the prevalence of a BGL <50 mg/dL in the two groups was not significantly different (0.3 vs 0.5%, p=0.30).
In conclusion, BBI is effective, safe, and sustainable outside of the formal study setting across a wide range of patients and is superior to SSI. We recommend that protocols for inpatient glycemic control based around BBI be widely implemented.

1. Umpierrez GE et al 2007. Diabetes Care 30:2181-2186

Sources of Research Support: Grant from Sanofi-Aventis to GWR and SNS.

Nothing to Disclose: GWR, NRA-L, AE, SNS, MGB

sort_order 2536
Pub # P3-467
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title Efficacy and Safety of the Partial PPAR γ Agonist Balaglitazone Compared with Pioglitazone and Placebo: A Phase III, Randomized, Parallel-Group Study in Patients with Type 2 Diabetes on Stable Insulin Therapy
Author String K Henriksen, I Byrjalsen, P Qvist, H Beck-Nielsen, G Hansen, BJ Riis, H Perrild, OL Svendsen, J Gram, MA Karsdal, C Christiansen
Nordic Bioscience A/S, Herlev, Denmark; Center for Clinical and Basic Research (CCBR), Ballerup, Denmark; University Hospital of Southern Denmark, Odense, Denmark; Bispebjerg University Hospital, Copenhagen, Denmark; Hospital of Southwest Denmark, Esbjerg, Denmark
Body Treatment of patients with full PPAR γ agonists is associated with weight gain, heart failure, peripheral oedema and bone loss. However, the safety of partial PPAR γ agonists has not been established in a clinical trial.
The BALLET trial aimed to establish the glucose-lowering effects and safety parameters of the partial PPAR γ agonist balaglitazone in diabetic patients on stable insulin therapy. 409 subjects from 3 countries with type 2 diabetes on stable insulin therapy were randomised to 26 weeks of double-blind treatment with once daily doses of 10 or 20mg balaglitazone, 45 mg pioglitazone, or matching placebo (n=139 in each group). The primary endpoint was the efficacy of balaglitazone 10mg and 20mg versus placebo on the absolute change in HbA1c. Secondary endpoints included levels of fasting serum glucose (FSG), and changes in body composition and bone mineral density as measured by DXA, with comparison to pioglitazone 45mg. Clinicaltrials.gov identifier: NCT00515632.
In the 10 and 20mg balaglitazone groups, and in the pioglitazone 45mg group, significant reductions in HbA1c levels were observed (-0.99%, -1.11% and -1.22% respectively (p<0.0001)) versus placebo. FSG was similarly reduced in all treatment arms. DXA analyses showed balaglitazone 10mg led to less fat and fluid accumulation and no change in bone mineral density, when compared to pioglitazone.
In the balaglitazone 10mg treated group clinically relevant reductions in HbA1c and glucose levels were observed, although it appeared to be less potent than pioglitazone 45mg. On the other hand significantly less fluid and fat accumulation were observed, highlighting this drug candidate for further studies.

Sources of Research Support: The Danish Research Foundation.

Disclosures: KH: Employee, Nordic Bioscience A/S. IB: Employee, Nordic Bioscience A/S. PQ: Employee, Nordic Bioscience A/S; Employee, Nordic Bioscience A/S. GH: Employee, Nordic Bioscience A/S. BJR: Employee, Nordic Bioscience A/S; Employee, Nordic Bioscience A/S; Employee, Nordic Bioscience A/S. MAK: Employee, Nordic Bioscience A/S; Employee, Nordic Bioscience A/S. CC: Chairman, Nordic Bioscience A/S; Chairman, Nordic Bioscience A/S. Nothing to Disclose: HB-N, HP, OLS, JG

sort_order 2537
Pub # P3-468
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title The Association of Fasting Blood Glucose (FBG) with the Timing and Magnitude of Prior Nocturnal Hypoglycemic Episodes
Author String Z Parveen, P Zachariah, C Barsano, B Theckedath, S Singh
Captain James A Lovell Federal Health Care Center, North Chicago, IL; Chicago Medical School, North Chicago, IL
Body
Previous studies have shown that fasting blood glucoses (FBG's) following episodes of nocturnal hypoglycemia (post-hypoglycemia FBG's, PH-FBG) are not often elevated, in contrast to what would be expected if the nocturnal hypoglycemia had triggered counter-regulatory hormone (Somogyi) responses. We have examined the association of 7:00 a.m. PH-FBG's with their preceding hypoglycemic episodes using q5min continuous glucose monitoring over 3 days in patients with suspected nocturnal hypoglycemia. Patients who had nocturnal hypoglycemia on 1 or 2 of the 3 nights were selected for study since the other 1 or 2 nights would serve as individualized, control non-hypoglycemic nights associated with non-post-hypoglycemia FBG's, (nonPH-FBG). Thirty-four episodes of nocturnal (between midnight and 6:00 a.m.) hypoglycemia (glucose <70) collected from 28 patients were reviewed.
The timing and magnitude of a hypoglycemic episode was quantitated by measuring (a) the lowest glucose measured during the hypoglycemia (Nadir), (b) the duration of hypoglycemia (DH), (c) the sum of the products of the low (<70 mg/dl) glucose levels and their 5-min durations calculated by an area-under-the-curve (AUC) method, and (d) the interval from the end of the hypoglycemic episode until the time of the subsequent PH-FBG (recovery time, RT).
For the 34 hypoglycemic episodes, the corresponding mornings' PH-FBG's were elevated (>110 mg/dl) in 17 cases and normal ([ge]70, [le]110 mg/dl) in the other 17 cases, however, most PH-FBG's (26/34, 76%) were actually lower than their paired nonPH-FBG. For only 5 of the 34 hypoglycemic episodes were the PH-FBG's both elevated above 150 mg/dl and more than minimally greater (>50 mg/dl) than their paired nonPH-FBG's, features suggestive of the Somogyi effect.
CONCLUSION: These PH-FBG's (presumptive Somogyi responses) exhibited a characteristic set of relationships with their associated hypoglycemic episodes: (a) the PH-FBG's were associated with hypoglycemic episodes with Nadirs of <45 mg/dl, (b) the duration of the preceding hypoglycemic episodes did not appear to be exacting, ranging from only 1.0 hr up to 5.3 hrs, (c) the product of the depth of hypoglycemia and its duration (AUC) did not seem critical, ranging from 1,015 to 4,725 min-mg/dl, and (d) the PH-FBG's appeared to require at least 3.5 hrs, but no more than 5.5 hrs, after the hypoglycemic episode to rise to >150 mg/dl (recovery time, RT).

Nothing to Disclose: ZP, PZ, CB, BT, SS

sort_order

2538

Pub #

P3-469

Session Information

POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)

Title

BMI Changes during the First Year of Type 1 Diabetes on Intensive Insulin Therapy

Author String

K Bethin, M Schroeder, C Ma, T Quattrin
University @ Buffalo School of Medicine & Biomedical Sciences, Buffalo, NY; University @ Buffalo School of Public Health & Health Professions, Buffalo, NY

Body

Background: The rising rate of obesity is a global health concern. NHANES 2007-2008 data shows that 31.7% of children are overweight (BMI $\geq 85^{\text{th}}$), which is associated with increased risk of comorbidities including hypertension, insulin resistance, and dyslipidemia. In managing individuals with type 1 diabetes, the diabetologist must balance the benefit of tight metabolic control with the risk of weight gain, which may increase cardiovascular risk. The **aim** of this retrospective study was to examine BMI change from diagnosis (Dx) of type 1 diabetes (T1DM) through the first year in patients started on intensive insulin therapy. **Methods:** After IRB approval, charts from all patients diagnosed at our tertiary facility with T1DM between January 1, 2008 and June 30, 2009 were reviewed (n=146). Antibody-positive patients older than >2 years at Dx and data available at Dx and 1 year later were included (n=74). BMI-SDU was calculated at Dx, 2 months after Dx, and every 3 months to 1 year and compared to NHANES 2007-2008 data. Data are expressed as mean \pm SD. Linear mixed model was used for statistical analysis with a Tukey-Kramer adjustment when appropriate. **Results:** At Dx 24.3% of children (10.6 \pm 3.6 yrs of age) had a BMI $\geq 85^{\text{th}}$ and BMI-SDU was 0.09 \pm 1.2, which increased to 0.72 \pm 0.9 at the 2-month visit (p<0.001). While the BMI-SDU did not change significantly at 1-year (0.62 \pm 0.8), the % of patients with BMI $\geq 85^{\text{th}}$ increased to 36.5%, which is similar to what is observed in the general population. At Dx, HbA1c was higher in patients with BMI $\geq 85^{\text{th}}$ compared to those with BMI <85% (12.3 \pm 2.8 vs. 10.5 \pm 2.3, p=0.002). Higher HbA1c values were associated with higher BMI-SDU values at 3-5 and 12 months (r=0.29, 0.25; p=.02, .03, respectively). Insulin dose was not associated with BMI SDU. **Discussion:** The prevalence of overweight in patients newly diagnosed with T1DM was lower than the general population. We speculate that this may be the result of weight loss prior to Dx. Weight gain was significant between Dx and 2 months after Dx, but was stable over the next 10 months while on intensive insulin therapy. There was no difference in BMI-SDU in T1DM compared to the general population 1 year after Dx. Efforts should be made to avoid weight regain in children whose BMI is within normal limits at Dx. Specific counseling on activity and diet should be provided to children who were overweight prior to Dx and are likely to return to being overweight after Dx.

Nothing to Disclose: KB, MS, CM, TQ

sort_order 2539
Pub # P3-470
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title Testosterone Therapy Decreased Adiponectin and Subcutaneous Fat in Aging Men
Author String L Frederiksen, K Hojlund, DM Hougaard, TH Mosbech, R Larsen, A Flyvbjerg, J Frystyk, K Brixen, M Andersen
Odense University Hospital, Odense, Denmark; Statens Serum Institut, Copenhagen, Denmark; Technical University of Denmark, Kgs Lyngby, Denmark; Aarhus University Hospital, Aarhus, Denmark
Body **Background:** Testosterone therapy has a well-known positive effect on lean body mass in hypogonadal men (Isidori *et al*, JCEM 2005). We found a corresponding effect on lean body mass in ageing men with low normal bioavailable testosterone. We found, however, no significant effect on insulin sensitivity using the euglycemic hyperinsulinemic clamp technique. Adiponectin is an insulin-sensitizing adipokine secreted by the adipose tissue and in young men adiponectin has been inversely associated with subcutaneous fat on the abdomen (SAT) (Frederiksen *et al*, JCEM 2008).
Aim: We wanted to investigate the effect of testosterone therapy on adiponectin, SAT, visceral adipose tissue (VAT) and thigh fat area (TFA) in ageing men with low normal bioavailable testosterone.
Methods: A randomized, double-blinded, placebo-controlled study of six months testosterone treatment (gel) in 38 men, aged 60-78 years, with bioavailable testosterone < 7.3 nmol/l (Nielsen *et al*, JCEM 2006) and a waist circumference > 94 cm. Serum total testosterone was measured by tandem mass spectrometry. Adiponectin was determined by an in-house time resolved immunofluorometric assay. SAT, VAT and TFA were measured by magnetic resonance imaging (MRI). Coefficients (b) represent the placebo-controlled mean effect of intervention.
Results: Testosterone treatment decreased adiponectin (b=-1.308 mg/l, p=0.001), SAT (b=-0.03 fat area/total area, p= 0.018) and TFA (b=-0.03 area/total area, p<0.001) while VAT (b= 0.01 area/total area; p=0.54) remained unchanged.
Conclusion: In ageing men with low normal bioavailable testosterone levels, six months of testosterone treatment reduced serum adiponectin and subcutaneous adipose tissues on abdomen and thigh, whereas no significant changes in visceral adipose tissue were observed.
Nothing to Disclose: LF, KH, DMH, THM, RL, AF, JF, KB, MA

sort_order 2540
Pub # P3-471
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title Hydroxychloroquine-Associated Hyperinsulinemic Hypoglycemia
Author String A Johnson, LM Eck
Univesity of Kansas, Kansas City, KS
Body
Introduction:
Hypoglycemia secondary to hydroxychloroquine has been previously documented in humans. We describe a case of severe hyperinsulinemic hypoglycemia in a patient initiated on hydroxychloroquine.
Clinical Case:
A 66 year old female with a complex medical history including rheumatoid arthritis (RA) and pyoderma gangrenosum was initiated on hydroxychloroquine for management of her rheumatologic disorders. Soon after her first dose of hydroxychloroquine, the patient developed hypoglycemia with a glucose value of 28mg/dL on serum measurement. She was symptomatic with diaphoresis, tremors and confusion. Following obtainment of standard hypoglycemia laboratory, D50 was administered with initial improvement. However, hypoglycemia recurred throughout the day despite treatment. An immunoreactive insulin level at the time of hypoglycemia was found to be elevated at 146.7mIU/mL (2-23) as was a C-peptide level at 7667 pmol/L (297-1419). A sulfonylurea screen was negative. In light of hyperinsulinemic hypoglycemia, a CT of the abdomen was obtained and negative for any pancreatic mass. Due to prior case reports associating hydroxychloroquine with hypoglycemia, this medication was discontinued. Hypoglycemia persistently recurred over an approximately ten-hour period, and then resolved without recurrence.
Conclusion:
Hypoglycemia secondary to hydroxychloroquine has been previously documented in two separate case reports. The glycemic effects of hydroxychloroquine have been well-described in several studies evaluating its use in the treatment of DM; it has been found to improve glycemic control in patients with DM with and without autoimmune diseases. It has been associated with a decreased risk of development of DM in patients with rheumatoid arthritis. The mechanism of hydroxychloroquine induced hyperinsulinemic hypoglycemia has been inferred from studies on chloroquine, which is structurally similar. Studies have shown an increase in the level of plasma insulin in rats treated with chloroquine. This is thought to be due to enhanced insulin secretion from beta cells, as well as inhibition of insulin degradation by chloroquine. The proposed mechanisms behind chloroquine/hydroxychloroquine-induced hypoglycemia are consistent with the laboratory results of our patient.

Nothing to Disclose: AJ, LME

sort_order 2541
Pub # P3-472
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title Chromium Infusion in Hospitalized Patients with Uncontrolled Hyperglycemia
Author String T Drake, K Rudser, E Seaquist, A Saeed
University of Minnesota Medical School, Minneapolis, MN; University of Minnesota, Minneapolis, MN; University of Minnesota, Minneapolis, MN
Body Anecdotal reports suggest that intravenous (IV) infusions of chromium (Cr) may be of benefit to acutely ill patients with uncontrolled hyperglycemia and severe insulin resistance, but the impact of this therapy has not been systematically evaluated. Therefore, we reviewed the hospital course of all patients at our institution over the past 3 years who received IV Cr per a standard protocol for this indication, with the aim of testing the hypothesis that Cr will decrease the insulin needs and improve glucose control at 12 and 24 hours (hrs) following the initiation of Cr. Hospital pharmacy records from 01/01/08 - 12/01/10 were reviewed to identify patients for whom IV Cr was ordered at our academic medical center. To be included, patients were required to demonstrate profound insulin resistance and uncontrolled hyperglycemia (defined as the inability to achieve a blood glucose value <200 mg/dl at any point during the 12 hrs before chromium was given despite administration of a continuous IV insulin infusion at a rate >20 units/hr) and to have received a continuous infusion of Cr chloride at 20 mcg/hr for 10-15 hrs for a total dose of 200-240 mcg, the dose recommended by our pharmacy protocol for this indication. 14 patients met our criteria. Over the hour preceding IV Cr, the mean \pm SD rate of insulin infusion was 31 ± 15 u/hr and blood glucose was 326 ± 86 mg/dl. 12 hrs after the initiation of Cr, these values were 16 ± 16 u/hr and 162 ± 76 mg/dl, respectively ($p=0.011$ for differences between insulin rates, $p<0.001$ for differences between blood glucose) and 24 hrs after these values were 12 ± 12 u/hr and 144 ± 48 mg/dl, respectively ($p<0.001$ for both). All patients were in the ICU: 8 following solid organ transplants, 1 following bone marrow transplant, 3 post cardiac procedures, 1 for esophageal perforation, and 1 following thymectomy. 4 of the patients had a known history of type 2 diabetes (2 of whom were on insulin prior to admission) and 1 with type 1 diabetes. IV Cr decreased insulin needs and improved glucose control at 12 and 24 hrs compared to baseline values. Cr appears to improve hyperglycemia and insulin resistance in acutely ill patients and represents a potential new therapy, with future prospective randomized controlled studies needed to confirm these results.
Nothing to Disclose: TD, KR, ES, AS

sort_order 2542
Pub # P3-473
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title Efficacy of Physical Activity Advice Only or Structured Exercise Training to Reduce HbA1c in Patients with Type 2 Diabetes. A Systematic Review and Meta-Analysis of Randomized Clinical Trials
Author String BD Schaan, D Umpierre, PAB Ribeiro, CK Kramer, CB Leitao, ATN Zucatti, MJd Azevedo, JL Gross, JP Ribeiro
Hospital de Clinicas de Porto Alegre/UFRGS, Porto Alegre, Brazil; Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil; Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil
Body **Background:** Structured aerobic and resistance training alone or in combination improve glucose control in type 2 diabetic patients, but the magnitude of effects of each type of exercise on HbA1c is controversial. Moreover, no systematic review evaluated the effect of physical activity advice only, which is largely used in daily clinical practice.
Objectives: To assess the effect of structured exercise training (aerobic, resistance or combined) and physical activity advice with or without dietary co-intervention on HbA1c in type 2 diabetes by a systematic review and meta-analysis of RCTs.
Methods: MEDLINE, Cochrane CENTRAL, EMBASE, LILACS, and SPORTDiscus without language restriction (1980-2010). RCTs of [sup3]12 weeks duration of structured exercise training or physical activity advice vs. no intervention that reported HbA1c changes in type 2 diabetic patients were selected. Two independent reviewers carried out data extraction and quality scoring. Sources of heterogeneity were searched for with meta-regression analyses considering baseline HbA1c, exercise intensity, frequency, session duration and program duration (structured exercise) and baseline HbA1c and dietary co-intervention (physical activity advice) as covariates.
Results: Of 4,191 articles retrieved, 47 RCTs (8,538 patients) were included. Structured exercise training (23 studies, 1533 patients) reduced HbA1c by 0.67% (95% CI: -0.84 to -0.49; I²: 91.3%). This effect was observed with aerobic (-0.73%; 95% CI: -1.06 to -0.40; I²: 92.8%), resistance (-0.57%; 95% CI: -1.14 to -0.01; I²: 92.5%), or combined exercise (-0.51%; 95% CI: -0.79 to -0.23; I²: 67.5%). In a sensitivity analysis, >150 min of exercise weekly was associated with a 0.89% HbA1c reduction (95% CI: -1.26 to -0.51; I²: 91.4%) and [le]150 min with a reduction of 0.36% (95% CI: -0.50 to -0.23; I²: 78.6%). Physical activity advice (24 studies, 7025 patients) reduced 0.43% in HbA1c (95% CI: -0.59 to -0.28; I²: 62.9%). When dietary advice was added to physical activity advice, the reduction of HbA1c was 0.58% (95% CI: -0.74 to 0.43; I²: 57.5%). No HbA1c changes occurred with physical activity not accompanied by dietary advice (-0.16%; 95% CI: -0.50 to +0.18; I²: 61.2%).
Conclusion: Structured exercise training (aerobic, resistance or combined) reduces HbA1c in type 2 diabetes, especially when performed for more than 150 min/wk. Physical activity advice reduces HbA1c less than structured exercise training and only if associated with dietary advice.

(1) Boule NG et al. *Jama*. Sep 12 2001;286(10):1218-1227.
(2) Boule NG, et al. *Diabetologia*. Aug 2003;46(8):1071-1081.
(3) Snowling NJ et al. *Diabetes Care*. Nov 2006;29(11):2518-2527.
(4) Thomas DE et al. *Cochrane Database Syst Rev*. 2006;3:CD002968.
(5) Sigal RJ et al. *Ann Intern Med*. Sep 18 2007;147(6):357-369.
(6) Church TS et al. *Jama*. Nov 24;304(20):2253-2262.

Sources of Research Support: Hospital de Clinicas de Porto Alegre; Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq); Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

Nothing to Disclose: BDS, DU, PABR, CKK, CBL, ATNZ, MJdA, JLG, JPR

sort_order

2543

Pub #

P3-474

Session Information

POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)

Title

Otelixizumab Anti-CD3 Monoclonal Antibody DEFEND-1 Study: Characterization of C-Peptide Levels in New-Onset Type 1a Diabetes Mellitus

Author String

T Donner, J Sandahl Christiansen, P Miller, W Liu, AM Brennan
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Body

Type 1a diabetes mellitus (T1DM) is characterized by autoimmune destruction of beta cells, which results in decreased endogenous insulin and C-peptide secretion. An earlier investigator led Phase 2 study showed that otelixizumab, an anti-CD3 targeted T cell immunomodulator, preserved beta cell function for at least 4 years after a short course of treatment (1, 2). DEFEND-1 is the first of 2 randomized, placebo-controlled, Phase 3 studies in adult and adolescent subjects with new-onset T1DM (NOT1DM) evaluating the safety and efficacy of otelixizumab. Key inclusion criteria: 12-45 years of age, diagnosis of T1DM within 90 days, screening stimulated C-peptide > 0.20 and [Ile] 3.50 nmol/L following a mixed meal tolerance test (MMTT; Boost[reg]), and positivity for at least 1 diabetes-associated autoantibody. In addition to baseline characteristics, C-peptide change in response to an MMTT is described. There were few subjects (N=11) who screen failed due to a poor C-peptide response. Of the 272 enrolled subjects, data were based on 269 who had a baseline C-peptide area under the curve (AUC) that could be calculated. Mean age was 25.0 years, 65.1% were male, 93.3% were Caucasian, mean BMI was 23.4 kg/m², mean time from diagnosis was 68.0 days, and 91.4% were positive for glutamate decarboxylase (GAD) and 69.3% for islet antigen-2 (IA2). At the baseline MMTT, mean C-peptide consistently increased during the 2-hour test period, from 0.31 nmol/L pre-test to 1.14 nmol/L at 120 minutes. Mean C-peptide AUC was 0.89 (nmol/L x min)/min. Mean maximum stimulated C-peptide was 1.25 nmol/L. Maximum stimulated C-peptide was observed in 43.1% of subjects at 120 minutes, 36.4% at 90 minutes, 16.4% at 60 minutes, 3.7% at 30 minutes, and 0.4% at 15 minutes. These results suggest that the majority of patients with NOT1DM have a meaningful C-peptide response within 90 days of diagnosis, and may therefore be candidates for interventions which preserve beta cell function.

(1) Keymeulen et al., Diabetologia 2010;53:614-623

(2) Keymeulen et al., N Engl J Med 2005;352:2598-2608

Disclosures: JSC: Speaker Bureau Member, Novo Nordisk; Consultant, Roche Pharmaceuticals. PM: Employee, Tolerx, Inc. WL: Employee, Tolerx, Inc. AMB: Employee, Tolerx, Inc. Nothing to Disclose: TD

sort_order

2544

Pub #

P3-475

Session Information

POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)

Title

Change of Management Status in Korean Type 2 Diabetic Patients: 3-Year Follow-Up of Korean Type 2 Diabetes Prospective Cohort Study

Author String

MC Choi, YJ Lee, SO Chin, SY Rhee, S Chon, YC Hwang, IK Jeong, S Oh, KJ Ahn, HY Chung, JT Woo, SW Kim, JW Kim, YSS Kim
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Body

There has been no representative national data for type 2 diabetes mellitus in Korea. Korea national diabetes program (KNDP) been launched at 2005, which construct the type 2 diabetes cohort consisting of 12 university hospitals. KNDP cohort was prospective observational study to establish efficient preventive, diagnostic, and therapeutic measures based on the characteristics of Korean diabetics. In cohort study, patients were performed regular metabolic check up and questionnaire without any intervention. This study is to investigate 3-year metabolic status of cohort patients. Of 4,256 patients enrolled to the cohort, all 1,187 type 2 diabetics who reached 3-year follow-up period were participated in this study. 3-year follow-up data including metabolic profiles and complication status were compared with baseline data.

Mean diabetes duration of patients at baseline was 6.7 ± 6.5 years. Mean age at baseline was 54.5 ± 10.0 years. During 3-year follow-up, blood pressure and lipid profile improved significantly compared with the baseline ($P < 0.001$). The glycemic control was improved in all glycemic parameter; fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and HbA1c (FPG; 142.9 ± 51.2 vs. 135.5 ± 38.4 mg/dL, $P < 0.001$, PPG; 231.6 ± 88.8 vs. 185.2 ± 68.7 mg/dL, $P < 0.001$, and HbA1c; 7.5 ± 1.7 vs. 7.3 ± 1.1 , $P < 0.001$). Insulin secretory function measured by insulinogenic index was improved from 0.16 ± 0.22 to 0.25 ± 0.38 ($P = 0.002$). At 3-year follow-up period, diabetic nephropathy assessed by urine albumin excretion was 24.6% of the patients, as compared with 23.9% at the baseline ($P < 0.001$). Prevalence of diabetic retinopathy assessed by funduscopy was 19.3%, as compared with 20.5% at the baseline ($P < 0.001$). There was significant improved carotid intima media thickness after 3-year follow-up ($P < 0.001$). In conclusion, there had been an improvement in the management of glycemic control and cardiovascular risk factors while management status to prevent chronic complication was not enough. The introduction of intensive and systematic care into clinical practice should be necessary to prevent diabetes related chronic complication.

Nothing to Disclose: MCC, YJL, SOC, SYR, SC, YCH, IKJ, SO, KJA, HYC, JTW, SWK, JWK, YSK

sort_order 2545
Pub # P3-476
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title Mildly High Aldosterone-Renin Ratio May Also Progress Diabetic Nephropathy
Author String A Yoshifuji, T Ichijo, E Yoshida, K Yamashita, R Iga, H Ouchi, M Higa
Saiseikai Yokohamashi Tobu Hospital, Yokohama, Japan; Toho University School of Medicine, Ota-ku, Japan
Body It has been revealed that diabetes mellitus (DM) changes renin-angiotensin-aldosterone system (RAAS) and then provokes various complications. Therefore, we studied the relationship between the aldosterone-renin ratio (ARR), which is often calculated to screen primary aldosteronism, and uric albumin excretion (UAE) as a useful indicator of diabetic nephropathy, and other various parameters of arteriosclerosis, hyperlipidemia or insulin resistance.
We examined 60 patients with type 2 diabetes in this study, who had been admitted to our hospital during 2010, age from 30 to 65 years old, excluding following criteria; taking angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs), ARR >20 (PAC in ng/dl), UAE <5 or >300mg/day, fasting plasma glucose (FPG) >400 mg/dl, the plasma rennin activity (PRA) >10 ng/ml/h, and the aldosterone concentration (PAC) >20 ng/dl. We measured FPG, PAC and PRA to calculate ARR and UAE for diabetic nephropathy classification, and also the following parameters to examine the relationship between ARR and arteriosclerosis; systolic and diastolic blood pressure, the average of intima media thickness (IMT), ankle-brachial indexes (ABI) and brachial ankle Pulse Wave Velocity (baPWV) in both carotid arteries, and LDL-cholesterol, HDL-cholesterol, triglyceride (TG), and the TyG index as a parameter of insulin resistance.
The mean age was 50.4 ± 9.5 years old including 42 males and 18 females. The mean BMI, SBP, DBP, FPG, IMT, ABI, baPWV, LDL-C, HDL-C, TG, or TyG index were 26.4±4.8 kg/m², 126.7±16.6 mmHg, 77.2±11.9 mmHg, 185±63.2 mg/dl, 0.71±0.19 mm, 1.12±0.08, 1614.0±312.6 cm/sec, 121.8±38.5 mg/dl, 50.0±19.1 mg/dl, 135.3±56.9 mg/dl, and 459.7±176.0, respectively. The correlation between ARR and BMI, SBP, DBP, FPG, PAC, PRA, IMT, ABI, baPWV, LDL-C, HDL-C, TG, or the TyG index were not statistically significant. However, the ARR was significantly correlated with UAE (r=0.38, p<0.05). In conclusion, our study revealed even mild increase of aldosterone, below the aldosteronism screening criteria of ARR, may cause increase of the UAE in mild diabetic nephropathy categorized up to the second stage. This means the patients with mildly high ARR, even less than 20, may more often progress the diabetic nephropathy than those with low ARR. Therefore not only the glycemic control but also the control of RAAS activity is very important to prevent the progression of diabetic nephropathy especially in the early stage.
Nothing to Disclose: AY, TI, EY, KY, RI, HO, MH

sort_order

2546

Pub #

P3-477

Session Information

POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)

Title

The Prevalence of Hypothyroidism and Celiac Disease in Patients with Type 1 Diabetes in the West of Ireland

Author String

R Casey, A Eddie, M Bell, B Dineen
University Hospital, Galway, Ireland; University of Aberdeen, Aberdeen, UK

Body

Autoimmune thyroid disorders (TD) are the most common immunological disorders seen in patients with type 1 diabetes (T1DM). Cross sectional studies have reported a two to three-fold increased risk of TD in patients with T1DM. The incidence of Coeliac disease (CD) is also higher in patients with T1DM compared to the general population. Studies in both children and adults have shown that CD occurs in 1.5-10% of patients with T1DM compared with 0.5% in the general population. Current guidelines from the American Diabetes Association recommend screening all patients with newly diagnosed T1DM for TD and CD at the time of diagnosis.

Aims

1. To identify the prevalence of hypothyroidism and CD in patients with T1DM in the West of Ireland.
2. To assess the screening practices for these conditions, in patients with T1DM.

Methods

Patient data was obtained using a computer based laboratory system and a diabetes database.

Results

Data on 911 patients with T1DM was analysed (477 males, 434 females). Thyroid function tests (TFT) were available for all 911 patients. A sub-group of 201 patients underwent delayed thyroid testing or had TFT performed at least one year after their initial diagnosis. Proportionally more males (64.7%) than females (35.3%) had delayed thyroid testing, with the mean time in years to thyroid testing being greater in this sub-group for males (3.3 v 2.7; t-test p=0.01).

Thyroid peroxidase (TPO) antibody testing was performed on 208 patients; of these 50 were positive. No significant difference, by gender, existed for the presence of positive TPO antibodies ([chi]² p=0.23). Mean TPO titre was greater for females (173 v 103units/ml), however, this difference was not significant (t-test p=0.21).

Anti-transglutaminase antibody (anti-tTg) testing was performed on 276 subjects; 25 subjects were anti-tTg positive (12 males, 13 females).

16% of patients were hypothyroid, 1.4% were hyperthyroid and 82.6% euthyroid. 2.7% of patients had CD; of these 24% were hypothyroid and the remainder 76% euthyroid. CD prevalence, though higher in those with hypothyroidism (4.1%) rather than in euthyroid (2.5%) subjects, was not significantly different ([chi]² p=0.29).

Conclusion

1. The prevalence of hypothyroidism in patients with T1DM in the West of Ireland is 16%. TFT were carried out on all patients, but only 28% had TPO antibodies.
2. CD was diagnosed in 2.7% of patients with T1DM. CD screening was found to be suboptimal in this population with only 30% of patients screened.

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Nothing to Disclose: RC, AE, MB, BD

sort_order 2547
Pub # P3-478
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title Children Randomized to Long-Acting Insulin Glargine or Detemir from Diagnosis of Type 1 Diabetes Mellitus Have Lower HbA1c after One Year as Compared to Those Randomized to NPH Insulin
Author String P Bang, J Salemyr, K Ekstrom, A-L Brorsson, M-A Pulkkinen, C Carlsson-Skwirut, E Ortqvist
Karolinska Institutet, Stockholm, Sweden
Body
Long acting insulin analogs have been found to improve HbA1c in children with Type 1 Diabetes Mellitus in retrospective but so far not in prospective controlled studies.
In the present prospective controlled study, 120 patients (7 -17 years of age) were randomized at diagnosis of Type 1 Diabetes Mellitus (T1DM) to receive NPH, Glargine or Detemir (1:1:1) as basal insulin combined with insulin Aspart in a meal insulin therapy (MIT) regimen. Patient randomization was stratified for pubertal status resulting in a similar ($P = 0.368$) ratio of pre-pubertal to pubertal children in the treatment groups. At the time of this preliminary analysis, 26 patients had met exclusion criteria (incl. Celiac disease in 8 patients) or had requested to discontinue the study. One year data were still not obtained for 6 patients (1 on NPH, 2 on glargine and 3 on detemir) with study completion expected February 2011. After one year the mean (SD) HbA1C in patients with long acting insulin analogues Glargine or Detemir was 53 (9) mmol/mol, significantly lower than 58 (11) mmol/mol in the NPH group ($P = 0.046$). There was no difference in the median (range) age (10.7 (8.9 - 13.7) vs. 11.5 (9.6 - 13.8) years; $P = 0.576$) or the sex distribution (20 F / 40 M vs. 8 F/ 19 M; $P = 0.738$). Pre-pubertal children randomized to long acting or NPH insulin did not obtain different HbA1c after one year (54 (7) vs 55 (10) mmol/mol; $P = 0.749$) while children that have entered puberty at diagnosis demonstrated significantly better metabolic control when receiving long acting insulin analogues Glargine or Detemir (52 (11) vs. 60 (12) mmol/mol; $P = 0.035$).
Preliminary results from this randomized controlled study suggest that patients treated from T1DM diagnosis with long acting insulin Glargine or Detemir in a MIT regimen have better metabolic control after one year of treatment. This overall effect appears to be dependent on improvements in pubertal patients. These results may impact on the clinical practice and choice of basal insulin at diagnosis of T1DM in children.

Sources of Research Support: Grants from Sonafi Aventis and Novonordisk; Stockholm County Research Foundation.

Nothing to Disclose: PB, JS, KE, A-LB, M-AP, CC-S, EO

sort_order

2548

Pub #

P3-479

Session Information

POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)

Title

Cord Blood C-Peptide Levels Are Related to the Metabolic Profile of Women with and without Gestational Diabetes

Author String

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Université Laval Medical Research Center, Quebec, Canada; Université Laval Medical Research Center, Quebec, Canada; Université Laval, Quebec, Canada; Université Laval, Quebec, Canada

Body

Insulin modulates fetal growth and plasma C-peptide has been found to reflect the insulin-secretory activity of pancreatic β -cells. We tested the hypothesis that cord blood C-peptide levels would be higher in women with gestational diabetes mellitus (GDM) than in women with normal glucose tolerance (NGT) and would be related to measurements of glucose-insulin homeostasis as well as offspring weight. The study included 18 women with GDM and 23 women with NGT. GDM was diagnosed at 26.3 ± 3.2 weeks of pregnancy using a 75-g oral glucose challenge (OGTT). Plasma insulin, glucose and C-peptide levels were measured fasting and at 15, 30, 60, 90 and 120 min after the OGTT. Insulin sensitivity was estimated by calculating HOMA, Cederholm and Matsuda indices. In cord blood from GDM women, C-peptide ($P = 0.09$) and glucose levels ($P = 0.08$) tended to be higher than those from NGT women. In the entire group, cord blood C-peptide levels correlated significantly with maternal insulin concentrations at 0, 60, 90 and 120 min following OGTT. Cord blood C-peptide concentrations also predicted maternal C-peptide levels (fasting), insulin sensitivity indices, IL-6 levels, maternal weight and BMI measured at GDM screening ($[\rho]$ from 0.34 to 0.48, all $P < 0.05$) as well as offspring weight ($[\rho] = 0.28$, $P = 0.08$) and glycemia in the first 24h of life ($[\rho] = -0.39$, $P = 0.06$). There were seven macrosomic babies in the sample. Cord blood C-peptide and insulin levels were significantly higher in macrosomic babies compared to normal weight (all $P < 0.01$). In conclusion, newborns of GDM women tended to have elevated cord blood C-peptide levels compared to newborns of NGT women. This parameter correlated with maternal insulin values as well as with indices of insulin sensitivity, anthropometric measures at diagnosis, offspring weight and early post-natal glycemia. This suggests that insulin-secretory activity of the newborn is related to maternal metabolic parameters.

Nothing to Disclose: M-CD, A-SM, AT, SJW

sort_order 2549
Pub # P3-480
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title Testosterone Levels in Type 1 Diabetic, Type 2 Diabetic and Non-Diabetic Men
Author String M Ng Tang Fui, P Nguyen, EJ Giannatti, JD Zajac, M Grossmann
Austin Health, Heidelberg, Australia; University of Melbourne, Heidelberg, Australia
Body
Background
Population studies have consistently shown that 50% of ageing obese men with type 2 diabetes have low testosterone levels. The prevalence in men with type 1 diabetes is less clear.
Aim
To determine the prevalence of low testosterone levels in men with type 1 diabetes, compared to men with type 2 diabetes and non-diabetic men.
Design
Morning fasting serum testosterone levels were measured in patients with type 1 diabetes presenting to clinic from January '07-'10, in patients with type 2 diabetes and men without diabetes. Anthropometric data was also collected.
Results:
We analysed 76 men with type 1 diabetes (mean age 46 years, range 18-88y), 74 men with type 2 diabetes (58y, range 18-86y) and 16 men without diabetes (49y, range 33-71y), p<0.001 type 1 vs. type 2. Mean BMI was 27kg/m² in the type 1 diabetics and higher in both type 2 diabetics and non-diabetics (31 and 28kg/m² respectively; p<0.001 type 1 vs. type 2). Stroke, peripheral vascular disease and ischaemic heart disease were more prevalent in type 2 diabetics (42%) compared to type 1 diabetics (18%) and non-diabetics (20%). Type 1 diabetics had higher total testosterone levels, (mean 19.2nmol/L, range 8.7-34.6nmol/L), compared type 2 diabetics (mean 12.6nmol/L, range 6.6-22.5nmol/L; p<0.001) and non-diabetics (mean 13.0nmol/L, range 8.1-20.7nmol/L; p=0.0045). Mean SHBG was higher in type 1 diabetics (54nmol/L) compared to type 2 diabetics (37nmol/L; p<0.001) and non-diabetics (32nmol/L; p<0.001). Mean calculated free testosterone was also higher in type 1 diabetics (331pmol/L) compared to type 2 diabetics (257pmol/L; p<0.001) but was not statistically different in non-diabetics (284pmol/L). The prevalence of low total (defined as <10nmol/L) and calculated free testosterone (<230pmol/L) was 4% and 22% respectively in type 1 diabetics, compared to 25% (total) and 39% (free) in type 2 diabetics. The prevalence of low total testosterone was 19% and low free testosterone was 25% in non-diabetics. Total testosterone was inversely correlated with obesity in both groups.
Conclusion:
Type 1 diabetic men had a lower BMI and higher total testosterone level compared to type 2 diabetics and non-diabetic but borderline obese men. Type 1 diabetics also had higher calculated free testosterone than type 2 diabetics suggesting their differences in testosterone levels is not only mediated by SHBG. Despite this there was still a number of men with type 1 diabetes who had lowered testosterone levels.

Nothing to Disclose: MNTF, PN, EJG, JDZ, MG

sort_order 2550
Pub # P3-481
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title Maternal Fasting Plasma Active Ghrelin Levels at Second Trimester of Pregnancy Predict Neonatal Waist Circumference at Birth
Author String G Valsamakis, D Papatheodorou, A Margeli, S Kumar, I Papassotiropoulos, G Mastorakos
Medical School, University of Athens, Athens, Greece; Aghia Sophia Children's Hospital, Athens, Greece; University Hospital Coventry and Warwick Medical School, Coventry, UK
Body
Introduction
Endometrial environment determines to an extent the final birth weight. The latter is an important predictor for the development of metabolic diseases in adulthood. Gut hormones are involved in insulin and glucose metabolism after food ingestion but have also direct effect into CNS, affecting appetite. Pancreatic hormones are co-released with insulin, affecting glucose metabolism.
Aims and Methods
Aim of the study was to explore the role of maternal fasting gut and pancreatic hormones in the fetal growth in normal pregnancy. One hundred healthy pregnant Caucasian women aged 28.2 ± 3.8 (mean \pm SD) years with body mass index (BMI) 23.9 ± 2.6 kg/m² before pregnancy were seen at 24th-26th week and at 32-34th week of pregnancy in the Obstetrics and Gynecology outpatient clinic. Subjects received a 75gr OGTT and had insulin resistance (HOMAR), insulin sensitivity (ISI), first (1st PHIS) and second phase (2nd PHIS) insulin secretion calculated. Plasma fasting active GLP-1, total GIP, active ghrelin, total PYY, active amylin, glucagon, pancreatic polypeptide (PP), and lipids were measured. During the above periods fetal ultrasound (U/S) was performed. At birth neonates had weight, height and waist circumference checked.
Results
GLP-1 active levels correlated negatively with 1st PHIS ($p=0.03$, $r=-0.58$), 2nd PHIS ($p=0.04$, $r=-0.48$), HOMA-R ($p=0.001$, $r=-0.69$) and triglycerides ($p=0.03$, $r=-0.53$). Amylin active correlated negatively with HDL ($p=0.01$, $r=-0.56$) and with glucagon ($p=0.04$, $r=-0.45$). PP correlated positively with total cholesterol ($p=0.01$, $r=0.56$) and glucagon negatively with HOMAR ($r=-0.45$). By longitudinal regression model maternal active ghrelin change and active GLP-1 change were positive ($p=0.02$) and negative ($p=0.03$) predictors of U/S measured fetal abdomen circumference change during the second and third trimesters of pregnancy among maternal plasma active GLP-1, total PYY, GIP, active amylin, and PP level changes. At second trimester stepwise multiple regression analysis revealed maternal active ghrelin as the best positive predictor ($p=0.03$, $\beta=0.84$) of neonatal waist circumference at birth among maternal plasma of active GLP-1, total PYY, GIP, active amylin, and PP levels.
Conclusions
Maternal gut hormones seem to affect fetal growth in pregnancy. Most importantly maternal appetite, as defined by the active ghrelin levels, correlates to neonatal waist circumference and so affect the neonatal energy deposits at birth.
Nothing to Disclose: GV, DP, AM, SK, IP, GM

sort_order 2551
Pub # P3-482
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title Sitagliptina (DPP-4 Inhibitor) and Bedtime NPH Insulin as Third-Line Antidiabetic Agents in Patients with Type 2 Diabetes (DM2) Inadequately Controlled with Sulfonylurea and Metformin: Interim Results
Author String KC Nogueira, RT Fukui, FB Rossi, AS Santos, MER Silva
HC-FMUSP, São Paulo, Brazil
Body Glucose control is a main goal of diabetes treatment. The aim of this study is to compare the efficacy of an oral agent sitagliptin (SITA that increases glucagon like peptide-1) *versus* bedtime NPH insulin (NPH) as a third-line agent in DM2 patients inadequately controlled on metformin plus glyburide therapy. Methods: 23 patients with DM2, with comparable distributions of age, gender, diabetes duration, HbA1c and glucose (G) levels were randomized to the addition of SITA (S group, n=12) or NPH (NPH group, n=11). Fasting and post meal (every 30 min for 4 h) blood samples were collected pre- and after 24 wks of both therapies. Results: HbA1c levels decreased in S group (8.1±0.6 vs 7.3±0.7%, $p=0.001$) and NPH group (8.1±0.7 vs 7.2±0.6%, $p=0.0002$), with no differences between them ($p=0.842$). After treatment, G levels decreased at fasting (154.5±28.3 vs 110.9±29.2 mg/dl, $p=0.001$) and at 30 to 120 min post meal in NPH group and at 60 and 180 min in S group ($p<0.05$). Triglycerides (TG) levels decreased at fasting and was kept lower post meal in NPH group ($p<0.05$). TG increment was lower after 180 and 240 min post meal in S group ($p<0.05$). In comparison, TG levels were lower in NPH group than S group at 30 and 60 min post meal ($p<0.05$). Fasting free fatty acids (FFA) were lower in NPH group (0.52±0.14 vs 0.70±0.19 mEq/L in S group, $p=0.025$) but LDL cholesterol levels were higher (119.6±23.6 vs 94.9±24.6 mg/dl in S group, $p=0.023$). SITA increased fasting insulin (16.9±6.1 vs 22.0±8.5 mU/mL, $p=0.023$) and C-peptide levels (at fasting= 2.66±0.94 vs 3.04±1.10 ng/mL, $p=0.046$ and 30 min after meal= 3.85±1.25 vs 4.41±1.47 ng/mL, $p=0.012$). Unlike, NPH decreased C-peptide at fasting and post meal ($p<0.05$). Both therapies reduced pro-insulin levels: at 60 min (43.6±28.7 x 38.6±25.9 pmol/L, $p=0.042$) in the S group and between 60 and 180 min in the NPH group ($p<0.05$), suggesting improvement in β cell function. Only SITA reduced glucagon levels - at 60 min after meal (100.6±38.7 x 85.4±27.7, $p=0.038$). No changes on liver enzymes levels, IMC and blood pressure were noted in both groups. In conclusion, SITA administered as a third therapeutic agent was as effective as bedtime NPH in reducing HbA1c and post meal glucose levels and it may be an alternative to insulin therapy. Both therapies reduced pro-insulin levels. Only SITA decreased glucagon after meal. Bedtime NPH promoted additional beneficial effect in reducing fasting G and FFA and fasting and postprandial C-peptide levels.

Sources of Research Support: FAPESP.

Nothing to Disclose: KCN, RTF, FBR, ASS, MERS

sort_order 2552
Pub # P3-483
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title Linagliptin Improves Glycemic Control Independent of Gender in Patients with Type 2 Diabetes
Author String M Rendell, SG Chryasant, A Emser, M Von Eynatten, S Patel, A Trujillo, H-J Woerle
Creighton Diabetes Center, Omaha, NE; Oklahoma Cardiovascular & Hypertension Center, Oklahoma City, OK; Boehringer Ingelheim Pharma GmbH & Co, Ingelheim, Germany; Boehringer Ingelheim, Bracknell, UK; Boehringer Ingelheim, Ridgefield, CT
Body **Background:** Some studies in patients with type 2 diabetes (T2D) have shown a gender-dependent response to treatment with antidiabetic agents. We conducted a subgroup analysis of pooled data to determine whether the safety and efficacy of linagliptin was different in men versus women. Three randomized, double-blinded, placebo-controlled, phase 3 trials examined the safety and efficacy of the DPP-4 inhibitor linagliptin for glycemic control as monotherapy, add-on to metformin, or add-on to metformin + sulfonylurea in patients with T2D. Subgroup analyses of pooled data from these studies are facilitated by identical study designs with respect to endpoints, linagliptin dosing, study duration, and a large cohort size (N=2,258).
Methods: The primary efficacy outcome in all three studies was mean change from baseline HbA1c at 24 weeks. The incidence of any adverse events (AE) was recorded.
Results: The pooled cohort had an equal gender distribution (50.4% female). The mean (\pm SD) patient age and baseline BMI were 57 \pm 10 years and 29.0 \pm 4.9 kg/m², respectively. Patients were predominantly White (58%) and Asian (42%), and 57% of patients had a mean disease duration of >5 years. Mean baseline HbA1c (\pm SD) and HOMA-IR were 8.1% (\pm 0.8) and 4.7 \pm 5.3 mU/L [bul] mmol/L, respectively. In the pooled analysis of efficacy, linagliptin showed significant reductions in HbA1c levels in both men and women. The adjusted placebo-corrected mean changes in HbA1c from baseline (\pm SE) were -0.62 \pm 0.06 in men and -0.65 \pm 0.06 in women, with no significant effect of gender on treatment efficacy (P=0.427) or gender-treatment interactions (P=0.697). No linagliptin-related safety concerns were identified. Total AE rates (treatment vs placebo) in the pooled data were 56.0% vs 59.6% (men) compared with 62.3% vs 56.7% (women). The overall hypoglycemic event rates with linagliptin in monotherapy or as add-on to metformin therapy were <1.0%. A higher rate (>1.0%) of hypoglycemic events occurred in the study that used a background therapy including a sulfonylurea. The incidence of gender-specific drug-related AEs such as sexual dysfunction or reproductive/breast disorders were <1%, and not significantly different from placebo.
Conclusions: The safety and efficacy of linagliptin are not affected by gender. Treatment with linagliptin provided clinically meaningful reductions in HbA1c in both men and women with type 2 diabetes, with a safety profile comparable to placebo.

Sources of Research Support: Boehringer Ingelheim.

Disclosures: AE: Employee, Boehringer Ingelheim. MVE: Employee, Boehringer Ingelheim. SP: Employee, Boehringer Ingelheim. AT: Employee, Boehringer Ingelheim. H-JW: Employee, Boehringer Ingelheim. Nothing to Disclose: MR, SGC

sort_order 2553
Pub # P3-484
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title Trends in Gestational Diabetes That Serve as Predictors for Treatment and Fetal Outcomes
Author String W Clayton, N Agarwal, S Jagasia
Vanderbilt University Medical Center, Nashville, TN; Vanderbilt University Medical Center, Nashville, TN
Body
Introduction: Suboptimally treated gestational diabetes (GDM) leads to an increase in the incidence of both maternal and fetal complications. There is a short window of opportunity for optimal treatment. The point-of-care A1c (POC A1c) test provides results within minutes and is cheaper. We hypothesized that POC A1c would be able to predict need for medication in patients with GDM, and would correlate with fasting blood glucose (FBG).
Methods: The cohort included patients referred to the GDM clinic at a large academic medical center. Data were collected through an established patient registry in an IRB approved study. FBGs were obtained from GDM diagnostic test results, and POC A1c results were obtained from test results at the first GDM clinic visit. Initiation of medication was determined by documentation in clinic notes or electronic prescriptions. Wilcoxon rank sum test was used to compare continuous variables among the groups. The Spearman correlation was used for correlation between POC A1c and fetal weight at delivery.
Results: The final cohort consisted of 142 patients. Sixty-nine patients (49%) required medication therapy for treatment of GDM after initial diagnosis, compared to 73 patients (51%) that did not. In univariate analyses, patients requiring medications had a higher median POC A1c [5.6% (range, 5.4 to 5.97) vs. 5.3 % (range, 5.1 to 5.7), $p<0.001$] and a higher median FBG [97 mg/dL (range, 90 to 105) vs. 83 mg/dL (range, 80 to 93), $p<0.001$]. There was no relationship between the POC A1c in the mother at diagnosis of GDM and the fetal weight at delivery (correlation coefficient: -0.010, $p=0.915$).
Conclusions: Higher POC A1c and FBG levels can help to predict the need for medication in the management of GDM. Optimal treatment can decrease immediate postnatal complications and long-term risk of obesity and type 2 diabetes. The lack of correlation between the POC A1c in the mother at diagnosis of GDM and the fetal weight at delivery suggests that appropriate treatment can decrease risk of fetal complications.

Sources of Research Support: Vanderbilt CTSA grant UL1 RR024975 from NCRR/NIH.
Nothing to Disclose: WC, NA, SJ

sort_order 2554
Pub # P3-485
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title Screening for Diabetes in Patients Administered Glucocorticoids Long-Term
Author String MG Burt, V Willenberg, M Smith, M Ahern, SN Stranks
Repatriation General Hospital, Adelaide, Australia; Repatriation General Hospital, Adelaide, Australia; Flinders University, Adelaide, Australia
Body
Chronic glucocorticoid therapy, which is commonly prescribed at mildly supraphysiologic doses to treat inflammatory and autoimmune disease, may increase the prevalence of diabetes. Patients are usually screened for diabetes by measuring fasting glucose, with an oral glucose tolerance test (OGTT) recommended by some guidelines when fasting glucose is non-diagnostically elevated (101-124 mg/dL)¹. As glucocorticoids increase postprandial more than fasting glucose, we hypothesized that fasting glucose would have poor sensitivity as a screening test for diabetes in patients receiving chronic glucocorticoid therapy. The aim was to compare the efficacy of fasting glucose to screen for diabetes in patients administered long-term prednisolone and a matched control group.
In a cross-sectional study, 60 subjects (62% female, age = 69.8±10.4 years, BMI = 28.9±5.9 kg/m²) who were not known to have diabetes and who were receiving chronic (>6 months) prednisolone 4-10 mg/day for inflammatory rheumatologic disease (Group 1) and 50 controls (62% female, age = 69.8±10.7 years, BMI = 26.1±4.6 kg/m²) without known diabetes with an inflammatory rheumatologic disease who had not received oral glucocorticoids for at least 6 months (Group 2) underwent an OGTT. The primary endpoint was the area under the receiver operator characteristic (ROC) curve for fasting glucose to diagnose diabetes, with the OGTT considered gold standard.
Mean ± SD prednisolone dose in Group 1 was 6.5±2.1 mg/day. Fasting glucose was significantly lower (90±2 vs 97±2 mg/dL, p=0.01) and post glucose-load glucose concentration significantly higher (144±7 vs 117±7 mg/dL, p=0.005) in Group 1 than in Group 2. Based on the results of the OGTT, the prevalence of diabetes was 15% in Group 1 and 8% in Group 2 (p=NS). The area under the ROC curve for fasting glucose to diagnose diabetes was significantly lower in Group 1 than in Group 2 (0.71±0.10 vs 0.99±0.03, p=0.01). A fasting glucose of [ge]101 mg/dL (threshold for an OGTT)¹ had 33% and 100% sensitivity in Group 1 and 2 respectively.
In summary, there is discordance between fasting and post glucose-load glucose concentration in patients on long-term prednisolone. As such, fasting glucose has poor sensitivity as a screening test for diabetes in prednisolone-treated patients. Therefore, we conclude that patients administered prednisolone long-term should be screened for diabetes with an OGTT.

1. 2006 Global Guideline for Type 2 Diabetes: recommendations for standard, comprehensive, and minimal care. Diabet Med 23:579-593.

Sources of Research Support: Grant from Foundation Daw Park.

Nothing to Disclose: MGB, VW, MS, MA, SNS

sort_order 2555
Pub # P3-486
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title Potentiation of Early-Phase Insulin Response by Previous Meal Is Responsible for the Second-Meal Phenomenon in Type 2 Diabetes
Author String S-H Lee, A Tura, A Mari, K-H Baik, S Moon, K-H Yoon, K-W Lee, Y-B Ahn
The Catholic University of Korea, Suwon, Republic of Korea; National Research Council, Padua, Italy
Body
Aims: Improved glucose tolerance following sequential meal is known as the second-meal phenomenon. We aimed to investigate its extent and mechanisms in patients with type 2 diabetes.
Methods: Metabolic responses after lunch in 12 diabetic patients were compared on 2 separate days; one with (day BL) and another without (day FL) breakfast. The secretions of islet and incretin hormones were calculated by area under the curve (AUC) values for 180 min after each meal (0-180 min for breakfast and 180-360 min for lunch). Indices of early-phase insulin secretion were assessed and β -cell function was estimated by mathematical modeling analysis.
Results: Incremental AUCglucose(180-360 min) was significantly lower on day BL compared with day FL (181 ± 43 vs. 472 ± 29 mmol/L[\cdot min, $P = 0.0005$) and the extent of the second-meal phenomenon (incremental AUCglucose(180-360 min) on day BL/day FL) was $35 \pm 30\%$. The peak levels of insulin and C-peptide were attained earlier after the second meal (at 45 min) than after the first meal (at 90 min). Incremental AUCglucose(180-360 min) was negatively correlated with incremental AUCinsulin(180-210 min) ($r = -0.443$, $P = 0.0300$), insulinogenic index at lunch ($r = -0.769$, $P < .0001$), acute C-peptide response at lunch ($r = -0.596$, $P = 0.0021$), potentiation factor ratio [180-360]/[0-20] ($r = -0.559$, $P = 0.0045$) and potentiation factor ratio [200-220]/[160-180] ($r = -0.471$, $P = 0.0201$), while positively correlated with free fatty acid level before lunch ($r = 0.679$, $P = 0.0003$).
Conclusions: Second-meal phenomenon was evident in patients with type 2 diabetes. Potentiation of early-phase insulin response by previous meal is responsible for the second-meal phenomenon in type 2 diabetes.
Nothing to Disclose: S-HL, AT, AM, K-HB, SM, K-HY, K-WL, Y-BA

sort_order 2556
Pub # P3-487
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title The Effect of Whole Body Vibration Training on Insulin Sensitivity in Overweight Adolescents: A Randomized Controlled Trial
Author String KA Ramjan, CR Broderick, JN Briody, N Van Doorn, S Burrell, K Chisholm, SP Garnett, E Lawrie, K Winning, F Barzi, LA Baur, CF Munns, CT Cowell
The Children's Hospital at Westmead, Westmead, Australia; University of Sydney, Sydney, Australia; Royal North Shore Hospital, St Leonards, Australia; The Children's Hospital at Westmead, Westmead, Australia; University of New South Wales, Kensington, Australia; The Children's Hospital at Westmead, Westmead, Australia; The Children's Hospital at Westmead, Westmead, Australia;
Body
Background
The obesity epidemic has led to a rise in the number of adolescents with clinical insulin resistance and Type 2 diabetes. Lifestyle interventions are effective in improving body composition and may improve insulin sensitivity. Whole body vibration training is a novel technique to improve muscle power and mass with results similar to resistance training. This is the first study to examine the metabolic effects of whole body vibration training in adolescents at risk of Type 2 diabetes.
Aim
To determine whether three months of whole body vibration training enhances the effect of lifestyle intervention on insulin sensitivity in overweight adolescents with clinical features of insulin resistance.
Methods
43 overweight adolescents with clinical insulin resistance (fasting insulin >90 & <300 pmol/L and acanthosis nigricans) were recruited to the VIBRATE study, a 3 month randomized control trial, with randomization to two treatment arms: LIFESTYLE (diet & exercise) or VIBRATION (diet +exercise+15 min/day whole body vibration training with a Galileo™ platform). The primary outcome, whole body insulin sensitivity was calculated from the oral glucose tolerance test. Secondary outcome measures examined: anthropometry, musculoskeletal parameters using peripheral quantitative computed tomography, dual x-ray absorptiometry and Leonardo^R mechanography; cardiorespiratory fitness and adipocytokines.
Results
42 participants (14 male, mean age 13.3±2.1 yrs) completed the trial. There was no change in insulin sensitivity in either group. We saw a reduction in BMI z-score -0.1 (p=0.039) in the LIFESTYLE group only. Whole body vibration training produced skeletal changes, increasing total BMD/Ht-z-score (0.1 p=0.04) but soft tissue body composition was unchanged when total adiposity and lean tissue mass for height were examined. All participants exercised for a longer duration on the treadmill (p=0.047) but relative VO_{2max} was not altered. Muscle force, power and efficiency of jump did not improve in either group.
Conclusions
Whole body vibration training did not enhance the effect of lifestyle intervention on insulin sensitivity in our study however variable adherence to lifestyle measures and a belief in a [ldquo]magic cure [rdquo] may have affected the outcome. Larger studies of longer duration are required to investigate the effect of whole body vibration training in this cohort, as change in insulin sensitivity involves a complex interplay of various organ systems.

Sources of Research Support: Australasian Paediatric Endocrine Care Grant 2008; Regional Diabetes Support Scheme Grant 2008/9; Australasian Paediatric Endocrine Group Grant 2008; National Health and Medical Research Council Medical Postgraduate Scholarship all awarded to KAR.

Nothing to Disclose: KAR, CRB, JNB, NVD, SB, KC, SPG, EL, KW, FB, LAB, CFM, CTC

sort_order 2557
Pub # P3-488
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title Impact of Treatment with Salsalate on Pain Scores in Patients with Type 2 Diabetes: Results from TINSAL-2D
Author String JB McGill, V Fonseca, L Pyle, KA Jablonski, MA Staten, SE Shoelson, AB Goldfine
Washington University School of Medicine, St Louis, MO; Tulane University Health Sciences Center, New Orleans, LA; The George Washington University, Rockville, MD; NIDDK, Bethesda, MD; Harvard University, Boston, MA
Body The TINSAL-T2D (Targeting Inflammation Using Salsalate in Type 2 Diabetes) study tested the hypothesis that reducing inflammation with salsalate would improve glucose control in patients with T2DM. Results of the study showed that salsalate, in doses of 3, 3.5 and 4 grams per day lowered HbA1c levels by 0.36%, 0.34% and 0.49% respectively after 14 weeks of treatment when compared with placebo.¹
The effect of salsalate on osteoarthritis-type pain was tested by administering the Western Ontario MacMasters' Index (WOMAC) questionnaire at the beginning and end of the study. Of the 104 patients who completed both questionnaires, the median age was 57 years, and 59.2% were male. Patient self-reported races were: 50.5% white, 37.9% black, 3.9% Asian, 1% AIAN, 1% Pacific Islander, 3.9% other and 1.9% missing. 5.8% reported Hispanic ethnicity. Results of the subscales for pain, stiffness and ADL, and the total score of the WOMAC index in this population analyzed by the Kruskal-Wallis test were not significant for pain ($P=0.10$), stiffness ($P=0.09$), ADL ($P=0.12$) or in total ($P=0.12$). We then tested whether the treatment groups differed in the rate of participants whose pain score increased from baseline to W14 by analyzing the following raw data from the pain subscale:
The number of patients reporting no increased pain score were: 12, 11, 16 and 17 in the placebo, 3.0 g, 3.5 g and 4.0 g groups respectively; total 56/103 subscale respondents. The number of patients responding yes to increased pain scores were: 14, 16, 10 and 7 in the placebo, 3.0 g, 3.5 g, and 4.0 g groups respectively, total 47/103 subscale respondents. The association between escalating doses of salsalate and change in the pain subscale was significant, Mantel-Haenszel Chi-Square $P=0.034$.
Conclusion: there appears to be a significant linear association between the dose of salsalate and the rate of increased pain scores, with those in the higher dose groups having reduced odds of an increased pain score after 14 weeks of treatment. Consistent with its known anti-inflammatory effect, salsalate may provide relief from pain or prevent an increase in osteoarthritis-type pain in a dose-dependent manner in patients with T2DM.

(1) Goldfine AB et al., Ann Int Med 2010;152:346

Sources of Research Support: NIH Grants U01 SK74556 and P50 HL83813, NIDDK (Dr. Staten), NIH GCRC and CTSA at multiple sites, and the Tullis-Tulane (Dr. Fonseca) and Helen and Morton Adler (Dr. Shoelson) Chairs. Caraco pharmaceuticals provided salsalate and placebo; Lifescan provided meters and test strips and Merckodia provided insulin assay kits.

Nothing to Disclose: JBM, VF, LP, KAJ, MAS, SES, ABG

sort_order 2558
Pub # P3-489
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title Recurrent Diabetic Ketoacidosis in Inner-City Populations: Behavioral, Socioeconomic and Psychosocial Factors
Author String D Smiley, L Randall, J Begovic, M Hudson, L Peng, G Umpierrez
Emory University School of Medicine, Atlanta, GA; Emory University Rollins School of Public Health, Atlanta, GA
Body Poor treatment adherence is a major precipitant of diabetic ketoacidosis (DKA) in minority populations. To understand factors driving poor compliance and DKA recurrence, we prospectively analyzed behavioral, socioeconomic and psychosocial factors in patients with DKA admitted to Grady Hospital in Atlanta from 7/2007 to 8/2010. Questionnaires and medical records were used to obtain demographics, outpatient follow-up, DM education, mental illness and lab values. The Patient Health Questionnaire (PHQ-9) and SF-36 health survey were used to screen for depression and assess quality of life. Among 164 patients (95.7% AA, 41±13 years; 85M/79F, BMI 28±9 kg/m², length of stay 4.2±3 days [mean ± SD]), 73 patients were admitted with first episode and 91 had multiple admissions with a mean of 3.54 admissions prior to and 0.99 after the index case. Precipitating cause included new-onset diabetes in 15 (9.2%) patients, insulin discontinuation in 121 (73.8%), infection in 19 (12%) and medical illness in 7 (4.3%). Among those who stopped insulin, 32.5% gave no reasons for stopping, 27.6% reported lack of money to buy insulin, 18.7% felt sick, 14.6% were away from supply and 4.9% were stretching supply. Compared to first-time DKA, those with recurrent DKA had longer duration of DM (p<0.01), younger age at DM onset (p=0.04), higher rates of depression (p=0.03), alcohol abuse (p=0.04), drug abuse (p<0.01) and homelessness (p<0.01). There were no significant differences in PHQ-9 and SF-36 scores for depression or quality of life, psychiatric illnesses or antipsychotic treatment or insurance coverage between groups (p=NS). Despite having received more DM education (88% vs. 56%, p<0.01), patients with > 10 episodes of DKA compared to first-time DKA did not have a significantly greater understanding of A1C (46% vs. 33%, p=0.07). In conclusion, poor adherence to insulin therapy is the leading cause of recurrent diabetic ketoacidosis in inner-city patients. Multiple behavioral, socioeconomic and psychosocial factors contribute to poor treatment adherence. Identification of such factors and intervention with support groups and education might decrease recurrence and reduce the high costs associated with diabetic ketoacidosis.

Sources of Research Support: Takeda, NIH-K12 RR-017643.

Nothing to Disclose: DS, LR, JB, MH, LP, GU

sort_order 2559
Pub # P3-490
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title Epidemiological Data of Brazilian Type 1 Diabetes (T1D) Patients Followed at São Paulo Clinical Hospital
Author String TC Mattana, VS Costa, RT Fukui, MRS Correa, DDTOM Mainardi-Novo, M Gamberini, MO Ruiz, MER Silva
Laboratory of Medical Investigation-LIM18, FMUSP, São Paulo, Brazil; Clinical Hospital, São Paulo, Brazil; Laboratory of Immunology of Marília, Marília, Brazil
Body T1D is an autoimmune disease characterized by insulin deficiency. Genetic and environmental factors contribute to disease risk and to different phenotypes, according to geographic region and ethnicity. Its incidence is low in South America and few data are known about its epidemiology. **Objective:** Characterize T1D patients according to clinical, laboratorial and genetic data. **Patients and Methods:** Plasma glucose, C peptide, autoantibodies and HLA alleles were analyzed in 623 T1D patients according to gender and race. **Results:** The age of diagnosis was 11,7±7,9y (75,2% of them [le] 15y). Diabetes duration was 10,5± 9,8y being 59,2% female and 44,5% the offspring first born. The majority was white (82,4%). ICA was present in 22,7% and anti-IA2 in 42%. Anti-GAD was positive in 45,7%, and more frequent in females(53,5% x42,8% p=0,025). The highest mean anti-GAD values were seen in females(12,7±34,2 x 6,7±14,6 U/mL-p= 0,02) and in whites(11,3±30,5 x 6,3±13,1 U/ml; p=0,018). Residual insulin secretion(C peptide>0,5ng/ml) was observed in 15,8%. The autoantibodies against non pancreatic tissues were: anti-TPO (positive in 23,4%), anti-TG (23,3%), TRAB (7,5%), anti-21-OH (12,9%), anti-parietal cell (6,7%), FAN(24,7%), anti-smooth muscle (5,4%), anti-endomysium(7,4%), anti-mitochondrial and anti-LKM1 antibodies(<0,7%) and ANCA(2,1%). HLA-DR alleles were determined in 461 patients and compared to 701 controls. The HLA-DR3 allele (61,8%, mainly -DR*0301= 97,2%) and -DR4 (62,3%, mainly -DR*0405=30,8%) were the most frequent whatever the gender or race (OR= 3,8 and 3,3 respectively) and conferred susceptibility to diabetes (p<0,0013) as well as -DR9 (p<0,0026;OR=2,9). Protection to T1D was associated with HLA-DR*0302, -DR*0411, -DR7, -DR11, -DR13, -DR14, and -DR15 alleles (p< 0,0013). HLA-DQ*0201 (OR=3,602) and -DQB1*0302 (OR=4,19) alleles conferred susceptibility to T1D (p=0,025) and HLA-DQ*0301, *0402, *0503, *0602 e *0603 alleles conferred protection (p<0,02). **Conclusion:** In this population of 623 T1D patients of São Paulo the disease predominated in youngsters (<15y), whites, bearing HLA-DR3 or -DR4 alleles. Anti-GAD and anti-IA2 were present in less than 60 % of T1D probably due to the long time of disease. Anti-GAD prevailed in females and in whites. Other autoantibodies were rare, except those against thyroid. These results are similar to the others populations suggesting that the miscegenation existing in our population does not influence the disease phenotype.

Sources of Research Support: FAPESP.
Nothing to Disclose: TCM, VSC, RTF, MRSC, DDTOM-N, MG, MOR, MERS

sort_order 2560
Pub # P3-491
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title Mesenchymal Stem Cell Transplantation in Treatment of Type 1 Diabetic Patients
Author String B Larijani, E Nasli Esfahani, K Ali Moghaddam, N Mojahed Yazdi, P Amini, B Nikbin Moghaddam, A Ghavam Zadeh
Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran
Body
Introduction: Mesenchymal stem cells (MSCs) are multipotent progenitor cells that have immunomodulatory capacities. In this study we aim to examine the safety and efficacy of MSC transplantation in treatment of type 1 diabetic patients.
Method: Clinical trial was performed on 23 diabetic type 1 patients aged 5 to 30 years. These patients were in stages before the beginning of severe irreversible complications, had FBS level less than 200 mg/dL and had diabetes for up to 20 weeks. Patients who had history of DKA presentations and had acute infectious diseases were excluded from the trial. Anti GAD test was used for diagnosis of diabetes type 1. Culture expanded autologous mesenchymal cells (in DMEM-LG and FCS10%) were injected with the dosage of 2 million MSCs/kg. 6 month after the first injection patients who did not become insulin free underwent second injection of MSCs. Medical care services were performed to achieve glucose and HbA1c control before and after cell transplantation.
Results: No side effects have been noticed in patients up to know. The initial results of this study, six month after the first injection, indicate that 2 patients became insulin independent, the mean dosage of insulin came down from 24 to 16.75 unit/day and level of C-Peptide went up from 1.30±0.7 to 1.69±0.6 ng/ml. In the other hand, no significant changes were seen in the mean of FBS, post prandial glucose and HbA1c level. In the group who underwent second injection two patients became insulin free for two months but after that regained insulin dependence. Now one patient is still insulin free with one injection of MSCs.
Conclusion: The findings of this study support the idea that MSC transplantation might become a novel treatment for type 1 diabetes; in spite of this fact, long term evaluation of this trial after the second injection is essential and will be reported soon.
Nothing to Disclose: BL, ENE, KAM, NMY, PA, BNM, AGZ

sort_order 2561
Pub # P3-492
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title Durability of Effects of Exenatide Treatment on Glycemic Control, Body Weight, hsCRP, Lipid Concentrations and Bone Mineral Density
Author String M Gupta, MA Siddiqui, N Gupta, SK Wangnoo
Indraprastha Apollo Hospital, New Delhi, India
Body
OBJECTIVE:
To determine the sustainability of beneficial effects of treatment with exenatide on glycemic control and related non-glycemic parameters - hsCRP, lipid concentrations, body weight and bone mineral density (BMD) and whether these effects persist after discontinuation of exenatide.
RESEARCH DESIGN AND METHODS:
We included 109 overweight patients (BMI 34 ± 3.2 Kg/m²) (according to Asian-Indian criteria) of type 2 diabetes (average duration 9.3 ± 3.2 years) (M:79, F:30) attending the endocrine outpatients clinic initiated on exenatide and who had continued it for 14 months. The patients were earlier on stable doses of metformin alone or a combination of metformin and sulfonylurea but still not achieving adequate glycemic control. All the patients underwent detailed dietary counselling prior to initiation of exenatide. Biochemical investigations included HbA1c, hsCRP, lipids (triglycerides, LDL, HDL). BMD was measured by dual-energy X-ray absorptiometry alongwith serum calcium, alkaline phosphatase and phosphorus.
RESULTS:
Exenatide decreased HbA1C (0.7%), weight (9 Kg), hsCRP (0.9 mg/L) and triglyceride (46 mg/dl), LDL (16 mg%) and HDL increased by 2 mg% (p<0.05 for all). The reduction in CRP concentration was significantly related to the baseline CRP concentration (r = 0.58, P < 0.001) and to change in HbA1C (r = 0.78, P = 0.01). BMD and fasting serum alkaline phosphatase, calcium, and phosphate remained unaffected during the course of treatment. Patients who stopped taking exenatide had a reversal of the benefits within 4 months of cessation of treatment with significant increases in levels of hsCRP and triglycerides. Weight gain was not significant.
CONCLUSIONS:
Exenatide treatment has durable and persistent beneficial effects on glycemic control, hsCRP, Lipid profile, and weight. Cessation of treatment reverses all these beneficial effects within succeeding 4 months. There was no evidence of loss of its effects while exenatide treatment was continued. There was no effect on BMD or calcium homeostasis.
Nothing to Disclose: MG, MAS, NG, SKW

sort_order 2562
Pub # P3-493
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title The Stress Hypothalamic Connection in DM
Author String S Sakkal
MCC, Aleppo, Syrian Arab Republic
Body
Normal physiology: The hypothalamus is the well known location of the **Glucostat** responsible about the set point of blood glucose at 90±10mg/dl an absolutely needed level for brain cells. The molecular gauge is considered today AMP Kinase in hypothalamic cell.
Glucostat functions use hormonal and neuronal mechanisms. The hormones pathways have been delineated well: GHRH, GH, IGF1, CRH, ACTH, Cortisol, sympathetic, epinephrine, Glucagon and Insulin, always considered auto regulated by its own sensors. The neuronal pathways has been elusive for years, detailed neuronal circuits as important as hormones, specialized neurons controls hepatic glucose output, insulin secretion and even insulin resistance, considered for a peripheral phenomenon of fat, muscle and liver.
The multi potential Hypothalamic cell is both: endocrine cell producing hormones with slow prolonged and neuronal cell producing neurotransmitters with rapid short responses for strict blood glucose at the Glucostat level.
This should not be surprising since the Hypothalamus is responsible for vegetative, metabolic maintenance of Internal Milieu, coordinating interface between higher brain centers and body living status. It is the location of: Adipostat, Osmostat, Energy stat, sympathostat, Emotional stat, Libido stat and Prolactin control, gonadal, Temperature stat, Stress level stat (external and internal metabolic or personality related), Satisfaction stat with the nuclear Acembens. The feedback loop from all peripheral organs and tissues: serum, carotids, oxidative cell ingredients, adrenals, gonads, fats and Nuclear Acembens/ limbic system give the most extraordinary control system ever imagined after interaction with brain centers for neurotransmitters response and pituitary for hormonal response. What happens in Diabetes?
Hypothalamic dysfunction after catastrophic acute stress as a cause of Diabetes onset: We asked 200 patients how they felt the onset. (80) reported catastrophic stressful events within 1-6 week before the onset of diabetes. At onset hypothalamic symptoms: fatigue, muscle pain 90%, Mood, weight, appetite, Sleep disturb. 80%, Temperature deregulation, autonomic dysfunction %60, gonadal and Libido changes %50. An average of 12 painful trigger points for fibromyalgia present. After therapy disturbances persisted in 36%. Only 4 trigger points present. All were statistically significant at 0.001 p value or less.
We conclude Hypothalamic Glucostat reset leads to DM onset.

Modafinil improved hypoglycemia-related warning signals compared to placebo without differences on hormonal responses or cognitive function [Thomakos, P. et al., Abst 590]. European society for the study of Diabetes)

Nothing to Disclose: SS

sort_order

2563

Pub #

P3-494

Session Information

POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)

Title

Liver Fat Accumulation and Islet Graft Survival

Author String

CB Leita0, AC Westphalen, EML Peixoto, LG Mireles-Zavala, V Lauriola, K Bernetti, C Ricordi, R Alejandro
Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil; University of Miami, Miami, FL; University of California, San Francisco, CA

Body

This study aimed at determining the fat content of the liver of type 1 diabetes mellitus (DM) patients after islet transplantation (ITx) and to evaluate its association with islet graft survival. The liver fat content was evaluated by MRI [fat liver score = $(SI_{in} [\text{minus}] SI_{opp})/SI_{in}$ times 100, where SI is average liver signal intensity divided by the average spleen signal intensity, SI_{in} is signal intensity on in phase images, and SI_{opp} is signal intensity on opposed-phase images] 16 months (interquartile interval: 11-31) after graft failure in 33 type 1 DM ITx recipients. Correlations between clinical and laboratorial variables and fat liver score were done by Spearman test. Comparisons were performed between subjects below and above the median value of the fat liver score. Differences in outcomes (time-to-graft dysfunction or failure) were compared by Kaplan-Meier curves. The only baseline variable associated with the fat liver score was the waist circumference ($r: 0.64; p = 0.044$). Regarding the islet function outcomes, an inverse correlation was observed between time-to-graft failure and fat liver score ($r: -0.39; p = 0.026$). Patients with a longer islet survival (define as functional islets for more than 40 months) had lower fat liver scores (1.68 ± 0.50 vs. $2.01 \pm 0.38; p = 0.046$) in comparison with those with shorter functional grafts. As well, a tendency towards longer islet survival was observed among subjects with liver fat score below the median (63.6 ± 6.7 vs. 43.9 ± 6.9 months, $p = 0.053$). In conclusion, a shorter islet graft survival was associated with increased liver fat after graft failure. Prospective clinical trials may confirm the cause-effect association between liver fat accumulation and islet failure and evaluate if strategies focusing its reduction may prolong islet graft survival.

Sources of Research Support: NIH, JDRF, DRI foundation, FIPE do Hospital de Clinicas de Porto Alegre.

Nothing to Disclose: CBL, ACW, EMLP, LGM-Z, VL, KB, CR, RA

sort_order 2564
Pub # P3-495
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title The Effects of Pioglitazone on Beta-Cell Function and Insulin Sensitivity in Subjects with Ketosis-Prone Diabetes
Author String D Smiley, M Hudson, L Randall, J Begovic, L Peng, G Umpierrez
Emory University School of Medicine, Atlanta, GA; Emory Rollins School of Public Health, Atlanta, GA
Body The majority of patients with new-onset T2DM presenting as diabetic ketoacidosis (DKA) or blood glucose (BG) [ge] 400 mg/dL are able to achieve near-normoglycemic remission after [le]12 weeks of insulin therapy; however, many of these patients have glycemic relapse on diet alone. This study determined if pioglitazone therapy could delay a relapse by improving or preserving β -cell function and insulin sensitivity in overweight AA with a history of hyperglycemic crises.
Ninety newly-diagnosed, African-American (AA) subjects were recruited shortly after resolution of hyperglycemic crises (35 DKA/55 HG; 53M/37F; age:43.8 \pm 10.3 yrs; BMI:38.5 \pm 10.3 kg/m²; BG:642 \pm 245 mg/dL, mean \pm SD); of them, 67 % discontinued insulin in [le]12 weeks. Patients in remission (20 DKA/24 SH) were randomized in a double-blinded fashion to receive daily pioglitazone 30 mg (n=22, PIO) or placebo (n=22, PBO). b-cell function (BCF) and insulin sensitivity (IS) were assessed by IV glucagon and glucose stimulation tests and minimal model analysis (MinMod) within 1 week of diagnosis and 1 week after insulin discontinuation. Oral glucose tolerance tests (OGTT) were done at remission, 3 months and every 6 months during the remission phase. Remission was defined as fasting BG <130 mg/dl and A1C <7.0%.
Both groups were comparable in age, sex, BMI, A1C, GAD antibody status and weeks of insulin therapy and were followed up to 2.9 years (mean 357 days). Compared to PBO, PIO treatment significantly reduced the recurrence of hyperglycemia (p = 0.01) despite weight gain in this arm (3.4 vs 1.1 kg, p=0.40). There were no significant differences in measures of BCF or IS between PIO and PBO groups at time of remission. Although not statistically significant, there were trend differences in OGTT indices. The PIO group compared to those treated with PBO had lower glucose and insulin levels, better b-cell function as indicated by a higher c-peptide index, and higher IS as shown by higher Matsuda index and lower HOMA-IR values during repeated OGTT tests.
In conclusion, pioglitazone compared to placebo resulted in prevention of recurrence of hyperglycemia and prolonged the insulin-free period of near-normoglycemic remission in overweight AA patients with new-onset, hyperglycemic crises. This effect appears to correlate with the positive effects of pioglitazone on b-cell function and insulin sensitivity. Larger studies are needed to better determine the mechanisms underlying continued pharmacological remission.

Sources of Research Support: Takeda and NIH-K12 RR-017643.

Disclosures: DS: Investigator, Takeda. GU: Investigator, Takeda. Nothing to Disclose: MH, LR, JB, LP

sort_order 2565
Pub # P3-496
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title Time Course Effects of Short-Term Standard Dose Prednisone Therapy on Basal and Meal-Time Responses of Glucose, Insulin and Free Fatty (FFA) Profiles in Subjects with Varying Degrees of Glucose Tolerance
Author String KCJ Yuen, PA McDaniel, MC Riddle
Oregon Health & Science University, Portland, OR
Body
Rationale: Chronic high dose glucocorticoid (GC) exposure induces undesirable effects on glucose homeostasis, but the time course effects of a standard dose of prednisone, the most commonly used GC in clinical practice, on basal & meal-time β -cell function & lipolysis is less clear. We, thus, assessed 24h time profiles of glucose, insulin & FFAs following 3-day prednisone (20 mg/day) therapy in subjects with varying degrees of glucose tolerance.
Methods: Three groups of subjects were studied: mild Type 2 diabetes (T2DM) ($n = 7$, BMI 32.7 ± 2.7 kg/m², FPG 115 ± 11 mg/dl, A1c $7.8 \pm 0.2\%$), impaired glucose tolerance (IGT) ($n = 8$, BMI 29.9 ± 2.8 kg/m², FPG 92 ± 4 mg/dl, A1c $6.0 \pm 0.1\%$) & controls (C) ($n = 5$, BMI 31.7 ± 1.6 kg/m², FPG 85 ± 2 mg/dl, A1c $5.2 \pm 0.1\%$). Before & 3 days after pre-breakfast prednisone therapy, subjects underwent frequent 24h blood sampling. Eucaloric meals (20% breakfast, 30% lunch and 50% dinner) were served at 0800h, 1200h & 1800h. Glucose, insulin & FFA profiles were analyzed a time blocks 0800-1200h, 1200-1800h, 1800-0000h & 0000-0800h. Insulinogenic index was used to assess β -cell function.
Results: Prednisone therapy did not affect fasting glucose & insulin in all 3 groups, but increased fasting FFAs in C (0.36 ± 0.09 to 0.50 ± 0.08 mmol/L, $P < 0.01$). Prednisone therapy also increased post-meal AUC_{gluc} in T2DM by 12% (0800-1200h), 97% (1200-1800h) & 19% (1800-0000h), but less so in the IGT & C groups. Insulin secretion decreased initially in T2DM by 39% (0800-1200h), but increased later in T2DM by 30% (1800-0000h), in IGT by 53% (1200-1800h) & 70% (1800-0000h), & in C by 89% (1200-1800h) & 55% (1800-0000h). Post-meal AUC_{FFA} increased in IGT and C from 1200-0000h, but not in T2DM. From 0000-0800h, glucose, insulin and FFA levels were at baseline levels in all 3 groups.
Conclusion: Standard 3-day dose of prednisone therapy induces meal-time hyperglycemia in T2DM that begins after breakfast but returns to baseline by midnight. The cause of hyperglycemia in T2DM is most likely due to an initial suppression of β -cell function followed by insulin resistance without lipolysis. The 24h time profiles also indicate apparent delayed yet transitory insulin resistance and lipolysis that contributes to the hyperglycemia in the IGT & C groups. Thus, the therapeutic use of standard dose prednisone should take into account of its 18h duration of action, effects on β -cell function & insulin resistance, & differences in degrees of glucose tolerance.

Nothing to Disclose: KCJY, PAM, MCR

sort_order 2566
Pub # P3-497
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title Linagliptin Effectively Reduces Blood Glucose Independent of Age in Patients with Type 2 Diabetes
Author String M Rendell, SG Chrysan, A Emser, M von Eynatten, S Patel, A Trujillo, H-J Woerle
Creighton Diabetes Center, Omaha, NE; Oklahoma Cardiovascular & Hypertension Center, Oklahoma City, OK; Boehringer Ingelheim Pharma GmbH & Co, Ingelheim, Germany; Boehringer Ingelheim, Bracknell, UK; Boehringer Ingelheim, Ridgefield, CT
Body **Background:** Previous studies have identified patient age as an underlying cause for heterogeneity of response to treatment with antidiabetic agents. We analyzed pooled data from more than 2,000 patients treated with linagliptin, an investigational DPP-4 inhibitor, to evaluate whether patient age had an effect on the safety and efficacy of linagliptin.
Methods: Identical endpoints, dosing, and a large cohort size (N=2,258) in 3 randomized, double-blinded, placebo-controlled studies of linagliptin facilitate subgroup analyses using a pooled dataset. The primary efficacy outcome in all 3 studies was mean change from baseline HbA1c at 24 weeks. The incidence of any adverse event (AE) was recorded. Patients were categorized by age: [le]50 (n=550), 51-64 (n=1134), 65-74 (n=465), and [ge]75 years (n=75).
Results: Mean baseline BMI was 29.0±4.9kg/m². Patients were mostly White (58%) and Asian (42%), with 50.4% female. Overall, 57% of patients had a mean disease duration of >5 years. Mean baseline HbA1c (±SD) and HOMA-IR were 8.1% (±0.8) and 4.7±5.3 mU/L[bulld]mmol/L. Mean age within each subgroup was 44±5, 58±4, 69±3, and 77±1 years. In the pooled analysis of efficacy, linagliptin showed significant reductions in HbA1c levels in all 4 age groups, with no effect of age on linagliptin efficacy (P=0.48) and no age-treatment interaction (P=0.65). The mean adjusted placebo-corrected changes in HbA1c from baseline (±SE) were -0.58±0.08 (age [le]50 years), -0.68±0.06 (age 51 to 64), -0.60±0.09 (age 65 to 75), and -0.77±0.24 (age [ge]75). Overall incidence of AEs in linagliptin-treated patients were similar to or less than placebo for all age groups. Rates of serious AEs were 2.5, 3.1, 4.3, and 3.3% for linagliptin-treated patients in each age group, versus 3.7, 2.6, 4.8, and 6.7% for placebo. Hypoglycemia incidence for each respective age category was 8.3, 11.8, 12.1, and 28.3% in the pooled treatment group, compared with rates of 4.3, 7.2, 12.9, and 20% for placebo. However, the incidence of hypoglycemia was <1% in studies using linagliptin as monotherapy or as add-on to metformin (MET). Increased frequency (>1%) of hypoglycemia only occurred in the third study, where background therapy was MET + sulfonylurea. No linagliptin-related safety concerns were identified.
Conclusions: Linagliptin safety and efficacy did not differ between the age groups studied. Linagliptin was effective for the treatment of T2DM in all age groups (including elderly), with a safety profile comparable to placebo.

Sources of Research Support: Boehringer Ingelheim.

Disclosures: AE: Employee, Boehringer Ingelheim. MvE: Employee, Boehringer Ingelheim. SP: Employee, Boehringer Ingelheim. AT: Employee, Boehringer Ingelheim. H-JW: Employee, Boehringer Ingelheim. Nothing to Disclose: MR, SGC

sort_order 2567
Pub # P3-498
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title Subcutaneous Administration of Exenatide Increases Nocturnal Cortisol Levels in Saliva of Type 2 Diabetic Patients
Author String W Guanipa-Sierra, I Alonso-Troncoso, V Munos-Leira, JR Villar, M Lorenzo, A Leon-Justel, MdR Infantes-Fontan, Y Castro-Laque, A Leal-Cerro, PF Catalina, F Mallo
Faculty of Biology, University of Vigo, Vigo, Spain; Hospital Montecelo, Pontevedra, Spain; Biomedicine Institute of Seville CSIC, Junta de Andalucia, University of Seville and University Hospital Virgen del Rocio, Seville, Spain
Body Insulinotropic peptides (GLP-1 & Exendin-4) have been shown to markedly increase circulating levels of glucocorticoids in Type 1 diabetes mellitus 1 and 2 rodent models, as well as in healthy and DM1 humans (GLP-1). Synthetic Exendin-4 is already in use for treatment of DM2 and therefore, raises the question of whether glucocorticoids production might be affected in these patients. Here, we addressed this question studying the responses of the Hypothalamus-Pituitary-Adrenal axis to s.c. administration of EXD (5[μg] twice daily for seven days) in DM2 patients. To this end, cortisol levels in saliva were measured in DM2 patients before starting EXD administration and the 1st (N1), 2nd (N2) and 7th (N7) day after administering the first injection. As an additional control group, healthy controls receiving no drug were also included in the study. 8 DM2 patients and 8 sex and age matched controls were included in the study, after obtaining written consent. Saliva samples were obtained at 12.00 pm, 8.00 am and 12.00 am, the day before starting the EXD treatment, and at N1, N2 and N7. EXD was administered as prescribed by protocol indication 5 [micro]g twice daily. Both groups showed similar circadian variations for cortisol levels in saliva. However, DM2 patients before EXD treatment showed higher salivary cortisol levels than healthy controls at all studied time points: 12:00 P.M. (p<0.05), 08:00 A.M. (p<0.001) and 12:00 A.M. (p<0.05). The first injection of EXD (8:05 am) increased salivary cortisol levels at 12:00 P.M. in DM2 patients, compared with the values obtained the night before (p<0.01). Salivary cortisol increased 24.56% the first night (N1), and 13.20% the second night (N2), returning to baseline the seventh night (N7). In healthy volunteers, no changes in cortisol levels at N1 (0.04%) were found but a significant decrease both at N2 (-17.46% and N7 (-10.86%), were observed. Our data show that synthetic exendin-4 increases circulating cortisol levels in DM2 patients for at least 48 hours, compared to levels obtained before EXD administration in the patients as well as levels observed in healthy controls, despite the higher basal saliva cortisol levels already present in DM2 patients. Our results are in agreement with previous studies performed in animal models (Ex4) and DM1 patients (GLP-1). Our results suggest that GLP-1/Ex4 family peptides have a significant role, although transitory, in the regulation of the HPA axis in DM2.

(1) Gil-Lozano M et al., Endocrinology 2010; 151:2629

Nothing to Disclose: WG-S, IA-T, VM-L, JRV, ML, AL-J, MdRI-F, YC-L, AL-C, PFC, FM

sort_order 2568
Pub # P3-499
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title An Outpatient-Based Clinical Program for Diabetes Prevention: Three Years' Experience at Mayo Clinic Arizona
Author String CM Swanson, S Bersoux, MH Larson, RT Aponte-Furlow, SS Flatten, CL Olsen, PM Verona, CB Cook
Mayo Clinic Arizona, Scottsdale, AZ; Mayo Clinic Arizona, Scottsdale, AZ; Mayo Clinic Arizona, Scottsdale, AZ; Mayo Clinic Arizona, Scottsdale, AZ; Mayo Clinic Arizona, Scottsdale, AZ
Body Lifestyle changes delay onset of type 2 diabetes, and at risk persons should have access to outpatient diabetes prevention programs. Only limited data exist about the success of a diabetes prevention program in an outpatient clinic setting. The Diet-Exercise-Activity-Lifestyle (DEAL) program was established for patients with prediabetes and consists of 4 weeks of nutrition classes, exercise counseling, and medical follow-up visits at 6 and 12 months (1). To evaluate program effectiveness, changes in weight, fasting glucose, and 2-hr glucose following a 75 gm oral glucose tolerance test were determined in patients enrolling in DEAL between January 2007 and August 2009. Mean age of 221 participants at enrollment was 62 years, weight 87.4 kg, BMI 31.2 kg/m², fasting glucose 109 mg/dL and 2-hr glucose 138 mg/dL; 67% were women, 89% white; 56% had isolated impaired fasting glucose, 5% had only impaired glucose tolerance, and 39% had both. Over 80% of participants attended all nutrition classes, 62% kept their 6 month medical follow-up appointment but only 45% kept their 12 month visit. Among those with 6 month follow-up 59% had lower fasting glucose levels (decreasing from 110 mg/L to 103 mg/dL, P < .0001) and 59% had improvement in 2-hr glucose values (decreasing from 146 mg/dL to 115 mg/dL, P < .0001); 7% developed diabetes. Additionally, 61% of participants lost weight at 6 months (decreasing from 87.7 kg to 84.2 kg, P < .0001) with average reduction of 4.0%. Patients with lower fasting glucose, 2-hr glucose, and weight at 6 months had significantly higher values at time of enrollment compared to persons who did not show improvement. There was no significant difference in the number of nutrition classes attended between persons who did and did not show improvement at 6 months. At 12 months (evaluated through September 2010 for patients enrolling in August 2009) there was no significant change in weight, fasting glucose, or 2-hr glucose compared to 6 months. Our analysis shows that most DEAL participants were able to lower their glucose levels and weight, but some did not benefit and factors underlying non-response need to be identified. As there was no additional improvement in outcomes between 6 and 12 months, changing medical follow-up visits to 3 and 6 months may be reasonable and could possibly reduce attrition with a more compressed time frame. Ongoing experience and analysis should permit revisions to DEAL to assure maximal benefit to participants.

Bersoux S et. al. An Outpatient-Based Clinical Program for Type 2 Diabetes Prevention. Endocrine Practice. 2010;16:21-29.

Nothing to Disclose: CMS, SB, MHL, RTA-F, SSF, CLO, PMV, CBC

sort_order 2569
Pub # P3-500
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title The Relationship between Serum Vitamin D and Hemoglobin A1c Levels in Adolescents with Type 1 and Type 2 Diabetes
Author String BU Nwosu, L Maranda, Z Stavre, KA Cullen, L Greenman, MM Lee
University of Massachusetts Medical School, Worcester, MA
Body **Objective:** The relationship between hemoglobin A1c (HbA1c) and vitamin D in children and adolescents with type 1 (T1DM) and type 2 (T2DM) diabetes is not well known. Our aim was to examine the relationship between vitamin D and hemoglobin A1C in patients with both type 1 and type 2 diabetes.
Design and Patients: A retrospective analysis of the clinical and biochemical profiles of 81 adolescents with T1DM and 25 adolescents with T2DM of > 6 month duration of ages 11-19 years who underwent simultaneous HbA1c and 25-hydroxyvitamin D (25OHD) evaluation at a tertiary care institution. We further analyzed the HbA1c levels drawn 3 months before the simultaneous 25OHD and HbA1c estimation. Multivariate linear regression was used to analyze the association after accounting for potential confounders. Comparisons between groups were made using two-tailed Student's t test.
Results: Thirty percent of our T1DM subjects had vitamin D deficiency (25 OHD < 20 ng/mL), and forty-four percent had vitamin D insufficiency (25 OHD of 20 - 29 ng/mL). Seventy-six percent of T2DM subjects had vitamin D deficiency and 33% had vitamin D insufficiency. Multiple regression analyses confirmed an independent inverse relationship between HbA1c and 25OHD concentration in the T2DM subjects ($p=0.035$; $r=-0.423$), but not in the T1DM subjects ($p=0.615$, $r=-0.057$). The relationship found in the T2DM subjects remained significant when adjusted for BMI and age ($p=0.041$; $r=-0.203$), but became non-significant when BMI, age, and sex were adjusted together ($p=0.060$, $r=-0.204$).
Conclusion: The data support the hypothesis that vitamin D deficiency correlates negatively with glycemic control in patients with T2DM, but not in patients with T1DM. This finding could be due to the prevalent insulin resistance in T2DM, but not in T1DM.
Nothing to Disclose: BUN, LM, ZS, KAC, LG, MML

sort_order 2570
Pub # P3-501
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title Time Trends in Age of Onset of Type 1 Diabetes Mellitus throughout the Last Thirty Years in Central West Region, Brazil
Author String ACA Bezerra, AA Amato, AA Lofrano-Porto, NM Alves, MS Fleury, ME Barbosa, EV Marques, AL Carvalho-Furtado, LCG Castro
University of Brasilia, Brasilia, Brazil; University of Brasilia, Brasilia, Brazil; Distrito Federal Secretary of State for Health, Brasilia, Brazil
Body **Background:** Epidemiological studies have reported trends toward decreasing the age of onset of type 1 diabetes mellitus (*T1DM*) throughout the last decades in many countries, having the higher incidence rates being observed among the group under 5 years of age.
Aim: To study the age of onset of *T1DM* and its distribution throughout the last thirty years among patients followed at medical units in Brasilia-DF, Midwest Brazil.
Patients and Methods: Retrospective multicenter study of the records of 529 patients (273 females; 51.6%) with *T1DM* followed at hospitals and medical units in Brasilia and who have had the diagnosis of *T1DM* between the years 1980 and 2010.
Results: The current ages of the patients ranges from 1.1 to 53.8 years. The whole group's mean age of onset of *T1DM* throughout the last 3 decades was 8.9 ± 6.1 years (from 0.3 to 40 years); with no statistical difference between sexes ($p = 0.25$). It was observed a bimodal distribution of the age of onset, being the higher peak at 9 years and a second peak between 2 and 4 years of age. After grouping the patients according to the decades in which *T1DM* was diagnosed, the mean age of onset and the proportion of patients who became diabetic younger than 5 years of age and between 5 and 10 years, were, respectively: decade of 1981-1990 ($n = 51$): 11.9 ± 8.6 years, 29.4%, 19.6%; 1991-2000 ($n = 104$): 7.1 ± 5.2 years, 41.4%, 29.8%; 2001-2010 ($n = 374$): 7.9 ± 4.2 years, 27.8%, 34.2%. The difference among all those proportions were statistically significant ($p < 0.05$). The proportion of girls, but not boys, under 5 years of age becoming diabetic significantly increased from the 1980 to 1990 decade ($p = 0.0003$), but this proportion remained stable for both sexes from 1990 to 2000 decade ($p = 0.13$).
Conclusions: For this population, it was observed a new peak of age of onset of *T1DM* between 2 and 4 years throughout the last 3 decades. There was a significant decrease in the age of onset of *T1DM* from 1980 to 1990 decade ($p = 0.0005$), but it remained stable from 1990 to 2000 decade ($p = 0.21$). The 5 to 10 years of age group was the one who experienced a continuous, the higher and a significant increase in the number of patients becoming diabetic since 1980.

Nothing to Disclose: ACAB, AAA, AAL-P, NMA, MSF, MEB, EVM, ALC-F, LCGC

sort_order 2571
Pub # P3-502
Session Information POSTER SESSION: CLINICAL - Diabetes: Observations, Interventions & Trials (1:30 PM-3:30 PM)
Title Inter-Individual Variations in Response to Pioglitazone Monotherapy among Asian Indian T2DM Patients
Author String P Mathur, SK Mathur, P Punjabi, S Lalwani, M Mathur
SMS Medical College, Jaipur, India; SMS Medical College, Jaipur, India; SMS Medical College, Jaipur, India; Birla Institute of Scientific Research, Jaipur, India
Body
AIM
To study inter-individual variations in response to pioglitazone mono-therapy among newly diagnosed Asian Indian T2DM patients and its relation with some patient characteristics.
SUBJECTS AND METHODS
One hundred and four newly diagnosed type-2 diabetes mellitus patients (age 48 ± 9 yrs, M: F ratio 17:5) were treated with Pioglitazone 30 mg PO once daily for at least 6 months. Inclusion criteria were BMI < 30 and no contraindication to the drug. Relationship between its glucose lowering effect and following patient characteristics was studied: Age, BMI, W:H ratio, Fasting plasma glucose (FPG), post meal plasma glucose (PPG), triglyceride, HbA1c, HOMA-R and HOMA- β at the beginning of treatment.
RESULTS
Total 88 patients completed 6 month follow up, 14 were lost to follow up and two died of unrelated diseases. Mean reduction in FPG, PPG and HbA1c were 80.98 mg/dl, 123.67 mg/dl, 2.54% respectively. American Diabetes Association's glucose control targets (Fasting glucose < 130 mg/dl, & HbA1c < 7 % was achieved in 61(69.32%) and 48(54.55) subjects respectively. There was wide inter-individual variation in response (coefficient of variance was 68.80%, 97.80%, and 81.36% respectively for FPG, PPG and HbA1c). 23(26.13%) patients were primary non-responders (<20% fall in FPG) while 25(28.41%), 31(35.23%), 9(10.23%) respectively had fall in range of 20-40, 40-60, >60% in FPG.
No correlation was found between the glycemic response to pioglitazone and studied patient characteristics (Age, Waist: Hip, BMI, triglycerides, HOMA-B, HOMA-R). Only significant positive correlation was found between the FPG at the beginning of treatment and fall in FPG ($p=0.0052$), and fall in HbA1c ($p=0.0013$). There was no statistically significant difference in the patient characteristics between responders and non-responders. However responders had higher FPG at the beginning of treatment.
CONCLUSIONS
Though Pioglitazone is an effective anti diabetic drug for Asian Indian T2DM patients, but there is wide inter-individual variation in response and about one quarter of the patients were primary non responders. Also the non-responders could not be identified on the basis of patient characteristics studied.

Nothing to Disclose: PM, SKM, PP, SL, MM

sort_order 2572
Pub # P3-503
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title Conditional Deletion of Glucocorticoid Receptor Using Neurogenin 3-Cre Results in a Cushing Disease-Like Syndrome in Mice
Author String RR Banerjee, KY Liu, X Gu, SK Kim
Stanford University, Stanford, CA; Stanford University, Stanford, CA

Body Glucocorticoid receptors (GR) within the brain are critical in coordinating and regulating systemic endocrine stress responses. Dysfunctional GR signaling underlies Cushing's disease, when failure of negative feedback inhibition results in high ACTH production despite elevated cortisol. Recent studies suggest GR activity in the CNS regulates different aspects of the behavioral and metabolic stress response, but regional action of brain GR remains poorly understood (1). To create mice with a conditional deletion of GR in the brain, we intercrossed Ngn3-Cre and [floxed] GR mice (NGRKO) (2, 3). Neurogenin 3 (Ngn3) is a transcription factor widely studied for its role in endocrine fate specification in pancreas and intestine. Recent studies have shown ngn3 is also highly expressed in the brain (4, 5). Lineage tracing experiments demonstrated *ngn3* expression in the hypothalamus, temporal cortex, amygdala and brainstem. Immunohistochemical analysis confirmed NGRKO mice lack GR in these regions. Compared to littermate controls, NGRKO mice had a three-fold increase in corticosterone and a two-fold increase in ACTH, suggestive of Cushing's disease. NGRKO mice were normal in length, but showed an approximately 10% decrease in weight. Furthermore, NGRKO mice exhibited a significant 10-15% relative hyperglycemia in both random fed and fasted states from weaning through adulthood, as well as moderate glucose intolerance. A 60kcal% high-fat diet (HFD) exacerbated the random-fed hyperglycemia but not basal glucose or weight differences. HFD-NGRKO mice had two-fold higher serum insulin but unchanged glucagon levels. Surprisingly, NGRKO mice had similar insulin sensitivity as controls as assessed by insulin tolerance testing. HFD-NGRKO mice had significantly enlarged, fatty livers with a two-fold increase in triglyceride content versus controls. By contrast, pancreatic islets appeared grossly normal in preliminary studies. Together, these metabolic abnormalities are consistent with many features of altered glucose homeostasis seen in Cushing's disease. We propose NGRKO mice represent a novel model of a Cushing's Disease-like Syndrome. Ongoing studies will further elucidate the CNS role of GR signaling and expand our understanding of GR regulation of metabolism.

- (1) Kobler, BJ et al., Brain Res. 2009; 1293:85-90
- (2) Schonhoff SE et al., Dev Biol. 2004; 270(2):443-54
- (3) Brewer JA et al., Nat Med. 2003; 9(10):1318-22
- (4) Song J, et al., Genesis 2010; 48: 628-634
- (5) Simon-Arces et al., J Comp Neurol. 2010; 518:1814-1824

Sources of Research Support: RRB was supported as a Postdoctoral Fellow on the Stanford Endocrinology NIH Training Grant T5-T32-DK07217. SKK is supported by grants from the NIH, JDRF, and HHMI.

Nothing to Disclose: RRB, KYL, XG, SKK

sort_order

2573

Pub #

P3-504

Session Information

POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)

Title

De Novo Expression of Urocortin 1 (Ucn1) in Acinar Cells and Its Effect on Pancreatic Inflammation Is Mediated Via Corticotropin-Releasing Factor (CRF) Receptor 2

Author String

E Kubat, EF Grady, V Lyo, S Mahajan, M Liao, KS Kirkwood, A Bhargava
University of California San Francisco, San Francisco, CA

Body

Ucn1 and CRF mediate their effect on inflammation via two receptors: CRF₁ and CRF₂. Activation of the two receptors results in context-dependent pro- or anti-inflammatory actions. Patients with IBD have a higher frequency of pancreatitis, however the role of the CRF, Ucn1 and their receptors in pancreatitis is unexplored. Acute pancreatitis was induced with 6 hourly subcutaneous injections of cerulein in wild-type (WT), CRF₂ knockout (KO) or heterotype (HT) mice. In control mice, Ucn1 immunoreactivity (Ucn1-IR) was prominently expressed in islet cells, pancreatic duct cells, and endothelial cells, but undetectable in acinar cells of control. After induction of acute pancreatitis, *de novo* Ucn1-IR was detected in acinar cells of mice with pancreatitis that co-localized with cathepsin, but not LAMP1, in a secretory compartment. As expected, cerulein-treated animals had increased histologic damage scores compared with saline controls. Interestingly, the damage score was 2-fold higher in HT and astressin2B (A2B)-treated mice. Cerulein increased MPO activity and pancreatic edema in WT mice. Serum amylase activity was elevated compared to controls and similar among all cerulein-treated groups. To elucidate mechanisms of Ucn1 actions, rat pancreatic acinar cells, AR42J, were incubated with either 10⁻⁷M cerulein or vehicle for 1 hr. In untreated acinar AR42J cells, RT-PCR showed very low levels of Ucn1 and high levels of CRF. Stimulation of AR42J cells with CRF or Ucn1 resulted in a dose-dependent Ca²⁺ response. Treatment with 100nM CRF resulted in a 1.6 fold higher initial Ca²⁺ peak than Ucn1 treatment. Cerulein-treatment resulted in marked induction of both Ucn1 and CRF mRNA. CRF stimulation after cerulein treatment caused 20-30% decrease in [Ca²⁺]_i response, whereas Ucn1-stimulated [Ca²⁺]_i responses were decreased by 80-90%. We next inhibited CRF1 and CRF2 receptor function by pre-treatment with receptor-specific antagonists. Stimulation of A2B pre-treated AR42J cells with Ucn1 after resulted in 62% decrease in [Ca²⁺]_i response, whereas CRF1 (CP15426) inhibition has no effect on Ucn1-stimulated [Ca²⁺]_i response and remained unchanged from control. Our data suggest that during inflammation, acinar cells maintain their responses to CRF, but their response to Ucn1 is markedly attenuated probably due to *de novo* induction of Ucn1. Autocrine response of Ucn1 in pancreatic injury may be key and Ucn1 and CRF₂ may be potential therapeutic targets.

Sources of Research Support: NIH DK080787 (AB), DK080787-02S1 (EFG & AB) & T32 DK07573-22.

Nothing to Disclose: EK, EFG, VL, SM, ML, KSK, AB

sort_order 2574
Pub # P3-505
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title Modulatory Effect of Bell GR Gene Polymorphism on the Phenotype of Obesity in Cushing Disease
Author String RPP Moreira, TASS Bachega, MC Machado, MD Bronstein, AM Lerario, BB Mendonca, MCBV Fragoso
Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil; Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil
Body Cushing's disease presents wide phenotypic variability with different severities of obesity and different prevalence of diabetes and hypertension. The disease is determined by glucocorticoid (GC) exposure as well as by peripheral GC sensitivity, mediated by the glucocorticoid receptor (GR). Several GR gene polymorphisms are associated with alterations in GC sensitivity and some of them are associated with increased risk to adverse metabolic profile in the general population. However, the influence of GR polymorphisms on clinical manifestations of Cushing's disease has not been evaluated. Objectives: To analyze the association of GR gene variants with severity of obesity, diabetes and hypertension prevalence in Cushing[acute]s disease. Patients and Methods: 67 patients (54 fem) with mean age of 25.2 ± 5.2 yrs, diagnosed by at least two increased 24-h urinary total cortisol (FU) levels and serum cortisol > 2 [micro]g/dL after 1-mg overnight dexamethasone suppression test. All patients had measured ACTH levels (79.1 ± 69 pg/mL). Histopathological analysis after transphenoidal surgery, confirmed ACTH-producing pituitary adenoma. The p.A3669G (which decreases GC sensitivity) and Bell (which increases GC sensitivity) variants were screened by sequencing and allele-specific-PCR, respectively. Association of clinical features with GR alleles were analyzed by ANOVA, Chi-square and t-test. Results: All variants were in Hardy-Weinberg equilibrium and the Bell and p.A3669G alleles were found in 36% and 14%, respectively. There were no differences in the duration of disease nor in FU levels between patients carrying Bell and p.A3669G alleles ($P > 0.05$). The mean BMI of A3669G allele carriers was 34.7 ± 7 kg/m² and of wild type (wt) carriers was 28.3 ± 4.2 kg/m² ($P = 0.02$). We also identified a significant higher BMI in Bell allele carriers in comparison with wild type carriers (34.4 ± 6 kg/m² versus 28.3 ± 4.2 kg/m², $P = 0.004$). In Bell, A3669G and wt carrier groups, the prevalence of diabetes was 25%, 10% and 28%, respectively ($P > 0.05$), and the prevalence of hypertension was 59%, 80% and 57%, respectively ($P > 0.05$). Conclusion: for the first time, we identified a modulatory effect of GR gene polymorphisms on the phenotype of obesity in Cushing's disease, since their carriers presented a significant higher BMI.

Sources of Research Support: FAPESP # 09/54238-2 and 09/54238-2, CNPq # 305117/2009-2.

Nothing to Disclose: RPPM, TASSB, MCM, MDB, AML, BBM, MCBVF

sort_order 2575
Pub # P3-506
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title Activation of PKC β by High-Glucose Conditions Enhances Mineralocorticoid Receptor Expression and Its Transcriptional Activity
Author String T Hayashi, H Shibata, I Kurihara, A Murai-Takeda, Y Mitsuishi, Y Motosugi, R Jo, T Ohyama, H Itoh
School of Medicine, Keio University, Tokyo, Japan
Body [Aim] Diabetes mellitus is often associated with resistant hypertension and administration of mineralocorticoid receptor(MR) antagonist is shown to protect renal function in diabetic nephropathy, indicating pathological MR activation in diabetes even with normal aldosterone level. It is also believed that chronic activation of protein kinase C (PKC) by hyperglycemia play crucial roles in the development of both micro- and macrovascular complications in diabetic patients. We therefore hypothesized that activation of PKC by hyperglycemia has a crosstalk with MR activation in diabetes. [Methods] The MR transcriptional activities were investigated in reporter-based transient transfection assays and real time RT-PCR in stably MR-expressing 293-MR cells. Levels of expression of MR protein were examined with western blot analysis. [Results] 1) The MR transactivation is enhanced by PKC agonist as well as high glucose conditions; Transient transfection in COS-7 cells showed that treatment with 100 pM aldosterone increased transactivation of a MR-responsive reporter construct by 100-fold. Treatment with phorbol 12-myristate 13-acetate (PMA), a PKC agonist, enhanced aldosterone-induced MR transactivation by 2-3 fold. The enhanced MR activities were also observed in endogenous MR target gene mRNA, SGK-1 and PAI-1. Similarly, high glucose concentration (30mM) increased MR transactivation by 3-fold compared with normal glucose concentration (5.6mM). 2) PKC agonist and high glucose conditions increase level of expression of MR; Interestingly, treatment with PMA increased levels of expression of protein of MR in a dose- and time-dependent manner. The increase in protein of MR was attenuated by conventional PKC antagonist. Similarly, high glucose (30mM) increased levels of protein of MR by 1.625-fold. 3) Role of endogenous PKC in MR expression and its transactivation; Introduction of siRNA for PKC beta, but not PKC alpha attenuated MR transactivation. In parallel with MR transcriptional activities, levels of expression of protein of MR were decreased by introduction of siRNA for PKC beta, but not PKC alpha. [Conclusion] These data showed that activation of PKC beta by high glucose conditions increases MR expression and its transcriptional activity in cultured cells. These data suggest that pathological MR activation by enhanced PKC beta signaling is associated with microangiopathy of diabetes mellitus.
Nothing to Disclose: TH, HS, IK, AM-T, YM, YM, RJ, TO, HI

sort_order 2576
Pub # P3-507
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title Association of Variants in GABA(A) Receptor Subunit Gene Cluster on Chromosome 4 with Hypothalamic-Pituitary-Adrenal (HPA) Axis Response to Stress
Author String M Uhart, ME McCaul, EM Weerts, N Li, HR Kranzler, GS Wand
The Johns Hopkins University School of Medicine, Baltimore, MD; The Johns Hopkins University School of Medicine, Baltimore, MD; Cedars-Sinai Medical Center, Los Angeles, CA; University of Pennsylvania School of Medicine, Philadelphia, PA
Body Individual variability in the hypothalamic-pituitary-adrenal (HPA) axis response to stress, a risk factor for metabolic disorders (e.g., metabolic syndrome) and neuropsychiatric illness (e.g., substance use disorders), has a strong genetic component. The neurotransmitter GABA (γ -aminobutyric acid) inhibits hypothalamic CRH activity and thus HPA axis function. Therefore, genes encoding GABA-related proteins are candidates to influence the HPA axis response to stress. Human GABA_A receptor subunits are encoded by distinct genes, including the α -2 (*GABRA2*) and γ -1 (*GABRG1*) isoforms. We sought to determine the influences on the response to psychosocial stress of single tagging nucleotide polymorphisms (SNPs) previously associated with alcohol dependence. Methods: 280 healthy subjects with no history of medical or psychiatric illness [41% males, 79% Caucasian, 23.1 yrs (SD=3.4)] participated in the Trier Social Stress Test (TSST), which consisted of 5 min of public speaking followed by 5 min of mental arithmetic. Three baseline and five post-TSST blood samples were drawn. Genotype effects were analyzed using linear mixed effects models. Linear regression models were applied to area under the curve (AUC) outcomes. Ancestry was estimated by the Structure 2.3.3 software and was included as a covariate in the association analyses. Results: Longitudinal analysis showed a significant interaction between SNP rs279858 (*GABRA2*) and sex on the cortisol response to stress ($p=0.0038$). Women ($n=165$) with the minor allele had a lower cortisol response to the TSST than those homozygous for the common allele. Conversely, men ($n=115$) with the minor allele had a greater cortisol response to the TSST than those homozygous for the common allele. A significant interaction effect of SNP rs279858 with sex ($p=0.0346$) was also present for cortisol concentration AUC. Conclusion: Our results suggest that variation in the gene encoding the GABA_A α -2 subunit modulates the cortisol response to psychosocial stress and thus may influence susceptibility to stress-related disorders. Identification of specific genetic determinants of differences in the quality or magnitude of the response to stress may help to explain why some individuals are vulnerable to, or protected from, the deleterious effects of exposure to environmental stressors.

Sources of Research Support: NIH grants AA10158 (GSW), AA017466 (MU), MH076953 (GSW), AA013736 (HRK).

Nothing to Disclose: MU, MEM, EMW, NL, HRK, GSW

sort_order

2577

Pub #

P3-508

Session Information

POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)

Title

Glucocorticoids Rapidly Modulate NMDA Receptor Activity Via Multiple Signaling Pathways in Hippocampal Neurons

Author String

Y Zhang, H Sheng, J Qi, B Ma, X Ni
Second Military Medical University, Shanghai, China; Shanxi Medical University, Taiyuan, China

Body

Glucocorticoids (GCs) have been demonstrated to act through both genomic and nongenomic mechanisms. The present study demonstrated that corticosterone rapidly regulated the activity of N-methyl-D-aspartate (NMDA) receptors in cultured hippocampal neurons. The effect was maintained with corticosterone conjugated to bovine serum albumin and blocked by inhibition of G-protein activity with intracellular GDP-b-S application. Corticosterone stimulated the expression of GTP-bound G_s protein and cAMP production, and at meantime it activated phospholipase C_b (PLC b) and induced inositol-1, 4, 5-triphosphate (IP $_3$) production. Blocking PLC and the downstream cascades with PLC inhibitor, IP $_3$ receptor antagonist, Ca^{2+} chelator and protein kinase C inhibitors prevented the actions of corticosterone. Blocking adenylate cyclase and protein kinase A caused a decrease in NMDA-evoked currents. Further application of corticosterone potentiated the NMDA currents. Intracerebroventricular administration of corticosterone significantly suppressed LTP in the CA1 region of hippocampus within 30 min *in vivo*. Taken together, our results demonstrated that GCs act on a putative G-protein coupled receptor to modulate NMDA activity through multiple signaling pathways in hippocampal neurons. It is implicated that GCs can allow the brain to change its function within minutes.

Sources of Research Support: National Basic Research Program of China 2007CB512303; Natural Science Foundation of China 30900434; Technology Commission of Shanghai Municipals 09XD1405600 and 09ZR1439800.

Nothing to Disclose: YZ, HS, JQ, BM, XN

sort_order 2578
Pub # P3-509
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title Urocortin-Dependent Effects on Adrenal Structure and Function *In Vivo*
Author String A Hill, A Spyroglou, A Neufeld-Cohen, A Chen, F Beuschlein
Medical Clinic Innenstadt, LMU, Munich, Germany; Weizmann Institute of Science, Rehovot, Israel
Body Urocortin (Ucn) 1, 2, and 3 are members of the Corticotropin-Releasing Factor (CRF)-family and important modulators of stress responses, the control of anxiety, and their related disorders. In addition to the central nervous system, Ucns and CRFR are expressed in several peripheral tissues including the adrenal gland. Using knockout (KO) animals lacking Ucn individually or in combination we examined the potential role of the 3 different Ucns on the structure and function of the mouse adrenal gland. In H&E stained adrenals of age matched male animals cell size and number was quantified by counting nuclei per high-power-field (hpf). With PCNA staining and real-time PCR analysis of Cyclin D1, effects on proliferation were investigated. The expression levels of important genes of steroidogenesis such as StAR, Cyp11a1, Cyp11b1 and Cyp11b2 as well as Th and Pnmt, responsible for catecholamine synthesis, were measured by Real-Time PCR analysis.
An increased proliferation rate in the adrenals of Ucn1^{-/-}/Ucn2^{-/-}, and triple KO mice could be demonstrated by elevated Cyclin D1 expression (WT: 100±8.4% vs. Ucn1/Ucn2 dKO: 333.4±42.2%, vs. tripleKO: 272.6±14.3% P<0.001) and increased PCNA staining. A relative hypotrophy of the adrenal cortex could be shown in those two genotypes and, additionally, in Ucn2^{-/-} mice. Regarding steroidogenesis, no significant effects could be observed in single KO mice. In Ucn2^{-/-}/Ucn3^{-/-} double KO, mRNA levels of StAR were increased, but decreased in Ucn1^{-/-}/Ucn2^{-/-} and triple KO animals (WT: 100±19.8% vs. Ucn1/Ucn2 dKO: 28.1±9.0%, vs. triple KO 31.3±4.6%, P<0.05). Downregulation of Pnmt was seen in Ucn2^{-/-}, however, in Ucn2^{-/-}/Ucn3^{-/-} mice elevated levels of Th and Pnmt could be documented.
Taken together, these data demonstrated that double and triple UCN KO mice showed the most pronounced differences in adrenal structure and function in comparison to WT animals, suggesting that the lack of a single Ucn can be counterbalanced from the other two.
Nothing to Disclose: AH, AS, AN-C, AC, FB

sort_order

2579

Pub #

P3-510

Session Information

POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)

Title

Regulation of Corticotropin-Releasing Hormone (CRH) Expression in Human Carcinoid BON Cells by Stress Hormones

Author String

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VA Greater Los Angeles Healthcare System, Los Angeles, CA; UCLA, Los Angeles, CA; UCLA, Los Angeles, CA

Body

Background: CRH plays a key role in regulating stress responses. While CRH neurons in the hypothalamus of the HPA-axis are well characterized, the peripheral expression and function of CRH are less known. Whether human enterochromaffin (EC) cells possess similar stress-sensing property to provide local CRH is of clinical relevance in stress-related gastrointestinal (GI) disorders. **Aims:** This study was to determine: 1) if CRH and its related urocortin (Ucn) peptides are expressed and 2) how CRH and Ucn mRNA and peptides are regulated in response to stress hormones in human carcinoid BON-derived EC cell lines. **Methods:** A BON-4N cell line was isolated from a single colony grown on collagen-coated plate. This cloned BON-4N cells, with detectable CRH, were cultured in serum-containing DME/12 or in serum-free differentiation media for 7 days before treated with dexamethasone (Dex, 1-100 nM), 5-HT (0.1-10 [μ M]) and forskolin (Fsk, 1-100 [μ M]) for 30-60 min for hormone release, and 3-7 days for expression studies. BON-4N was also transfected with human neurogenin (NEUROG)-1 or NEUROG-3 (wild-type, R93L and R107S mutants) for 1-7 days to modify its growth and differentiation processes. CRH and urocortin transcripts were analyzed by RT-PCR and qPCR. ProCRH and CRH peptide were detected by immunocytochemistry or measure by western blot and RIA, respectively. **Results:** BON-4N cells differentially expressed multiple CRH mRNA transcripts in stimulated or differentiated state. Fsk (10-100 [μ M]) induced CRH and Ucn-1 mRNA increases by 2-5-fold, but reduced Ucn-2 and Ucn-3 expression. Dex at 10-100 nM, inhibited basal and stimulated CRH/Ucn-1 mRNA expression (>50 %). In contrast, 5-HT (> 1 [μ M]) increased CRH transcripts after 1-3 days but shown no or inhibitory effects after 7 days. NEUROG-3 induced significant CRH and Ucn-1, but not Ucn-2 expression after 4-7 days. However, NEUROG3 mutants or NEUROG1 did not show similar effects. Both ProCRH and CRH immunoreactivities were increased in Fsk-stimulated BON-4N cells. **Conclusion:** Human CRH gene expression is regulated by glucocorticoids, 5-HT and cAMP activator in BON-4N cells. Ectopic expression of NEUROG-3 changed the CRH/Ucn expression profile to a more differentiated EC cell type. Thus hormonally or transcriptionally induced BON-4N cells can be used to study the molecular mechanisms underlying CRH gene expression, synthesis and secretion similar to enteroendocrine EC cells under acute or chronic stress in the gut.

Nothing to Disclose: SVW, MCC, YT, MM, MGM, PY, HP, SS

sort_order 2580
Pub # P3-511
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title Basal AM Cortisol Levels as Well as AM/PM Cortisol Ratios Are Negatively Correlated with mRNA Expression of the Key Molecules for Inflammatory Reaction or Metabolic Activities in Fat Tissues of Normocortisolemic Obese Subjects
Author String MG Pavlatou, MC Skarulis, KC Vickers, AT Remaley, R Malek, S Varma, PW Gold, T Kino
Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD; National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, MD; National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD; National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD; National Institute of Mental Health, National Institutes of Health, Bethesda, MD
Body Glucocorticoids are secreted from the adrenal cortex into circulation in a circadian fashion and strongly influence fat tissue activity. Excess levels of serum cortisol and/or altered tissue sensitivity to glucocorticoids are associated with visceral obesity and development of metabolic syndrome. To examine molecule(s), which potentially mediate or alter glucocorticoid actions in fat tissues, we measured in subcutaneous fat mRNA expression of ~200 genes whose products are either responsive to glucocorticoids or regulate the transcriptional activity of the glucocorticoid receptor (GR) in cellular-based assay systems. We enrolled 26 healthy volunteers (10 women and 16 men), aged 34.4 ± 9.6 (mean \pm sem), with BMI ranging between 23.4 to 51.5 (31.1 ± 6.67 ; mean \pm sem) kg/m^2 who did not take prescribed medications or dietary and vitamin supplements. We subdivided the subjects into low normal (>5 but <9 [$\mu\text{g/dl}$]) intermediate (between 9-14) and high normal (>14 but <25) AM serum cortisol concentrations. We also divided them based on their AM/PM serum cortisol ratios into another 3 groups; low (<2.5), intermediate (>2.5 <4.5) and high (>4.5) ratios and compared mRNA levels between the low and high AM cortisol group and between the low-ratio and high-ratio group. The RT² Profile Custom PCR Arrays were used for simultaneously evaluating mRNA levels of ~186 genes indicated together with 3 control genes. We found that mRNA levels of RelA, p50 subunit of the nuclear factor of $[\kappa\text{B}]$ (NF $[\kappa\text{B}]$ 1), glycogen synthase kinase 3β (GSK- 3β) and $\alpha 1$ catalytic subunit of cAMP-activated protein kinase (PKAA1) were significantly reduced in the high cortisol group, while those of nicotinamide phosphoribosyltransferase (NAMPT) and fat mass and obesity-associated gene (FTO) were significantly lower in the low-ratio group. RelA, NF $[\kappa\text{B}]$ 1, GSK- 3β and PKAA1 are all implicated in the inflammatory reaction and energy sensing/expenditure, suggesting that a negative feedback system exists between the levels of basal cortisol and inflammatory as well as energy-organizing systems. Since levels of NAMPT and FTO have been implicated in the development of diabetes mellitus, our results suggest that reduced amplitude of cortisol circadian rhythm may contribute to the development of insulin resistance and overt diabetes mellitus frequently observed in obese subjects and associated with low-grade inflammation.

Nothing to Disclose: MGP, MCS, KCV, ATR, RM, SV, PWG, TK

sort_order 2581
Pub # P3-512
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title ACTH Induces Rapid Activation of Melanocortin Receptor Associated Protein (MRAP) during Adrenocortical Activation
Author String Y Liu, AG Coello, V Huang, F Spiga, S Lightman, G Aguilera
NICHD, Bethesda, MD; University of Bristol, Bristol, UK
Body Adrenocorticotrophic hormone (ACTH) stimulates the secretion of glucocorticoids by acting upon melanocortin type 2 receptors (MC2R) located in the adrenal zona fasciculata. However, translocation of MC2R from the endoplasmic reticulum to its active state in the cell membrane requires its interaction with the melanocortin receptor associated protein (MRAP). To determine whether adrenocortical activation during stress involves regulation of MRAP, we examined the effects of restraint stress and ACTH injection on HPA axis activity, MC2R mRNA, and the levels of MRAP primary transcript (hnRNA) and mRNA. Blood levels of ACTH and corticosterone showed peaks at 15 min and 1 hour restraint, respectively, and both return to basal levels by 2 hours. Real time PCR analysis of MC2R mRNA levels showed a progressive decrease up to 2h, and returned near basal levels by 4h after restraint. Conversely, there were rapid increases in MRAP hnRNA and mRNA levels, with peaks at 15 min and 1h, respectively. Similar changes in MC2R mRNA and MRAP hnRNA and mRNA levels were observed after a single injection of ACTH (4ng) in methylprednisolone-suppressed rats, suggesting that the effects of stress are mediated by ACTH. Studies in collagenase dispersed rats adrenal fasciculata cells revealed a dose dependent effect of ACTH on MRAP hnRNA levels with an ED₅₀ of about 0.1nM. Using 10nM ACTH, the maximal stimulation was at 30 min and levels remained elevated up to 2h. The PKA inhibitor, H89, prevented the stimulatory effect of all ACTH concentrations on MRAP hnRNA while the MAP kinase inhibitor, UO126 inhibited only the effect of low concentrations of ACTH. The data show rapid changes in MRAP transcription during stress or ACTH exposure. This effect is mediate by ACTH in a cyclic AMP and PKA-dependent manner. The rapid and transient increases in MRAP transcription during adrenal fasciculata activation suggest that regulation of MRAP levels plays an important role controlling ACTH receptor activity in the adrenals.

Sources of Research Support: Intramural Research program, NICHD.

Nothing to Disclose: YL, AGC, VH, FS, SL, GA

sort_order 2582
Pub # P3-513
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title ACTH Antagonist: The Activation of Human Melanocortin 2 Receptors Expressed in CHO Cells by ACTH(1-24) Can Be Blocked by Co-Incubation with ACTH(15-24)
Author String L Liang, JK Angleson, RM Does
University of Denver, Denver, CO
Body The overproduction of ACTH(1-39) by the anterior pituitary gland, as a result of Cushing's Syndrome, leads to the over-stimulation of melanocortin 2 receptors (MC2R) on adrenal cortical cells and the subsequent overproduction of cortisol. One strategy for disrupting this cascade would be to block the activation of MC2R by introducing an ACTH antagonist. From previous studies it is known that a) all melanocortin peptides activate melanocortin receptors via the HFRW motif present near the N-terminal of these peptides, b) α -MSH (NAc-SYSEHFRWGKPV-NH₂) has the HFRW motif but cannot activate MC2R, and c) ACTH(1-24) [SYSEHFRWGKPVGKKRRPVKVP] is as potent an activator of MC2R as ACTH(1-39). Collectively these data point to the KRRRPVKVP region in ACTH as a second site involved in the activation of MC2R. To test this hypothesis a human MC2R gene construct was transiently co-transfected with a mouse MRAP1 gene into CHO cells. Two days later transfected CHO cells were incubated with either ACTH(1-24) or analogs of ACTH(1-24) at concentrations ranging from 10^{-6} to 10^{-12} M. After a 15 minute incubation a direct cAMP EIA kit (Assay Designs Ann Arbor, MI) was used to measure cAMP in the CHO cells. While ACTH(1-24) produced a robust standard curve, the analog SYSEHFRWGKPVGAAAAVKVP was 1000 fold less potent. Although these data indicated a role for the KRRRP motif in the activation of the receptor, the KRRRPVKVP analog when incubated alone did not activate hMC2R. However, when concentrations of ACTH(1-24) ranging from 10^{-6} to 10^{-12} M were co-incubated with either 10^{-6} or 10^{-7} M KRRRPVKVP there was complete blockage of hMC2R activation. Co-incubation of ACTH(1-24) with KRRRPVKVP at 10^{-8} M resulted in a $34 \pm 5\%$ drop in activation. By contrast the analog RRPVKVP (10^{-6} M) did not block the activation of hMC2R by ACTH(1-24). These results point to the importance of K¹⁵ and K¹⁶ for the activation of hMC2R. In addition the analog KRRRPAAAA (10^{-6} M) did not block the activation of hMC2R by ACTH(1-24). These results suggest that residues in the VKVP region may facilitate the binding of the KRRRPVKVP analog to a site on hMC2R. In conclusion, the analog ACTH(15-24) [KRRRPVKVP] can function as an ACTH(1-24) antagonist in our *in vitro* system, and this analog may be useful as an *in vivo* antagonist of ACTH activation of MC2R under conditions in which it would be desirable to lower the levels of circulating cortisol.

Sources of Research Support: NSF IOB 0516958.

Nothing to Disclose: LL, JKA, RMD

sort_order 2583
Pub # P3-514
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title Absence of Circadian Expression Patterns of Genes Involved in Apoptosis in Peripheral Blood Cells of Cushing Syndrome Patients before and after Surgical Cure
Author String A Hong, Q Wei, PJ Munson, Y Yang, N Raghavachari, M Skarulis, LK Nieman
National Institute of Child and Human Development, Bethesda, MD; NIH Center for Information Technology, Bethesda, MD; National Heart, Lung and Blood Institute, Bethesda, MD; National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD
Body **OBJECTIVE:** In Cushing's syndrome (CS), constitutively high cortisol levels eliminate normal circadian cortisol fluctuations. We postulated that the circadian rhythm of cortisol influences peripheral blood gene expression, and that the influence would be lost in CS patients before and immediately after surgical cure (high and low invariant cortisol).
METHODS: Blood was drawn every 4 hours from 0600h to 0200h from 7 overweight control women (age 47.9 yrs; 3 Black, 4 White) and CS patients into PAXgene tubes before RNA isolation. CS patients were studied before and within 7 days of surgical cure without glucocorticoid treatment. Samples were analyzed by the Human Genome U133 Plus 2.0 Array; controls and CS (5 women, 1 man; mean age 38.8 y; all White) were in separate batches. Data were analyzed to identify genes whose expression had a significant (<20%FDR) sine wave amplitude over 24hrs, and differed by > 1.4-fold between 1000h and 0200h. These genes were subjected to pathway analysis using GeneGo and Genomatix. RT-PCR was performed on genes involved in apoptosis, with material from additional CS patients.
RESULTS:
In controls, 859 probe sets (655 annotated genes) met the specified criteria; pathway analysis suggested that genes involved in DNA damage-induced apoptosis were significantly changed between 1000h and 0200h. At 1000h, PRF1 and GZMB were both up regulated 1.5-fold and BIRC3, JAK2, SET, LIG4 and HMGB1 (which have GREs) were down regulated 1.4 to 1.7-fold; together this would promote apoptosis or decrease DNA repair. RT-PCR validated decreased expression of HMGB1, BIRC3 and JAK2 at 1000h compared to 0200h.
No genes showed periodicity in CS before or after surgery. Compared to controls at 1000h, cell proliferation genes FBXW1 and CDK6 were up regulated ($p < 0.002$) in pre-surgery CS by 3.5- and 5.5-fold. At 1800h the circadian genes PER1, CAMK2A and RPS6KA2 ($p < 0.002$) were down regulated 2.2-, 3.0- and 2.8-fold vs controls.
CONCLUSION: Individuals with a normal circadian cortisol rhythm show circadian variation in gene expression. In healthy people, compared to 0200h, cell functions at 1000h promote apoptosis. CS patients lacked circadian variation in any genes, including circadian regulators; in comparison to controls, at 1000h they had increased expression of translation and cell cycle transition regulation gene suggesting cell proliferation. We speculate that loss of circadian gene expression may underlie some of the clinical features of CS.

Nothing to Disclose: AH, QW, PJM, YY, NR, MS, LKN

sort_order

2584

Pub #

P3-515

Session Information

POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)

Title

Pulsatile ACTH Is Crucial for Maintaining Normal Responsiveness of the Adrenal Cortex

Author String

F Spiga, J Walker, Y Kershaw, SL Lightman
University of Bristol, Bristol, UK

Body

The activity of the hypothalamic-pituitary-adrenal (HPA) axis is characterized by an ultradian pulsatile pattern of glucocorticoid secretion. Although there is increasing evidence for the importance of pulsatility in regulating glucocorticoid-responsive gene transcription (1), little is known about the mechanism of pulsatility in the adrenal cortex. We have recently shown that pulsatile ACTH is crucial for the maintenance of normal basal adrenal activity (2). To test the hypothesis that pulsatile ACTH is also necessary to maintain a normal state of adrenal responsiveness ACTH (4 ng/h) was infused in either as constant or pulsatile (5 min pulse once per hour) pattern for 24 h into rats whose HPA activity had been suppressed by oral methylprednisolone (MP). At the end of the 24 h infusion, rats were injected with a higher dose of ACTH (16 ng/0.1 ml, i.v.) to simulate the adrenal response to an acute stress. Blood samples were collected every 10 minutes for subsequent corticosterone assay using an automated blood sampling system.

MP-treated (control) rats infused with saline (both constant and pulsatile) had very low plasma CORT levels with no detectable pulses. Pulsatile, but not constant, ACTH infusion restored pulsatile CORT secretion in MP-treated rats. Furthermore, the CORT response to an acute i.v. injection of ACTH was no different between untreated control rats infused with saline and MP-treated rats infused with pulsatile ACTH (AUC: 1230±133 and 1322±257, respectively). In contrast MP-treated rats infused with constant ACTH or MP-treated rats infused with saline showed a much reduced response to ACTH (AUC: 356±128 and 567±137, respectively, P<0.01 compared to untreated control rats infused with saline).

Our data clearly show that pulsatile activation of the adrenal cortex by circulating ACTH is not only critical for basal secretion of CORT, but that it is also important for maintaining physiological responsiveness of the adrenal to the surges of ACTH observed during an acute stress. Since constant infusion of identical amounts of ACTH resulted in a reduced CORT response to this pulse of ACTH, episodic activation of adrenal MC2 receptors must provide a more effective signaling system for the activation of adrenocortical activity.

(1) Lightman and Conway-Campbell, *Nat Rev Neurosci*. 2010 Oct;11(10):710-8.

(2) Spiga F et al., *Endocrinology* 2011 (in press).

Sources of Research Support: Biotechnology and Biological Sciences Research Council (BBSRC, grant BB/H015779/1).

Nothing to Disclose: FS, JW, YK, SLL

sort_order 2585
Pub # P3-516
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title New and Easy Extraction Method for Urinary Free Cortisol Assessment
Author String D Mercan, N Ouali, M Lambert, RW Rivest
Unilabs, Coppet, Switzerland
Body Urinary cortisol assessment is important in the diagnostic of Cushing's disease and syndrome. Even though the sensitivity of different assays has been improved over years, the extraction method has remained more or less the same, either a dichloromethane or a solid phase extraction, with recuperations that are not always optimal.
New extraction techniques have been proposed¹. It is uses a liquid-liquid microextraction based on solidification of floating organic drop. It is based on the use of a few microliters of a specific extractant, 1-undecanol². This extractant has a lower density than water, low toxicity and a melting point between 13-15[deg]C. In this method, 10 to 25 ml of the extractant is mixed in a diluted urine sample, thus limiting possible urine interferences. The aqueous solution is mixed for a few minutes and then the droplet can be collected easily by placing the urine tube in a cold bath, thus solidifying the 1-undecanol. The frozen droplet is picked with a small spatula and allowed to dissolve at room temperature in the mobile phase to be analyzed on an HPLC system. The HPLC works with a biphenyl phase column and the mobile phase a methanol-water 46-54 mix.
The sensitivity is adequate to measure urinary concentrations lower than 40 nmol/l (less than 15 mg/l). The extraction recovery is 99-100%, and reproducible. Different situations have been tested to optimize the separation and measure of cortisol simultaneously with cortisone in the urine. Results are being correlated with a standard I-125 radioimmunoassay.
In conclusion, the method is simple, does not necessitate special equipment other than a cooled water bath and an HPLC system with standard solvents, and gives a response in 10 minutes, with an internal standard coming out in 18 minutes. All together, a result from start to end will take about 30 minutes, with new results coming out every 18 minutes in an automated injection system.

(1) Rezaee M et al., J Chromatogr A 2010; 1217:2342
(2) Wang Y-Y et al., Chin J Anal Chem. 2010; 38:1517

Nothing to Disclose: DM, NO, ML, RWR

sort_order

2586

Pub #

P3-517

Session Information

POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)

Title

Glucocorticoids Are Required for Maintenance of Core Body Temperature in Mice Kept in a Cold (4C) Environment

Author String

TA Samra, B Chaker, NS Datta, AB Samra
Wayne State University School of Medicine, Detroit, MI; WSU, Detroit, MI

Body

We have recently reported that urocortin 1 knockout (UCN1KO) mice have a more stable core body temperature as compared to WT mice during a 2h cold exposure at 4C. Corticotropin-releasing hormone (CRH), which binds to CRF receptors like UCN1, may also have a role in regulating core body temperature in mice. To study the role of CRH in thermoregulation, littermate female mice (8-20 weeks of age) of different genotypes in the C57BL/6 background were examined. Wild type (WT), UCN1-KO, CRH-KO, and UCN1/CRH double KO (dKO) mice were exposed to 4C or to ambient room temperature (22C) for 2 h between 9 am and 5 pm. Internal body temperature was monitored by measuring rectal temperature at 10 minute intervals using an electronic rectal probe. At ambient temperature (22 C), UCN1-KO (n=6), WT (n=10), CRH-KO (n=2), and dKO (n=2) mice had a fairly stable internal body temperature (38.2 ± 0.2 C) over the 2 h period. As reported previously, at the end of 2 h period at 4C the inner body temperature of the UCN1 KO mice (37.3 ± 0.3 , n=11) was significantly higher than that of the WT (35.6 ± 1.0 , n=12) mice suggesting a role for UCN1 in the regulation of core body temperature in mice. However, the inner body temperature of the CRH-KO (19.0 ± 9.1 , n=2) and dKO (30.4 ± 3.8 , n=3) mice during the 4C exposure was dramatically decreased. The dramatic intolerance to 4 C of the CRH-KO and CRH/UCN1 dKO mice, both of which are deficient in glucocorticoids, suggests a possible role for glucocorticoids in the regulation of inner body temperature. To test whether glucocorticoids are involved in regulating the core body temperature, CRH-KO (n=2) and dKO (n=2) mice were given daily intra-muscular injections of 1[mu]g dexamethasone in 0.9% saline for 3 consecutive days. On the fourth day, the CRH-KO and dKO mice were exposed to 2 h of cold (4C) and their rectal temperature was measured as above. After 2 h at 4C, the inner body temperature in the CRH-KO (36.8 ± 1.1 , n=2) and dKO (36.9 ± 0.7 , n=2) mice was not different from the control mice (35.6 ± 1.0 , n=12). These data suggest an important role for glucocorticoids in the regulation of core body temperature.

Nothing to Disclose: TAS, BC, NSD, ABS

sort_order 2587
Pub # P3-518
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title Evaluation of a New Method for Measuring Long-Term Cortisol Levels in Health and Bipolar Disorder
Author String L Manenschijn, AT Spijker, AM Jetten, JW Koper, ELT van den Akker, E Hoencamp, J Haffmans, FG Zitman, SWJ Lamberts, EFC van Rossum
Erasmus MC, Rotterdam, Netherlands; Parnassia BAVO Group, The Hague, Netherlands; Leiden University, Leiden, Netherlands; Leiden University Medical Center, Leiden, Netherlands
Body
Introduction
Dysregulation of the Hypothalamic Pituitary Adrenal (HPA) axis is thought to play a role in the pathogenesis of bipolar disorder (BD). Until now, most studies addressed the relationship between cortisol in serum or saliva and BD. However, this is complicated by the pulsatile secretion of cortisol, the circadian rhythm of cortisol secretion and acute stress. Measurement of cortisol in scalp hair is a recently developed method to measure long term cortisol levels. In this study we evaluated whether there is a difference in hair cortisol levels of BD patients and healthy controls. The validity of hair cortisol measurements was tested in healthy controls and patients with Cushing's syndrome (CS) and Addison's Disease (AD).
Methods
Scalp hair was collected from 192 healthy individuals, 10 patients with CS, 2 patients with AD and 100 BD patients. Methanol was used to extract cortisol from the hair samples. Cortisol levels in hair were determined using a salivary ELISA cortisol kit. All participants filled out a questionnaire concerning hair conditions and medication use. Washout effect of cortisol from distal hair segments was tested by measuring cortisol levels in six consecutive 3 cm hair segments of 28 healthy women.
Results:
Hair cortisol levels were significantly higher in CS patients than in healthy controls and they were slightly influenced by hair treatment. Cortisol levels in consecutive segments of long hair showed variation over time, but no overall decline and they corresponded with clinical course in CS and AD patients. In BD patients, hair cortisol levels were significantly elevated compared to healthy controls ($p=0.004$). There were no differences in cortisol levels between disease states (stable disease, mania, depression). Also the number of manic or depressive episodes did not influence hair cortisol levels. Patients with early onset BD had normal cortisol levels, whereas patients with late onset BD had increased cortisol levels ($p<0.01$). Panic disorder as comorbidity in BD patients was associated with decreased cortisol levels ($p=0.01$).
Conclusions:
The results in healthy controls, CS and AD patients suggest that cortisol in hair is a feasible parameter to measure long term cortisol levels and to create a retrospective timeline of cortisol exposure. Cortisol levels in BD patients are elevated, suggesting dysregulation of the HPA axis in bipolar disorder in general, but not specifically relating to manic or depressive episodes.

Nothing to Disclose: LM, ATS, AMJ, JWK, ELTvda, EH, JH, FGZ, SWJL, EFCvR

sort_order 2588
Pub # P3-519
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title One Day of Corticosterone Treatment Via the Drinking Water Is Sufficient To Disrupt ACTH and Glucose Rhythmicity, and Suppresses Dark-Phase 5-HT-Neuronal Activation in the Dorsal Raphe Nucleus
Author String NC Donner, CD Montoya, CA Lowry
University of Colorado at Boulder, Boulder, CO
Body Research has recently identified important interactions between glucocorticoid and serotonergic systems, both of which are dysregulated in psychiatric disorders (1). In rats, a functional diurnal rhythm of corticosterone release appears necessary to maintain gene expression responsible for brain serotonin (5-hydroxytryptamine, 5-HT) synthesis (2). Very little, however, is known about the effects of a short-term elevation of plasma glucocorticoids on physiological parameters and 5-HT-neuronal activation. Therefore, we delivered low- (40 [micro]g/ml, CORT-40) or high-dose (400 [micro]g/ml, CORT-400) corticosterone or vehicle (0.45% 2-hydroxypropyl- β -cyclodextrin) to adult, male rats via the drinking water for one day. This non-invasive paradigm is defined by intermittent corticosterone intake associated with drinking bouts throughout the day, and may coincide with and boost naturally occurring pulses of corticosterone release. Half of the rats were killed after 24 h of treatment during their inactive (light) phase, the other half after 36 h during their active (dark) phase. Blood was collected from the tail-vein immediately before cardiac perfusion with 4% paraformaldehyde. Brains were analyzed for 5-HT-neuronal activation using dual-label immunohistochemistry for tryptophan hydroxylase, TPH, and the early activation marker protein c-Fos.
We found that weight gain and water consumption were significantly reduced in the CORT-400 group. Compared to vehicle controls, both CORT-40 and CORT-400 animals also displayed a disrupted diurnal rhythm of plasma adrenocorticotropin (ACTH) and glucose. In the serotonergic dorsal raphe nucleus (DR), the main source of 5-HT in the brain, corticosterone treatment decreased 5-HT-neuronal activation during the dark phase in a dose-dependent manner. This effect was present in all subregions of the DR, except the ventrolateral part/ventrolateral periaqueductal gray (DRVL/VLPAG). In the interfascicular (DRI) and caudal (DRC) part of the DR, corticosterone treatment induced a diurnal variation of 5-HT-neuronal activation that was absent in vehicle controls. In contrast, midbrain serotonergic neurons outside of the DR displayed a diurnal variation of 5-HT-neuronal activation (reduced during the dark phase) that was abolished by low-dose corticosterone treatment.
In summary, our study highlights the sensitivity of the hypothalamic-pituitary-adrenal (HPA) axis, metabolic parameters, and the brain serotonergic system to circulating glucocorticoids.

(1) Lanfumey L, Mongeau R, Cohen-Salmon C, Hamon M (2008): Corticosteroid-serotonin interactions in the neurobiological mechanisms of stress-related disorders. *Neuroscience & Biobehavioral Reviews*. 32:1174-1184.
(2) Malek ZS, Sage D, Pevet P, Raison S (2007): Daily rhythm of tryptophan hydroxylase-2 messenger ribonucleic acid within raphe neurons is induced by corticoid daily surge and modulated by enhanced locomotor activity. *Endocrinology*. 148:5165-5172.

Sources of Research Support: NIH-HHMI Scholars Program for Diversity in the Biosciences NIH Grant GM066728-05 (CDM) and NIH award number R01MH086539 (CAL). Pei-San Tsai (PhD, Department of Integrative Physiology & Center for Neuroscience, University of Colorado, Boulder, CO) was generous in sponsoring the submission of this abstract.

Nothing to Disclose: NCD, CDM, CAL

sort_order 2589
Pub # P3-520
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title Normalization of Cortisol Levels in Cushing Disease after Medical Pretreatment before Surgery: Consequences for Somatostatin Receptor Subtype Expression and *In Vitro* Response to Somatostatin Analogs
Author String R van der Pas, RA Feelders, C de Bruin, AM Pereira, DM Sprij-Mooij, AM Waaijers, PM van Koetsveld, SWJ Lamberts, LJ Hofland
Erasmus MC, Rotterdam, Netherlands; LUMC, Leiden, Netherlands
Body
Introduction
Corticotroph pituitary adenomas predominantly express dopamine receptor subtype 2 (D2) and somatostatin receptor subtype (sst) 5. The expression of sst2 is relatively low in these adenomas, which may result from downregulating effects of high endogenous cortisol levels. This may explain why the sst2 preferring somatostatin analog octreotide, compared to the multiligand receptor somatostatin analog pasireotide, is not effective in Cushing's disease (CD). To assess whether normalization of urinary free cortisol (UFC) levels modulates the sst expression pattern, sst profiles on corticotroph adenomas of patients pretreated before surgery were examined. In addition, the effects of pasireotide and octreotide on *in vitro* ACTH production by these adenomas were examined.
Methods
Corticotroph tumor tissue was examined from 10 patients with normalized UFC levels before pituitary surgery via treatment with pasireotide alone (n=1), pasireotide-cabergoline (n=2), pasireotide-cabergoline-ketoconazole (n=3) or ketoconazole alone (n=4). RT-PCR studies were performed to determine the sst expression profile of these adenomas, as well as of adenomas from patients with CD with elevated preoperative UFC levels (n=23) and somatotroph adenomas (n=10).
Results
Whereas sst5 expression levels were similar between the 2 groups of corticotroph adenomas, adenomas of patients with normalized preoperative UFC values had significantly higher sst2 expression (p<0.01). In the latter group, the sst2 expression levels were 2.5 fold higher than the sst5 expression levels and comparable to sst2 expression on somatotroph adenomas. Despite the elevated sst2 expression in these adenomas, octreotide was significantly less potent than pasireotide with respect to inhibition of ACTH levels in a concentration of 10 nM (-19±3.9% (n=4) vs -42±3.8% (n=6); p<0.0001).
Conclusion
Cortisol-mediated sst2 downregulation on corticotroph adenomas appears to be a reversible process upon normalization of UFC levels by medical therapy. Nonetheless, octreotide is less potent than pasireotide with respect to *in vitro* inhibition of ACTH production in these corticotroph adenomas. This suggests that the sst5 plays a key role in sst targeted therapy for CD. Further research is needed to explain the limited efficacy of octreotide, in the presence of a relative high sst2 mRNA expression, on ACTH production.

Nothing to Disclose: RvdP, RAF, CdB, AMP, DMS-M, AMW, PMvK, SWJL, LJH

sort_order 2590
Pub # P3-521
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title Kalirin Plays an Essential Role in POMC-Producing Cells
Author String PG Mandela, B Eipper, RE Mains
University of Connecticut Health Center, Farmington, CT
Body Kalirin, a GDP/GTP exchange factor for small GTP binding proteins of the Rho subfamily, is a major risk factor for cardiovascular disease, schizophrenia and ADHD. Kalirin was first identified as an interactor with an integral membrane protein known to be essential for the biosynthesis of many neuropeptides, Peptidylglycine α -Amidating Monooxygenase (PAM). Over-expression of the GEF domain of Kalirin or inhibition of the GEF activity of endogenous Kalirin also alters granule release. To understand the role of Kalirin in different tissues, we compared the phenotypes of control mice (wildtype or KalCKO) to those of mice lacking Kalirin expression in all tissues (KalTKO) and to mice lacking Kalirin expression only in cells that normally express proopiomelanocortin (POMC) (KalPOMC-KO); Kalirin expression was selectively eliminated in POMC cells by mating mice expressing Cre recombinase under control of the POMC promoter (Cre-POMC) to mice in which lox-p sites flank an exon common to all the major splice variants of Kalirin (KalCKO/CKO). Although KalTKO mice exhibited decreased ability to remain on the rotarod, KalPOMC-KO mice did not. KalTKO and KalPOMC-KO mice performed as well as wildtype mice in tests of novel object recognition. Anxiety-like behavior was evaluated in the elevated zero maze; KalPOMC-KO mice exhibited a decrease in anxiety-like behavior, spending 35% more time in the open area than control KalCKO mice. The decrease in anxiety-like behavior observed in KalPOMC-KO mice matched the decrease observed in KalTKO mice. In the passive avoidance test, KalPOMC-KO mice that received a footshock upon entering a dark chamber re-entered that same chamber more quickly than control KalCKO/CKO mice, revealing a deficit in fear-based learning; the deficit observed in KalPOMC-KO mice was similar in magnitude to the deficit observed in KalTKO mice. Serum glucocorticoid levels were evaluated under basal conditions and after 15 minutes of restraint stress. Basal corticosterone levels were indistinguishable in KalCKO, KalTKO and KalPOMC-KO serum. In both KalPOMC-KO and KalTKO mice, the stress induced increase in corticosterone levels was significantly higher in KalCKO female mice. Basal and stimulated secretion of ACTH in primary cultures prepared from the anterior pituitaries of KalCKO, KalTKO and KalPOMC-KO mice. Increased basal secretion of ACTH was observed in cultures prepared from KalTKO and KalPOMC-KO mice; stimulated secretion was unaltered.

Sources of Research Support: NIH grant DK32948.

Nothing to Disclose: PGM, BE, REM

sort_order 2591
Pub # P3-522
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title Corticotropin-Releasing Hormone Deficiency Unmasks Neuroprotective Effects of CRH *In Vivo*
Author String Y Koutmani, P Politis, E Remboutsika, K Karalis
BRFAA, Athens, Greece; Fleming, Vari, Greece; BRFAA, Athens, Greece; Children's Hospital, Boston, MA
Body Increasing evidence supports the theory linking stress to neuronal dysfunction, altered neurogenic activity and ultimately apoptotic death. Corticotropin Releasing Hormone or Factor (CRF or CRH) is a neuropeptide identified by its fundamental role in the development of adaptive responses following exposure to various stimuli. CRF is broadly expressed within the nervous system, in areas where active proliferation and programmed cell death processes operate in parallel to control the generation and maintenance of neuronal populations. We have previously demonstrated the expression of CRF receptors (CRHRs) in neural progenitor cells both in embryonic and adult brain by immunofluorescence with specific antibodies. The biological significance of the above findings was addressed in the *Crh*-null (*Crh*^{-/-}) mouse that lack endogenous *Crf*. Proliferating and apoptotic cell populations were measured in the cortical plate of E14.5 *Crh*^{-/-} and their wild-type littermates. BrdU administration in the pregnant mother identified a significant decrease in the number of BrdU⁺ cells in the ventricular (VZ) and subventricular zone (SVZ) of the *Crh*^{-/-} mice. Moreover the apoptotic population of VZ and SVZ neuroblasts as revealed by TUNEL assay, was significantly increased in the *Crh*^{-/-} mice. Since all embryos were exposed to the same glucocorticoid levels derived from the mother, these findings reveal direct proliferative and anti-apoptotic effects of CRF during development in the mouse brain. These findings show a new, neuroprotective role for CRF during normal embryonic brain development. The significance of this process for the neurogenesis-associated adaptive responses to stressful stimuli, including brain diseases, is under investigation.
Nothing to Disclose: YK, PP, ER, KK

sort_order 2592
Pub # P3-523
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title The Interrelationship between Birth Size, Cortisol, Adiponectin, IGF-I and Glucose Metabolism in Afro-Caribbean Young Adults
Author String DS Thompson, TS Ferguson, ME Samms-Vaughan, RJ Wilks, DI Phillips, C Osmond, TE Forrester, MS Boyne
The University of the West Indies, Mona, Jamaica; The University of the West Indies, Mona, Jamaica; University of Southampton, Southampton, UK
Body Background: Early life events may influence the development of obesity, insulin resistance and type 2 diabetes. We postulated that birth size is associated with cortisol levels, which in turn could alter serum adiponectin, serum IGF-I and glucose metabolism.
Methods: We randomly recruited 60 participants (33 men, 27 women), aged 23 years, with known birth anthropometry from the 1986 Jamaica Birth Cohort. Body composition was assessed by dual energy x-ray absorptiometry and a frequently sampled intravenous glucose tolerance test was performed. Serum adiponectin and IGF-I were measured by ELISA. Salivary cortisol was collected at home at 0800 and 2300 hrs. Insulin sensitivity (SI), acute insulin response (AIRg), disposition index (DI) and glucose effectiveness (S_g) were calculated using the MINMOD software. Cortisol, adiponectin, IGF-I, SI, AIRg, and DI were log-transformed to a normal distribution. Sex-adjusted multivariate analyses were used to explore the association of birth size, as well as cortisol, with metabolic variables.
Results: The participants' BMI (mean ± SD) was 24.8 ± 6.3 kg/m², birth weight was 3.22 ± 0.38 kg and crown-heel length was 50.0 ± 3.6 cm. Birth size did not correlate with BMI, fat mass, fat free mass or waist circumference (P-values > 0.12). Birth weight and length were not associated with 0800 hr cortisol (P-values > 0.2). Birth weight, but not length, was associated with 2300 hr cortisol (r = 0.32; P=0.04). Gestational age was associated with 2300 hr cortisol (r = 0.38; P=0.03). Ponderal index, but not birth weight or length, was associated with adiponectin (r = 0.27; P=0.04). Birth size was not significantly related to IGF-I, SI, AIRg, DI or S_g. Cortisol at 0800 and 2300 hrs were not correlated with adiponectin, IGF-I, SI, AIRg, or DI. However, 2300 hr cortisol was correlated with S_g (r = -0.31; P=0.04) even after adjusting for birth size.
Conclusions: In our data, larger birth size is positively associated with night-time cortisol and adiponectin. Higher levels of night-time cortisol may reduce glucose effectiveness, but this is not mediated by birth size. Ambient cortisol levels were not associated with adiponectin or IGF-I levels.
Nothing to Disclose: DST, TSF, MES-V, RJW, DIP, CO, TEF, MSB

sort_order 2593
Pub # P3-524
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title Inappropriately Low Levels of Salivary Cortisol and Cortisol Suppression in Recent-Onset and Longstanding Rheumatoid Arthritis
Author String R Quax, JW Koper, R van der Wal, P de Jong, C den Dulk, A Weel, M Huisman, D van Zeben, F de Jong, J Hazes, S Lamberts, R Feelders
Erasmus MC, University Medical Center, Rotterdam, Netherlands; Erasmus MC, University Medical Center, Rotterdam, Netherlands; Maastad Hospital, Rotterdam, Netherlands; Sint Franciscus Gasthuis, Rotterdam, Netherlands
Body
Background
A relative insufficiency of the hypothalamic-pituitary-adrenal axis (HPA-axis) has been postulated to play a role in the pathophysiology of rheumatoid arthritis (RA). Resistance to glucocorticoid treatment has a prevalence of about 30 % in RA. We examined free salivary cortisol levels and the negative feedback mechanism of the HPA-axis in recent-onset and longstanding RA. In addition, we examined whether free salivary cortisol concentrations before and after dexamethasone suppression have a predictive value for the *in vivo* response to standardized GC bridging therapy in RA patients.
Methods
A low-dose dexamethasone suppression test (LDST) was performed in a large cohort of healthy controls (HC, n=94), recent-onset (n=66) and longstanding RA (n=37). Basal salivary cortisol levels and central glucocorticoid sensitivity, expressed as percentage suppression of salivary cortisol after 0.25 mg dexamethasone, were studied in relation to disease activity at baseline and, in a subset of RA patients, to the percentage improvement in disease activity score (DAS28) after two weeks of GC bridging therapy.
Results
Basal salivary cortisol levels and percentage of cortisol suppression in the LDST were significantly lower in patients with active RA (DAS28>3.2) as compared to HC. In contrast, RA patients with low DAS28 (<3.2) did not differ significantly from HC. Basal salivary cortisol levels and percentage of cortisol suppression were not associated with efficacy of GC bridging therapy as measured by the relative decrease in DAS28.
Conclusions
In RA, active disease is associated with inappropriately low free salivary cortisol levels, pointing to a blunted HPA-axis. In addition, patients with active disease had less suppression of salivary cortisol in the LDST. These variables were in the normal range in patients with low disease activity, suggesting reversible defects in the HPA-axis in RA. None of these parameters were associated with improvement of disease activity after two weeks of GC bridging therapy. Central GC sensitivity seems therefore not predictive of peripheral GC sensitivity at inflammatory sites.

Sources of Research Support: The Dutch Arthritis Association.

Nothing to Disclose: RQ, JWK, RvdW, PdJ, CdD, AW, MH, DvZ, FdJ, JH, SL, RF

sort_order 2594
Pub # P3-525
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title Impaired, Glucocorticoid-Independent, Resolution of the Inflammatory Response in Corticotropin-Releasing Hormone (CRH)- Deficient Mice after DSS-Colitis
Author String P Giannogonas, Z Chaniotou, S Theocharis, C Pothoulakis, K Karalis
Biomedical Research Foundation of the Academy of Athens, Athens, Greece; University of Athens Medical School, Athens, Greece; David Geffen School of Medicine, Los Angeles, CA; Children's Hospital, Boston, MA
Body Inflammatory bowel disease (IBD) is a chronic, relapsing disease including ulcerative colitis and Crohn's disease. The aetiology of IBD has not been yet elucidated, while recent studies suggest the involvement of complex interactions between genes and the environment and the critical role of innate immune responses in these processes. In previous studies we have demonstrated the proinflammatory effects of Corticotropin Releasing Hormone, or Factor, (CRH or CRF), a neuropeptide acting as the major mediator of the stress response, in intestinal inflammation in rodents. Using an experimental model of innate immunity associated ulcerative colitis, the DSS model, we have recently shown that Crh deficiency is associated with increased susceptibility to disease development. To extend our understanding on the role of CRF in experimental IBD, we followed the course of DSS-colitis after the end of treatment, a period associated with tissue repair, reversal of body weight loss and return to homeostasis in the Crh^{-/-} mouse. To our surprise the disease was progressed in the Crh^{-/-} mice resulting in their severely compromised survival by 5 days after cessation of DSS treatment, while all wild-type mice recovered. This development was characterized by significant continuous reduction of body weight, lack of regeneration of the inflamed epithelium, increased angiogenesis and fibrosis. These findings were not eliminated by normalization of the glucocorticoid levels of the Crh^{-/-} mouse, in further support of the role of Crh in this process. Our findings demonstrate the requirement of CRH for the epithelial repair following DSS-colitis and raise the hypothesis for a critical contribution of the tissue expressed CRH in the development of adaptive responses to colitis and the resolution of inflammation.

Nothing to Disclose: PG, ZC, ST, CP, KK

sort_order 2595
Pub # P3-526
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title Androgen-Dependent Effects on HPA Axis Activation in a Fox Urine Stress Model in Male Mice
Author String MF Keil, N Gokarn, N Stojkov, D Larco, G Briassoulis, N Mirafraab, CA Stratakis, S Stojilkovic, TJ Wu
Uniformed Services University of the Health Sciences, Bethesda, MD; NICHD, National Institutes of Health, Bethesda, MD; NICHD/NIH, Bethesda, MD; USUHS, Bethesda, MD
Body Rodent response to predator odor is a useful model to examine an innate defensive behavior elicited by specific predatory cues. Prior studies document behavioral and neurobiological response to predator odor in rodents using fox urine (FU); however no standard methodology exists. There is a paucity of data regarding the effect of FU stress on serum androgens and interaction with the hypothalamic pituitary adrenal (HPA) response. The purpose of this study was to evaluate a dose-response of FU as a stimulant of the HPA- gonadotropin axis in young adult male mice (C57BL/6J) with a 4 x 4 factorial analysis, (dose (vehicle (VEH), 30ul, 300 ul, 5mL) X time (+5, +10, +25, +90 min)). Corticosterone (CORT), ACTH, testosterone, and progesterone were measured. Two-way ANOVA analysis of CORT showed significant interactions for dose (p<0.002) and time (p<0.001). Post-hoc analysis showed a significant difference between the 300ul group at +5min (VEH: 215 ±32 30ul: 113±22, 300ul: 335 ± 49, 5mL: 176 ± 75 pg/mL; p<0.01). There was a significant main effect of time for ACTH secretion (p<0.001); but not dose. A transient increase in androgens was noted in FU exposed animals compared to VEH. Results of basal in vitro androgenesis in the testes showed significant difference for dose (VEH vs 300ul and 5mL, p<0.05), with higher in vitro androgenesis in FU exposed mice. In conclusion, FU exposure resulted in significant and prolonged activation of serum CORT, ACTH, and androgens. The finding of a robust HPA axis response in the VEH group is consistent with the lack of attenuation, since androgen levels were not altered in this group. Prior studies support the role of androgens in suppression of the CORT response to acute physical or psychological stressors; however the mechanism by which androgens inhibit HPA activity is not well defined. Evidence for a testicular origin of androgen response is suggested by elevation of in vitro androgenesis in FU exposed mice only. The lack of increase in progesterone levels also supports a non-adrenal source of androgen increase. In summary, results of our study provide support for the inhibitory effect of androgens on HPA function after exposure to FU. Our results suggest that androgen levels may be useful to help differentiate a stress response to novelty versus defense/threat. Future studies are needed to determine if up-regulation of PKA and STAR protein expression mediates androgen increase after predator stress.

Sources of Research Support: USUHS, Graduate Student Grant 2009- 2010.

Nothing to Disclose: MFK, NG, NS, DL, GB, NM, CAS, SS, TJW

sort_order 2596
Pub # P3-527
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title Apelin Regulates the Hypothalamic-Pituitary-Adrenal Axis in Goat and Sheep
Author String K Sato, S Kato, N Okawa, S-h Song, S-G Roh, K Katoh
Tohoku University, Sendai, Japan
Body Apelin, a peptide recently isolated from bovine stomach extracts, appears to act as an endogenous ligand for the previously orphaned G-protein-coupled APJ receptor (1). Apelin consists of 77 amino acids that are processed to produce several smaller peptide fragments. Apelin and APJ mRNA are expressed in several tissues including supraoptic and paraventricular nuclei in the hypothalamus, related to regulate food and water intake. However, there was no report on the apelin secretion pattern and its regulatory response by food and water intake. The aim of this study was to investigate the apelin secretion pattern by food and water intake and effect of apelin on AVP and ACTH secretion in the ruminant. Experiments were performed with six Saanen goats (4 months old, 18.9±1.0 kg BW, castrated males) and five crossbred sheep (9 months old, 35.1±2.1 kg BW, castrated males). The animals had ad libitum access to water and minerals, and were fed orchardgrass hay once a day at 16h. In experiment 1, the changes of plasma apelin were demonstrated in Saanen goats deprived of water for 48 hour. In experiment 2, AVP and ACTH secretions were investigated before and after apelin ([Pyr1]-Apelin-13, 1mg) administration by i.v. in sheep. In experiment 3, whether ACTH release from sheep pituitary cells is altered by apelin treatment (10-7M) was studied. In the first two experiments, we measured plasma concentrations of apelin, AVP and ACTH during the experimental time at a frequency of at least 15 min with samples collected (from an indwelling jugular catheter). In experiment 3, pituitary cells isolated from sheep were incubated for 30 min in culture medium with apelin, and then the medium was collected for analysis of ACTH. In experiment 1, plasma apelin level was slightly increased after feeding and decreased to the basal level before feeding, and significantly increased after feeding during the deprivation of water. AVP and ACTH levels were also significantly increased after feeding in dehydration. In experiment 2, apelin administration significantly increased the plasma concentrations of AVP and ACTH. In experiment 3, ACTH secretion was significant increased by apelin treatment in cultured pituitary cells. These results demonstrate that plasma apelin level increases in response to stress of dehydration and food intake by the regulation of the hypothalamus pituitary adrenal axis in the ruminant.

(1) Tatemoto, K et al., *Biochem Biophys Res Commun* 1998; 251:471-6

Nothing to Disclose: KS, SK, NO, S-HS, S-GR, KK

sort_order 2597
Pub # P3-528
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title Interleukin-1 β Triggers Muscle Catabolism Via a Central Nervous System-Mediated Pathway
Author String TP Braun, XX Zhu, M Szumowski, GD Scott, AJ Grossberg, K Graham, S Kahn, S Damaraju, WF Colmers, VE Baracos, DL Marks
Oregon Health & Science University, Portland, OR; Oregon Health & Science University, Portland, OR; University of Alberta, Edmonton, Canada; University of Alberta, Edmonton, Canada; University of Alberta, Edmonton, Canada
Body Hypothalamic interleukin-1 beta (IL-1 β) production is induced in multiple inflammatory diseases associated with muscle catabolism. To determine whether IL-1 β signaling in the CNS plays a role in the muscle wasting of inflammatory disease, we examined the ability of intracerebroventricular (ICV) IL-1 β injection at pathophysiologically relevant concentrations, to generate catabolic changes in skeletal muscle. Acute ICV IL-1 β injection led to rapid induction of a catabolic program in skeletal muscle. When sustained by chronic infusion, central IL-1 β infusion caused myofibrillar atrophy. Importantly, these effects are CNS specific, as peripheral administration of low dose IL-1 β failed to have any measurable catabolic effect on skeletal muscle. Activation of the hypothalamic-pituitary-adrenal axis is essential to this effect, as adrenalectomy prevents IL-1 β induced atrophy. Contrary to an extensive literature predicated on direct cytokine mediation of muscle catabolism, these results demonstrate that IL-1 β signaling in the CNS is sufficient to induce muscle catabolism, and suggest that endogenous IL-1 β production in the CNS contributes to disease-associated wasting.

Sources of Research Support: NIH DK 70333, NIH DK 084646, Canadian Institutes of Health Research 200948 and Portland ARCS Chapter.

Nothing to Disclose: TPB, XZ, MS, GDS, AJG, KG, SK, SD, WFC, VEB, DLM

sort_order 2598
Pub # P3-529
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title Effects of Glycyrrhizic Acid on the Hypothalamic-Pituitary-Adrenal Axis in the Rat Model
Author String PM Zhang, J Schulkin, S Galli, H Amri
Georgetown University Medical Center, Washington, DC; Georgetown University Medical Center, Washington, DC; NCI-National Institutes of Health, Bethesda, MD
Body
Introduction: Glycyrrhizic acid is the main active compound found in licorice extract. Licorice is traditionally used for a variety of common health problems such as asthma to dry cough and even peptic ulcers. It has recently been reported that it could be beneficial in health conditions involving the hypothalamic-pituitary-adrenal axis, but to date very little is known about its actions on the HPA axis.
Methods: Six week-old, male Sprague-Dawley rats (n = 10) were treated once daily with 120 mg/kg of glycyrrhizic acid *per os* for 14 days. The control group (n = 10) received an equivalent volume of distilled water. The weights of all animals were monitored once a week. After 14 days, the animals were sacrificed and the blood, brain, and adrenals were collected for ELISA, immunohistochemistry, and PCR analysis.
Results: We found a significant 50% decrease in serum corticosterone ($p \leq 0.05$) and 52% increase of plasma adrenocorticotropic hormone (ACTH) when compared to the control group (109.06 ng/ml vs. 56.21 ng/ml; treated vs. control; $p \leq 0.009$). Interestingly, serum aldosterone levels also were significantly decreased when compared to the control group (0.23 ng/ml vs. 0.46 ng/ml; treated vs. control; $p \leq 0.0002$). Immunohistochemistry and PCR analysis on the collected tissue, including the brain, are ongoing. Weight gains in the animals were not affected by the treatment.
Conclusion: Glycyrrhizic acid affects both the zona fasciculata and the zona glomerulosa of the adrenal glands; these are the sites for glucocorticoid and mineralocorticoid synthesis, respectively. Thus, our preliminary results show that glycyrrhizic acid, the active ingredient in licorice, does exert a significant effect on the pituitary and adrenal glands by reducing both glucocorticoid and mineralocorticoid levels.

Nothing to Disclose: PMZ, JS, SG, HA

sort_order 2599
Pub # P3-530
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title Circadian CLOCK-Mediated Gene-Specific Regulation of Peripheral Glucocorticoid Receptor Transcriptional Activity by Acetylation in Man
Author String T Kino, E Charmandari, GI Lambrou, A Pavlaki, H Koide, SSM Ng, GP Chrousos
Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD; University of Athens Medical School, Aghia Sophia Children's Hospital, Athens, Greece; Biomedical Research Foundation of the Academy of Athens, Athens, Greece; Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD; Chinese University of Hong Kong, Shatin, China
Body
Circulating cortisol concentrations fluctuate diurnally under the control of the [ldquo]master[rdquo] circadian CLOCK system located in the hypothalamus, while we recently reported that the peripheral [ldquo]slave[rdquo] circadian CLOCK system regulates the transcriptional activity of the glucocorticoid receptor (GR) by acetylating it at local target tissues. To examine Clock-mediated GR acetylation and circadian changes in the sensitivity of peripheral target tissues to glucocorticoids (GCs) in humans, we examined the acetylation of the GR and the mRNA expression of the GR, Clock, Bmal1, and 8 known GC-responsive (4 transactivated and 4 transrepressed) genes in peripheral blood mononuclear cells (PBMCs) obtained from 10 healthy subjects at 8 am and at 8 pm. GR acetylation levels were higher in the morning than in the evening, in synchrony with fluctuations of Clock/Bmal1 mRNAs and the levels of circulating ACTH and cortisol. The mRNA expression of certain genes regulated positively (GILZ and tristetraprolin) or negatively (interferon γ , IL-1 α and IL-12 p40) by GCs demonstrated the expected concomitant diurnal fluctuations, while, surprisingly, those of other such genes (Annexin A1, dual phosphatase 1 and TNF α) did not fluctuate. To further examine details of the acetylation-mediated regulation of GC-responsive genes, we obtained PBMC from 6 additional healthy subjects and cultured them for 24h *ex vivo* with every 6h exposure to hydrocortisone, assuming continuing regulation of the diurnally oscillating cellular CLOCK system. In these cells, hydrocortisone-induced mRNA expression of the GC-responsive genes previously found to not correlate with circulating cortisol *in vivo* demonstrated the circadian fluctuations, mirroring the levels of GR acetylation and Clock mRNA expression, while that of the genes that correlated with circulating cortisol *in vivo* did not show fluctuation *ex vivo*. Knockdown of Clock by its siRNA in cultured PBMCs abolished this gene-specific fluctuation of GR transcriptional activity. These results suggest that the transcriptional activity of the human GR is modulated in a gene-specific fashion through circadian GR acetylation by the peripheral CLOCK, counteracting the transcriptional effect of circulating cortisol. Coordinated regulation of GC action at target tissues by circulating cortisol and peripheral CLOCK-mediated epigenetic modulation of the GR appears to be essential for the maintenance of GC homeostasis in man.

Sources of Research Support: Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, and the University of Athens, Athens, Greece.

Nothing to Disclose: TK, EC, GIL, AP, HK, SSMN, GPC

sort_order 2600
Pub # P3-531
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title Low-Dose, Stand Overnight and Low-Dose Dexamethasone Suppression Test in Patients with Mild and/or Episodic Hypercortisolism
Author String N Shayesteh, M Mangubat, M Haykani, ML Lee, IE McCutcheon, TC Friedman
Charles R Drew University, Los Angeles, CA; MD Anderson Medical Center, Houston, TX
Body
BACKGROUND The overnight 1 mg and low dose dexamethasone (DEX) suppression tests have been used for many years to evaluate patients with possible Cushing's syndrome. We recently reported the lack of utility of the 1 mg overnight DEX test in mild and/or periodic Cushing's syndrome as most patients with the condition suppressed to 1 mg DEX. It is possible that a lower dose of DEX as part of an overnight DEX test might be effect to distinguish between mild and/or periodic Cushing's syndrome and those without the condition.
PATIENTS A 0.25 mg and standard 1 mg overnight DEX suppression test and the two-day low-dose DEX suppression test was performed in 36 consecutive patients presenting to an Endocrinology clinic with signs and symptoms of hypercortisolemia who were later proven to have Cushing's syndrome and 25 patients who were later proven not to have the condition. At 0800 h following DEX (0.25 mg or 1 mg) given at 2400 h, or at 0900 h following DEX given every 6 hours for two days (last dose 0300 h), we measured serum cortisol and DEX levels and also calculated a cortisol/DEX ratio.
RESULTS Using ROC analysis, the optimum cutpoints for a morning cortisol following the 0.25 mg and 1 mg overnight DEX and the 2 mg-2 day DEX test was 304 nmol/L, 35.9 nmol/L and 6.9 nmol/L, respectively. The sensitivity, specificity and area under the ROC curve and p-value was as follows: 0.25 mg: 31%, 95%, 0.60, p=0.12; 1.0 mg: 30%, 91%, 0.55, p=0.25; 2 mg-2 day: 43%, 100%, 0.60, p=0.22. Suppression when expressed as cortisol/DEX ratio also yielded a non-significant area under the ROC curve. Interestingly, using a cutpoint of a DEX level <6750 pmol/L following the 1 mg overnight DEX test yielded a significant area under the ROC curve suggesting that measuring DEX levels may be helpful to distinguish mild Cushing's syndrome from those without the condition.
CONCLUSIONS The majority of patients with mild/periodic Cushing's syndrome suppress to the standard 1 mg overnight DEX test and the 2 mg-2 day and DEX test and that these tests are unable to distinguish mild Cushing's syndrome from those without the condition. Using a lower dose of DEX of 0.25 mg, we were unable to identify a cutpoint that could distinguish mild Cushing's syndrome from those without the condition, even with linear regression analysis. Our data suggests that DEX suppression testing should no longer be used to screen for Cushing's syndrome in patients who could have mild and/or periodic Cushing's syndrome.
Nothing to Disclose: NS, MM, MH, MLL, IEM, TCF

sort_order 2601
Pub # P3-532
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title Different Therapeutic Approaches in ACTH-Dependent Cushing Syndrome Due to Occult Ectopic ACTH Syndrome
Author String H Nicolielo, C Lauretti, MCBV Fragoso, MC Machado, MD Bronstein
University of São Paulo Medical School, São Paulo, Brazil
Body **Background:** The Ectopic ACTH Syndrome (EAS) accounts for 10-20% of ACTH-dependent Cushing's syndrome (ADCS). Surgical removal of the responsible tumor is the main therapeutic option. However, 8-19% of EAS cases are occults precluding its surgical resection. Bilateral adrenalectomy (BA) has been used in these cases. Otherwise, medical treatment has also been used for as an alternative of adrenal surgery.
Objective: To evaluate the different therapeutic options and follow up of EAS cases.
Material and Methods: Between 1975 and 2010, 32 EAS patients were evaluated including 25 which have been published previously. Of the 7 new cases, 5 are female patients, 29 years-old (13 to 53). The diagnosis of ADCS was established by elevated urinary cortisol, no suppression of serum cortisol (Fs) after low dose of dexamethasone, loss of circadian rhythm of cortisol secretion and normal or inappropriate ACTH. 3/5 responded to desmopressin test and 4/4 suppressed (>50%) Fs after high dose of dexamethasone. All patients did sellar MRI and 5 did bilateral inferior petrosal sinus sampling (BIPSS). The majority of patients were submitted to the other imaging exams (USG, CT, MRI, OctreoScan and PET-FDG). The diagnosis of EAS was confirmed after surgical procedure in 2 cases (lung carcinoids) and by absence of central gradient after BIPSS in other 5 cases. Follow-up was 45 months.
Results: One patient underwent resection of lung nodule and achieved clinical remission. One patient with nodule in right hilus was submitted to mediastinoscopy with lung carcinoid metastases without remission. In the other 5 occults EAS patients, 2 of them underwent BA, 2 are using octreotide-LAR (36 and 16 months) and 1 is receiving cabergoline (1.5 mg/week, 40 months). Of these 3 patients, 2 are controlled and 1 has presented fluctuating control (oct-LAR 16 months). In the previously reported, 2 patients with occult EAS had been submitted to BA. One of them remains with occult source and the other a pancreatic neuroendocrine tumor became detectable 60 months after the initial evaluation. All of occult EAS cases are submitted to annual image exams of neck, thorax, abdomen and pelvis regions (USG, CT and MRI).
Conclusion: BA remains the most common treatment of occult EAS mainly in severe cases. Nevertheless, medical treatment that acts in ACTH secretion can be used on long-time. The follow up with imaging exams is very important issue since the source of ACTH secretion may require many years before its identification.

Nothing to Disclose: HN, CL, MCBVF, MCM, MDB

sort_order

2602

Pub #

P3-533

Session Information

POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)

Title

Vaprisol Treatment for Hyponatremia after Surgery for Cushing Disease

Author String

N Rowland, LS Blevins, Jr
University of California, San Francisco, San Francisco, CA

Body

Hyponatremia is an infrequent consequence of surgical treatment of Cushing's Disease. When hyponatremia does occur in this population treatment can prove to be challenging. Conventional management of hyponatremia – free water restriction and sodium repletion – takes resource time and leads to additional days of hospitalization, both costly measures. The newest generation of pharmacological agents designed to treat hyponatremia – the arginine vasopressor receptor antagonists, or vaptans – have been shown effective in other disease states of arginine vasopressin excess. However, use of these agents has not been reported in Cushing's patients. We report the use of Conivaptan (Vaprisol[reg]) in two Cushing's patients at our institution and compare our experience in five conventionally treated post-operative Cushing's patients with hyponatremia. Two of the conventionally treated post-operative Cushing's patients were discharged with serum sodium (Na) levels less than 130, one after 2 days and the other after 9 days, with plans for close observation. The lowest serum Na values during these inpatient stays were 127 and 125, respectively. The remaining three conventionally treated post-operative patients had lowest serum Na values of 129, 133 and 134. They were discharged home after 2-5 days with normalized serum Na levels. In contrast, the two Vaprisol-treated post-operative Cushing's patients were both discharged with normalized serum Na values after 5 days. Their lowest serum Na values were also 127 and 125. Our data show a trend toward better control of sodium balance and less morbidity with Vaprisol[reg] in post-operative Cushing's patients compared to conventionally treated patients with similar degrees of hyponatremia. As our experience with these agents evolves, we foresee expanded use of Vaprisol[reg] for this population and a concomitant decrease in this post-operative complication.

Nothing to Disclose: NR, LSB

sort_order 2603
Pub # P3-534
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title Urine Steroid Profiling Differentiates between ACTH-Dependent and ACTH-Independent Cushing Syndrome
Author String RP Vincent, J Alaghband-Zadeh, CW le Roux, C Moniz, SJ Aylwin, K-M Schulte, NF Taylor
King's College Hospital NHS Foundation Trust, London, UK; King's College Hospital NHS Foundation Trust, London, UK
Body **Background:** Cushing's syndrome is caused by excess ACTH from a pituitary (65%) or ectopic tumour (15%) or by independent adrenal overproduction (20%). In most instances, measurement of ACTH is diagnostic although there are occasions where it remains difficult to differentiate between ACTH-dependent and -independent causes.
Aim: To identify specific differences in urine steroid metabolites between patients with pituitary-dependent and adrenal Cushing's.
Methods: Retrospective study of 21 adult patients who had had 24-hr urine steroid profiles (USP) analysed by Gas Chromatography-Mass Spectrometry (GC-MS): for suspected Cushing's syndrome. Subsequently, 14 had a confirmed diagnosis of Cushing's, based on radiology and/or histopathology (pituitary n=7; adrenal n=7) and 7 were normal.
Results: Demonstration of cortisol excess was based on elevated urine free cortisol and/or failure to suppress after overnight dexamethasone suppression and cause of cortisol excess was determined by histopathology. USP was reported as consistent with Cushing's, based on increase of 5 β /5 α -reduced and 11-hydroxy/11-oxo steroids, in the 14 patients who had the syndrome and as unlikely in the 7 who were normal. Age of the normal, pituitary and adrenal groups were 43 \pm 18, 46 \pm 18 and 54 \pm 22 (mean \pm SEM) years (p=NS). The following steroid metabolites were significantly higher (p<0.05) in the ACTH-dependent group compared to the normal group: androgen metabolites [aetiocholanolone (Ae), 11-oxo-Ae and androstenediol], pregnanediol, pregnanetriol, cortisol metabolites [tetrahydrocortisone, tetrahydrocortisol, α and β cortols and cortolones] and the corticosterone metabolite, tetrahydrocorticosterone. All 7 with pituitary Cushing's had an Ae>1000[micro]g/day (2412 \pm 910) however adrenal Cushing's had Ae>1000 or <1000[micro]g/day (1264 \pm 518).
Conclusions: USP by GC-MS is 100% sensitive and specific for the diagnosis of ACTH dependent Cushing's compared to adrenal causes or normal. Pituitary Cushing's can be ruled out where Ae<1000[micro]g/day (NPV=100%). USP is a potential non-invasive test to confirm ACTH-dependent Cushing's and may be of value in circumstances where the cause of cortisol excess is uncertain.
Nothing to Disclose: RPV, JA-Z, CWIR, CM, SJA, K-MS, NFT

sort_order 2604
Pub # P3-535
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title Pasireotide Treatment in Cushing Disease: Effects on the IGF-I System
Author String AJ Varewijck, RA Feelders, C de Bruin, AM Pereira, RT Netea-Maier, PMJ Zelissen, SWJ Lamberts, JAMJL Janssen, LJ Hofland
Erasmus Medical Center, Rotterdam, Netherlands; Leiden University Medical Center, Leiden, Netherlands; Radboud University Nijmegen Medical Center, Nijmegen, Netherlands; University Medical Center Utrecht, Utrecht, Netherlands
Body
Introduction Pasireotide is a somatostatin analog that binds with high affinity to somatostatin receptor subtypes 1-3 and 5. It reduces cortisol production in Cushing's disease (CD), reaching normalization of urinary free cortisol (UFC) in 25-30%. In preclinical studies pasireotide inhibited body growth and reduced IGF-I levels in rats. We studied the IGF-I system in untreated CD and its changes after pasireotide treatment.
Methods 17 Patients with CD were treated with pasireotide for 28 days. Main outcome measure was normalization of UFC. Patients received 100[micro]g of pasireotide subcutaneously three times daily, which was increased to 250[micro]g three times daily if UFC levels had not normalized at day 15. Blood was drawn in the fasted state at day 0 and day 28. Bioactive IGF-I was measured with the IGF-I KIRA bioassay and all other parameters with routine immunoassays.
Results Untreated CD was characterized by normal total IGF-I (mean: 22.9 nmol/L, 95% CI: 18.5-27.2) and IGF-I bioactivity (mean: 460 pmol/L, 95% CI: 357-562) and low-normal IGF-binding-protein (IGF-BP)-3 (mean: 3.8 mg/L, 95% CI: 3.5-4.2). Z-scores for total IGF-I and IGF-I bioactivity were $\geq +1SD$ in 47% of patients ($\geq +2SD$ in 24% and 20%, respectively). Two patients had Z-scores $< -1.5SD$.
After 28 days UFC had normalized in 29% of patients (mean baseline: 334 nmol/24 hrs, 95% CI: 255-447; mean day 28: 222 nmol/24 hrs, 95% CI: 152-325; NS). Total IGF-I and IGF-I bioactivity decreased significantly, independent of UFC reduction (mean total IGF-I: 12.6 nmol/L, 95% CI: 10.1-15.0; $p < 0.001$ and mean IGF-I bioactivity: 286 pmol/L, 95% CI: 220-353; $p = 0.02$). Z-scores for total IGF-I and IGF-I bioactivity were $< -1.5SD$ in 59% and 57% of patients ($\leq -2SD$ in 35% and 43%, respectively). IGF-BP3 and GH decreased and IGF-BP1 increased, although not significantly.
Conclusion Untreated CD is characterized by normal total IGF-I and IGF-I bioactivity. Low dose pasireotide normalized UFC in 29% of patients. Independently, one third of patients became IGF-I deficient ($\leq -2SD$). This effect of pasireotide may be, at least partially, mediated through somatotroph inhibition.

Sources of Research Support: Novartis.

Nothing to Disclose: AJV, RAF, CdB, AMP, RTN-M, PMJZ, SWJL, JAMJLJ, LJH

sort_order 2605
Pub # P3-536
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title Prolactin as a Marker of Successful Catheterization during Inferior Petrosal Sinus Sampling (IPSS) in Patients with ACTH-Dependent Cushing Syndrome
Author String ST Sharma, H Raff, LK Nieman
Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD; Aurora St Luke's Medical Center, Medical College of Wisconsin, Milwaukee, WI
Body **Background:** Inferior petrosal sinus sampling (IPSS) is the gold standard test for determining the etiology of ACTH-dependent Cushing's syndrome (CS). Abnormal venous drainage can lead to false negative results (1). Baseline ipsilateral inferior petrosal sinus to peripheral (IPS/P) prolactin (PRL) ratio >1.8 indicates successful catheterization (2). A normalized ACTH/PRL IPS/P ratio (peak ACTH IPS/P divided by baseline ipsilateral PRL IPS/P) >0.8 identifies Cushing's disease (CD), and a ratio of <0.6 identifies ectopic ACTH syndrome (EAS). In another series, false negative IPSS ACTH results had a PRL IPS/P ratio <1.3 (3). We further examined the utility of PRL as a marker of successful catheterization during IPSS.
Methods: Retrospective analysis of PRL levels in basal and CRH-stimulated IPSS samples from 29 patients (pts) with ACTH-dependent CS (2007-2010).
Results: Of the 29 pts, 17 had surgically proven CD, 8 had surgically proven EAS, and 4 had occult EAS. Of the 17 CD pts, 14 had peak ACTH IPS/P >3 consistent with a pituitary source and baseline PRL IPS/P >1.8 indicative of successful catheterization. Two CD pts with peak ACTH IPS/P >3 had misleading baseline PRL IPS/P ratios (0.8, 1.1) indicating failed catheterization; normalized ACTH/PRL IPS/P ratios (8.4, 11.6) correctly identified CD. In the one CD pt with a false negative peak ACTH IPS/P ratio of 1.3, baseline PRL IPS/P ratio of 1.0 showed unsuccessful catheterization and normalized ACTH/PRL IPS/P ratio of 1.3 accurately diagnosed CD. Of the 8 EAS pts, 7 had peak ACTH IPS/P ratios <3. Baseline PRL IPS/P in 6 of 7 pts indicated successful catheterization (>1.8) while it was indeterminate (1.8, ACTH/PRL IPS/P = 0.7) in one pt. One EAS pt had a peak ACTH IPS/P ratio of 9.5 (false positive), baseline PRL IPS/P ratio 1.7, and a normalized ACTH/PRL IPS/P ratio of 5.6 (cyclic EAS, sampled when eucortisolemic). All 4 occult EAS pts had peak ACTH IPS/P ratios <3. Baseline PRL IPS/P ratio in 2 pts was >3.0 (successful catheterization). The other 2 had baseline PRL IPS/P ratios of 1.6 and 1.2 suggestive of failed catheterization with ACTH/PRL IPS/P ratios of 1.1 (s/p transphenoidal surgery) and 0.9.
Conclusion: PRL measurement in IPSS can improve diagnostic accuracy in cases with an IPS/P ACTH ratio suggestive of EAS. It is not useful in cases with positive IPSS results and does not correct for false positive results in cyclic EAS. Confirmation of hypercortisolemia remains a prerequisite for IPSS.

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Sources of Research Support: Intramural program of the National Institute of Child Health and Human Development.

Nothing to Disclose: STS, HR, LKN

sort_order 2606
Pub # P3-537
Session Information POSTER SESSION: BASIC/TRANSLATIONAL - Glucocorticoid Disease & Physiology (1:30 PM-3:30 PM)
Title Paracrine Regulation of Cortisol Secretion by Serotonin (5-HT) Involving Illegitimate Membrane Receptors in Primary Pigmented Nodular Adrenal Disease (PPNAD)
Author String E Louiset, C Duparc, S Renouf, Z Bram, V Perraudin, R Libe, CA Stratakis, J Bertherat, H Lefebvre
University of Rouen, Mont Saint Aignan, France; University Paris V, Cochin Institute, Paris, France; NIH, Bethesda, MA; Institute for Biomedical Research and Innovation, University Hospital of Rouen, Rouen, France
Body In the normal adrenal gland, serotonin (5-HT), produced by mast cells, has been shown to stimulate cortisol secretion through activation of 5-HT receptor type 4 (5-HT4). Conversely, ectopic localization of 5-HT in steroidogenic cells as well as ectopic 5-HT7 receptors have been observed in some ACTH-independent macronodular adrenal hyperplasia (AIMAH) tissues causing Cushing's syndrome. The aim of the present study was to investigate the effect of 5-HT on cortisol secretion by PPNAD tissues by using pharmacological and molecular approaches. Graded concentrations of 5-HT induced a dose-response increase in cortisol production by cultured adrenocortical cells removed from 5 patients with PPNAD. The potency and efficacy of 5-HT to stimulate cortisol were higher in PPNAD than in normal adrenocortical cells. Quantitative RT-PCR showed that mRNA encoding 5HT4 receptor are overexpressed in PPNAD. Application of GR113808, a specific 5-HT4 receptor antagonist, significantly inhibited the stimulatory effect of 5-HT on cortisol secretion by both reducing the potency and efficacy of the indolamine. Conversely, the 5-HT4 receptor agonists cisapride and metoclopramide did not influence corticosteroidogenesis. In addition, the cortisol response to 5-HT was inhibited by the specific 5-HT7 receptor antagonist SB269970. These data indicate that, in PPNAD cells, the stimulatory action of 5-HT on cortisol release is mediated, at least partly, by an ectopic 5-HT7 receptor. In addition, they suggest that 5-HT-induced cortisol production also involves an isoform of the 5-HT4 receptor with an atypical pharmacological profile. The present study constitutes the first demonstration of the occurrence of functional ectopic receptors in PPNAD cells. Finally, incubation of PPNAD slices with antibodies against tryptophan hydroxylase, the key enzyme of 5-HT biosynthesis, revealed the presence of immunoreactive material in some steroidogenic cells suggesting that, in PPNAD tissues, 5-HT may modulate cortisol secretion through an autocrine/paracrine mechanism.

Sources of Research Support: INSERM U982, Institute for Biomedical Research and Innovation, the Carney Complex and COMETE (PHRC AOM06179) networks and ANR Genopat 2008.

Nothing to Disclose: EL, CD, SR, ZB, VP, RL, CAS, JB, HL

sort_order 2607
Pub # P3-538
Session Information POSTER SESSION: CLINICAL - Adrenal Cases: Insufficiency & Steroid Biosynthesis Disorders (1:30 PM-3:30 PM)
Title Unusual Late Presentation of 11 β -Hydroxylase Deficiency CAH with Novel Mutations in a Teenage Boy with TART: Classic or Non-Classic CAH?
Author String AK Mohyuddin, B Shah, RM Lind
New York University Medical Center, New York, NY
Body
Background: Congenital adrenal hyperplasia due to 11-beta hydroxylase is a rare genetic disorder. It is transmitted as an autosomal recessive trait. We describe a novel genetic mutation, in a 19 year old untreated male with 11-Beta hydroxylase deficiency, severe CAH with late presentation and TART.
Methods: A 19 years old Chinese male presented with testicular masses, hypertension and hypokalemia. Hormonal studies showed elevated 17-hydroxyprogesterone, androstenedione, DOC, ACTH and markedly elevated 11-deoxycortisol levels, low cortisol, aldosterone and plasma renin activity levels. Ultrasonographic imaging revealed markedly abnormal appearing testes, with diffuse hypervascularity and numerous confluent infiltrative nodules, suggestive of TART. Genetic analysis revealed novel R43Q in Exon1, A386V in Exon7 and G452V in Exon8 mutations on chromosome 8.
Results: Normalization of ACTH, reduction in 11-deoxycortisol, DOC and additional metabolites were achieved with steroid treatment.
Conclusion: This is a 19 yo male from China with CAH secondary to 11-beta hydroxylase who was found to have novel mutations.

Nimkam, S. et al. (2008) Steroid 11beta-hydroxylase deficiency congenital adrenal hyperplasia. Trends Endocrinol and Metab 19:96-99
White, P. (2001) Steroid 11beta-hydroxylase deficiency and related disorders. Endocrinology and Metabolism Clinics of North America 30:61-79
Claahsen-van der Grinten H. et al. (2009) Testicular adrenal rest tumours in congenital adrenal hyperplasia. Best Practice and Research Clinical Endocrinology and Metabolism 23:209-220

Nothing to Disclose: AKM, BS, RML

sort_order 2608
Pub # P3-539
Session Information POSTER SESSION: CLINICAL - Adrenal Cases: Insufficiency & Steroid Biosynthesis Disorders (1:30 PM-3:30 PM)
Title Variable Experience with Adrenalectomy as Treatment for Congenital Adrenal Hyperplasia (CAH)
Author String MK Crocker, CA Van Ryzin, DP Merke
National Institutes of Health, Bethesda, MD; National Institutes of Health, Bethesda, MD
Body
Background: Patients with CAH may undergo bilateral adrenalectomy in cases where adrenal androgens have been difficult to control medically.
Case 1: A 22-year-old female was noted to have ambiguous genitalia at two years of age and was diagnosed with CAH due to 21-hydroxylase deficiency. During adolescence, the patient had persistently high androgens and developed secondary amenorrhea from age 15 onward. Despite adding flutamide to her glucocorticoid and mineralocorticoid regimen, the patient continued to have amenorrhea and had hyperplastic adrenal glands on imaging. At 21 years of age she desired fertility and underwent laparoscopic bilateral adrenalectomy. Following the surgery, she had regular menses and no biochemical hyperandrogenism. She has conceived two pregnancies naturally without complications, 11 and 26 months following adrenalectomy.
Case 2: A 31-year-old female was born with Prader 4 genitalia and subsequently was diagnosed with 21-hydroxylase deficiency. Despite standard doses of suppressive glucocorticoid therapy, she developed significant virilization. At 16 years of age imaging revealed bilateral adrenal hyperplasia, and adrenal, ovarian, and renal venous sampling excluded other sources of androgens. She underwent bilateral adrenalectomy via laparotomy with initial improvements in her hyperandrogen symptoms. However, over the next 10 years with intermittent compliance of medications, her hyperandrogenism returned. Following a Liddle's dexamethasone suppression test (0.5 mg q6hr for 8 doses), her 17-OH-progesterone fell from 1750 ng/dL to <40, androstenedione from 494 ng/dL to 21, and testosterone from 339 ng/dL to 15. We suspect that a chronic course of noncompliance may have aggravated the production of ACTH, activating adrenal rest tissue. Imaging studies have not found the source of the adrenal rest tissue.
Conclusion: Following adrenalectomy, ectopic adrenal rest tissue may continue to produce androgens in CAH patients under the control of ACTH, leading to recurrence of virilization. Successful treatment of CAH with adrenalectomy may depend on the presence of adrenal rest tissue; however, identification and localization of adrenal rest tissue is difficult, especially in females. Future studies could use ¹⁸F-FDG-PET/CTs before and after cosyntropin stimulation testing to identify this tissue.

Sources of Research Support: The Intramural Research Programs of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Institutes of Health Clinical Center; The Congenital Adrenal Hyperplasia Research, Education and Support (CARES) Foundation; DPM is a Commissioned Officer in the United States Public Health Service.

Nothing to Disclose: MKC, CAVR, DPM

sort_order 2609
Pub # P3-540
Session Information POSTER SESSION: CLINICAL - Adrenal Cases: Insufficiency & Steroid Biosynthesis Disorders (1:30 PM-3:30 PM)
Title P450-Oxidoreductase Mutation Modulating 21-Hydroxylase Deficiency Phenotype
Author String ACL Pereira, RPP Moreira, TP Sickler, AAL Jorge, BB Mendonca, TASS Bacheqa, LG Gomes
Universidade de São Paulo, São Paulo, Brazil; Universidade de São Paulo, São Paulo, Brazil
Body Adrenal 21-hydroxylase deficiency (21OHD) is a monogenic disorder with a large spectrum of clinical manifestations, varying from prenatal external genital virilization to late onset symptoms. Despite good genotype/phenotype correlation, *CYP21A2* mutations do not explain some phenotypic variations, which could be explained by polygenic interactions. Recently, the case of a patient carrying a heterozygous P450-oxidoreductase (POR) p.A287P mutation minimizing the SW-21OHD phenotype was reported (1). Besides milder virilization, this patient also presented bone abnormalities typical of POR deficiency. Objective: To describe a patient carrying a POR mutation modulating the SW-21OHD phenotype. Case Report: A girl born from consanguineous parents with external genitalia virilization (Prader 3) and clubfoot at birth had adrenal crisis in the first month of life when 21OHD was diagnosed. She underwent genitoplasty and foot surgeries during early infancy. Treatment adherence was irregular during growth periods, she stopped the glucocorticoid and mineralocorticoid replacement for years, but did not present adrenal crisis. Follow up was restarted in our Institution when she was 28 yrs of age, height was 135 cm and weight was 44.8 kg. Basal 17OHP was 294 ng/mL, progesterone 42 ng/mL, 11-desoxycortisol 8 ng/mL, androstenedione 11 ng/mL, testosterone 340 ng/dL and PRA 16 ng/mL/h. CT scan showed enlarged adrenal glands (2.0x4.0 cm right and 2.0x6.5 cm left). Low dexamethasone dose of 0.15 mg/d was enough to normalize androgen levels. Patient started irregular menses at 34 yrs old despite good hormonal control and developed menopause at 44 yrs old. *CYP21A2* analysis confirmed compound heterozygous mutations (1759>T and the new mutation 1032-1037del) predicting the SW-21OHD phenotype. The presence of bone malformations and precocious ovarian insufficiency led to POR gene analysis, and the heterozygous p.C569Y mutation was found. This mutation was first described in compound heterozygosis with another POR mutation in a patient with primary amenorrhea and large ovarian cysts, characterizing the mildest POR deficiency phenotype (2). Conclusion: Although POR mutations seem to be rare, we described the second case of classical 21OHD associated with POR mutation. The POR mutation in SW-21OH patients may account for lower glucocorticoid needs during CAH treatment, premature ovarian insufficiency and bone abnormalities.

(1) Scott RR, Gomes LG et al., J Clin Endocrinol Metab 2007; 92:2318-2322
(2) Fluck CE et al., Nat Genet 2004; 36:2128-35

Sources of Research Support: CNPq # 305117/2009-2.

Nothing to Disclose: ACLP, RPPM, TPS, AALJ, BBM, TASSB, LGG

sort_order 2610
Pub # P3-541
Session Information POSTER SESSION: CLINICAL - Adrenal Cases: Insufficiency & Steroid Biosynthesis Disorders (1:30 PM-3:30 PM)
Title Novel and *De Novo* Mutation in the *STAR* Gene in a Japanese Patient with Congenital Lipoid Adrenal Hyperplasia
Author String N Katsumara, T Nakamura
National Research Institute for Child Health & Development, Tokyo, Japan; Kumamoto Central Hospital, Kumamoto, Japan
Body **Background:** Mutations in the *STAR* gene, encoding steroidogenic acute regulatory protein (StAR), cause congenital lipoid adrenal hyperplasia (CLAH), an autosomal recessive disorder in which synthesis of all the steroids is impaired. StAR facilitates the entry of cholesterol into mitochondria, where it is converted to pregnenolone by the side-chain cleavage enzyme (P450_{scc}). Affected infants are born with female external genitalia regardless of genetic sex, because the fetal testis fails to produce testosterone.
Patient: The patient was the first daughter born to healthy Japanese parents. She had been well until 3 months of age, but started to lose her weight since 4 months of age. At 7 months of age she developed adrenal crisis, and was referred to us. On admission, the patient had generalized skin pigmentation and normal female external genitalia with no ambiguity. Serum Na was low, and plasma ACTH and PRA were elevated. The karyotype was 46,XY. Abdominal MRI detected a blunt-ended vagina, no uterus, left inguinal and right intraabdominal testes, and normal adrenal glands. Based on these findings, the patient was diagnosed as having CLAH, and was successfully treated with hydrocortisone and fludrocortisone.
In vitro studies: Genetic analysis revealed that the patient was a compound heterozygote having a novel and *de novo* p.T204R mutation in the paternal allele and a previously described p.Q258X mutation in the maternal allele of the *STAR* gene. To determine the significance of the p.T204R mutation, we transiently expressed the wild-type and the mutant StAR along with an NH₂-P450_{scc}-adrenodoxin reductase-adrenodoxin-COOH fusion protein in COS-1 cells. The wild-type StAR efficiently facilitated the conversion of cholesterol to pregnenolone, but the p.T204R mutant did not enhance the conversion at all.
Conclusion: The novel and *de novo* p.T204R mutation as well as the p.Q258X mutation totally abolishes StAR activity and causes clinically manifest CLAH.
Nothing to Disclose: NK, TN

sort_order 2611
Pub # P3-542
Session Information POSTER SESSION: CLINICAL - Adrenal Cases: Insufficiency & Steroid Biosynthesis Disorders (1:30 PM-3:30 PM)
Title Virilized Female with Untreated Simple Virilizing Congenital Adrenal Hyperplasia (CAH) Due to 21-Hydroxylase Deficiency Who Is Living Successfully as a Male Presents with Multiple Extra-Adrenal Adrenal Myelolipomas
Author String NS Tarlin, AA Sheth, JP Dave, LY Lee
Elmhurst Medical Center, Elmhurst, NY; Elmhurst Medical Center, Elmhurst, NY; Elmhurst Medical Center, Elmhurst, NY
Body Background: Adrenal myelolipomas are uncommon tumors that have been reported with increased frequency in patients with CAH. Elevations of ACTH and possibly testosterone are thought to play a role in their development (1). Reports of extra-adrenal adrenal myelolipomas are extremely rare (2).
Clinical Case: Thirty-nine year old sexually active phenotypic male was found to have bilateral adrenal thickening with 2.2 cm right adrenal nodule and multiple heterogenous serpiginous suprarenal and periadrenal masses during an evaluation for cholecystitis. Patient was born with ambiguous genitalia. Initially the patient was raised as a female. At age 13 he began living as a male and at age 20 he was diagnosed with CAH. Chromosomal analysis was XX. Patient had a hysterectomy, followed by reconstructive surgery for the ambiguous genitalia. Except at the time of his initial surgery, he did not receive glucocorticoids. He was treated with testosterone up until seven years prior to his presentation. Physical exam revealed 5', 107 pound male with blood pressure 110/67. Genital exam showed small phallus with urethral meatus at its base and a partially fused labia.
Hormone values revealed ACTH 110 ng/dl (7-50 ng/dl), 17-hydroxyprogesterone 6984 ng/dl (42-196 ng/dl), androstendione 975 ng/dl (40-190 ng/dl), testosterone 276 ng/dl (270-1734 ng/dl males). On dexamethasone and fludrocortisone replacement, ACTH declined to 10 ng/dl (7-50 ng/dl), 17-hydroxyprogesterone to 88ng/dl (42-196 ng/dl), androstendione to 16 ng/dl (10-190 ng/dl), and testosterone to 4.6 ng/dl (270-1734 ng/dl males). CT imaging after four months of steroids showed decrease in adrenal nodule size, but only a slight decrease in the size of the masses. Laproscopic biopsy of the masses revealed adipose tissue, mature hematopoietic cells, and adrenal tissue.
Conclusion: This patient with simple virilizing CAH lived successfully as a male without glucocorticoid supplementation and in later years without androgen supplementation. Prolonged excess ACTH secretion led to adrenal hyperplasia as well as growth of presumed adrenal rest tissue with myelolipoma development. All patients with simple virilizing CAH should be encouraged to adhere to glucocorticoid and mineralocorticoid replacement as they are at risk for growth of adrenal rest tissue, and development of adrenal nodules and myelolipomas.

(1) Seyle H, Stone H. Hormonally induced transformation of adrenal gland into myeloid tissue. *Am J Pathol* 1950; 26:211-233
(2) Allison KH, Mann GN, Norwood TH, Rubin BP. An Unusual Case of Multiple Giant Myelolipomas: Clinical and Pathogenic Implications 2003; 14(1):93-100.

Nothing to Disclose: NST, AAS, JPD, LYL

sort_order 2612
Pub # P3-543
Session Information POSTER SESSION: CLINICAL - Adrenal Cases: Insufficiency & Steroid Biosynthesis Disorders (1:30 PM-3:30 PM)
Title Time and Degree of Salt-Wasting Crisis in Newborns with Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency (CAH)
Author String HG Doerr, C Loeffler, TK Voelkl, C Schoeff
University of Erlangen Nuremberg, Erlangen, Germany; University of Erlangen Nuremberg, Erlangen, Germany
Body The clinical presentation of CAH varies according to the severity of the enzyme defect and the sex of the child. In the present study, we retrospectively analysed the onset and extent of the salt-wasting (SW) crisis in 91 children with CAH (42 m, 49 f). The diagnosis based on clinical and laboratory values and was molecular-genetically confirmed in 90 cases. None of the children has died due to the SW-crisis. The children were born in 34 different hospitals between 1970 and 2008. The relevant data from the newborn period was taken from the medical reports or patient files of the given hospitals. Most genotypes belonged to the groups O (38%) and A (48.8%). Newborn screening, which was not introduced in Bavaria until 1 January 1999, was performed on 26 (15 m, 11 f) newborns. Forty of the 49 girls were admitted as in-patients due to their ambiguous genitalia. Weight loss occurred most frequently (71%), followed by the combination of poor feeding + vomiting with 53.6%, poor feeding + vomiting + poor weight gain (21.4%), poor weight gain (17.8%), and poor feeding (7.1%). The children were admitted at different times: 38/49 girls (77.5%) and 12/42 boys (28.5%) during their first postnatal week, and another 7 girls (7.7%) and 15 boys (35.7%) in their second week. 40/42 boys and 48/49 girls were admitted during the newborn period. The mean serum sodium concentrations (\pm SD) were 127.8 (\pm 8.7) mmol/L; the mean serum potassium concentrations were 6.76 (\pm 1.81) mmol/L. The boys showed statistically significantly lower sodium and higher potassium concentrations. The data indicates a close correlation between the clinical symptoms and the electrolyte levels in the serum: the more serious the clinical symptoms, the more serious the electrolyte changes. The lowest sodium value measured was 102 mmol/L. The analysis of the 26 children with newborn screening showed that the children included in the screening were admitted on average 5.0 days (range: 0 - 18 days) significantly earlier ($p < 0.01$) than those without screening. However, 15 (11 m, 4 f)/26 newborns (57.7%) already had low sodium values < 132 mmol/L at the time of admission. In summary, the analysis shows that children with classical CAH with SW were admitted as in-patients for various reasons. The number of boys admitted as in-patients does not exceed that of the girls until the second postnatal week. In 27 infants, the serum sodium concentrations are already pathologically low during their first postnatal week.

Nothing to Disclose: HGD, CL, TKV, CS

sort_order 2613
Pub # P3-544
Session Information POSTER SESSION: CLINICAL - Adrenal Cases: Insufficiency & Steroid Biosynthesis Disorders (1:30 PM-3:30 PM)
Title Effect of Ethosuximide on Cortisol Metabolism in the Treatment of CAH
Author String M Yau, M Vogiatzi
NYPH- Weill Cornell Medical College, New York, NY
Body
Background: There is an abundance of literature regarding antiepileptics, such as phenytoin and Phenobarbital, and cortisol metabolism. To our knowledge, there is no information about the effects of ethosuximide on cortisol metabolism.
Clinical case: Our patient is a 10 year old girl with salt wasting CAH, diagnosed at birth. Genotype was significant for deletion of both CYP21 genes. She was treated successfully with standard doses of hydrocortisone (HCT) and fludrocortisone until the age of 6 years. At that point, she developed absence seizures that required therapy with ethosuximide. Over the next couple of years, the patient experienced worsening adrenal control with rapid growth and bone age advancement that resolved with progressive increase in her hydrocortisone dose up to 28mg/m²/day. Since then, the patient is maintained on high doses of hydrocortisone with no evidence of Cushingoid features or negative effect on growth. Adrenal control is satisfactory and bone age advancement is appropriate. Further increases in ethosuximide dose resulted in worsening of adrenal control that was successfully treated with increasing doses of hydrocortisone.
Adrenal control was assessed by morning measurements of 17hydroxyprogesterone, androstendione and testosterone. Bone ages were obtained every six months. Weight, height and physical exam were performed every 3 months. We provide data over 4 years that demonstrate a clear correlation between adrenal hormone secretion, cortisol requirements and ethosuximide dose, indicating an effect of ethosuximide on cortisol metabolism.
Conclusion: This is the first case demonstrating an interaction between ethosuximide and HCT metabolism in the treatment of SW CAH. Other antiepileptics have been shown to increase HCT metabolism by increasing 6B-hydroxylase activity in the liver, but no such activity has been reported with ethosuximide use. Furthermore, there is a major role in ethosuximide metabolism for CYP3A which is part of the Cytochrome P450 (CYP) superfamily involved in the metabolism of a wide variety of endogenous and exogenous compounds. Corticosteroid hormone metabolism, also, involves members of the CYP superfamily. Although, no common enzymes in the metabolism of HCT and Ethosuximide have been described so far, we provide clinical evidence for such interaction.
Nothing to Disclose: MY, MV

sort_order 2614
Pub # P3-545
Session Information POSTER SESSION: CLINICAL - Adrenal Cases: Insufficiency & Steroid Biosynthesis Disorders (1:30 PM-3:30 PM)
Title Sex Reversal in Two Mexican-American Siblings Secondary to a Splice-Site Mutation in the Gene for Steroidogenic Acute Regulatory Protein (*STAR*)
Author String KA Hicks, L Karaviti, GS Jeha, S Gunn, N Sakkary, JE Dietrich, VR Sutton
Baylor College of Medicine, Houston, TX; Baylor College of Medicine, Houston, TX; Baylor College of Medicine, Houston, TX
Body Background: Mutations in *STAR* prevent adrenal synthesis of steroid hormones and cause a phenotype of adrenal insufficiency and feminization in males.
Clinical Case: Two Mexican-American siblings, ages 5 years and 22 months, with known adrenal insufficiency presented for sex assignment evaluation after a karyotype revealed both children were 46,XY. Physical exam demonstrated female external genitalia without clitoromegaly. Gender identity was female. Aldosterone, 11-deoxycortisol, and androgen precursors were undetectable in both patients. A 250 [micro]g ACTH stimulation test was performed and subsequent levels of 17-OH progesterone, 17-OH pregnenolone, and progesterone were undetectable (17-OH progesterone <8 ng/dl, 17-OH pregnenolone <6 ng/dl, and progesterone <0.1 ng/ml). Anti-mullerian hormone (AMH) was elevated, 16 ng/ml (0-7.1 ng/ml) in the 5 year old and 18 ng/ml (0-7.1 ng/ml) in the 22 month old. FISH results were positive for the SRY gene. Differential diagnosis included cholesterol desmolase deficiency with a P450 side chain cleavage enzyme mutation versus a mutation in *STAR*.
Gonadectomy was performed, and gonadoblastoma was absent. Lipid accumulation was present within the testicles. The 22 month old had abundant lipid deposition in comparison to her sibling. Despite the lack of adrenal hypertrophy on initial MRI, the abundance of testicular lipid deposition was consistent with the pathophysiology of congenital lipoid adrenal hyperplasia (CLAH) and was most severe in the 22 month old patient with the highest initial ACTH level, 1549 pg/ml. DNA sequencing of both children revealed a homozygous splice-site mutation in *STAR* at c.64+1G>T, at the first nucleotide within intron 1. This specific mutation was described before, in a Chilean patient (1), but most cases of CLAH have not been detailed within the Mexican-American population. Despite the perceived lack of consanguinity, the parents are of Mexican descent from the same geographical region in south Texas. DNA sequencing of the parents was obtained to determine if the parents are heterozygous carriers of the same mutation.
Conclusion: Common mutations of *STAR* have been described, the Q258X mutation of patients of Japanese or Korean ancestry and the R182L mutation of patients of Palestinian ancestry. We confirm the prior finding of a splice-site mutation at c.64+1G>T within the Latin American population, but within a unique subset, specifically two 46,XY siblings of Mexican-American descent.

(1) González AA, Reyes ML, Carvajal CA, Tobar JA, Mosso LM, Baquedano P, Solar A, Venegas A, Fardella CE 2004 Congenital lipoid adrenal hyperplasia caused by a novel splicing mutation in the gene for the steroidogenic acute regulatory protein. *J Clin Endocrinol Metab* 89: 946-951.

Nothing to Disclose: KAH, LK, GSI, SG, NS, JED, VRS

sort_order 2615
Pub # P3-546
Session Information POSTER SESSION: CLINICAL - Adrenal Cases: Insufficiency & Steroid Biosynthesis Disorders (1:30 PM-3:30 PM)
Title Infants and Children with Hyporeninemic Hypoaldosteronism -- A Case Series
Author String I Majumdar, CH Albini
Women and Children's Hospital of Buffalo, Buffalo, NY; University at Buffalo, School of Medicine and Biomedical Sciences, Buffalo, NY
Body **Background:** Hyporeninemic hypoaldosteronism is common in adults with chronic kidney disease (CKD) and renal acidosis(1). It is infrequently reported in children. We report a pediatric case series focusing on presentation, treatment, and clinical outcome.
Clinical Cases:
Case 1: A four-month former 29 week premature male presented with failure to thrive (FTT). Laboratory studies revealed normal renal function, hyponatremia (serum Na: 132-133mEq/L), hyperkalemia (serum K:6.3-6.5mEq/L), and mild non-anion gap acidosis. Physical examination was unremarkable except for corrected weight and length both <3rd percentile. Serum aldosterone and plasma renin activity were inappropriately low (3ng/dl and 5.2ng/ml/h, respectively). Testing for adrenal insufficiency was negative. Serum Na corrected with high dose fludrocortisone (0.2mg/day) and Na supplementation (8mEq/kg/day). Fludrocortisone was discontinued by 1 year. Hyperkalemia and acidosis resolved, while FTT persists.
Case 2: A five month former 26 week premature male presented with persistent hyperkalemia (serum K: 5.5-6.9 mEq/L) and borderline low Na (134 mEq/L) in the face of normal renal function. Physical examination was unremarkable. Aldosterone and plasma renin activity were inappropriately low (6 ng/dl and 1.7ng/ml/hr respectively). Adrenal function was otherwise normal. Hyperkalemia and hyponatremia corrected with fludrocortisone (0.25mg/day) alone which was weaned off by 13 months. Growth is normal.
Case 3: A 20-month girl with global developmental delay and FTT presented with persistent hyponatremia (serum Na: 121-123 mEq/L), normokalemia, normal renal function, and mild non-anion-gap acidosis. Physical examination revealed microcephaly, cleft palate (repaired), and left eye coloboma. No other mid-line defects were present. MRI brain ruled out a pituitary lesion. Aldosterone and plasma renin activity were inappropriately low (<1 ng/dl and <0.5ng/ml/hr, respectively). Fasting morning ACTH and cortisol levels were normal. Hyponatremia improved with high dose fludrocortisone (0.3mg/day) and oral Na supplementation which could not be weaned. Acidosis has resolved yet growth failure persists.
Conclusion: Clinical presentations and outcomes in children with hyporeninemic hypoaldosteronism differ markedly from adults. CKD was not seen in any case. All children responded to high dose fludrocortisone which was discontinued in two of three cases. Acidosis resolved in all. FTT persisted in two-thirds of cases.

(1)Weidmann P et al., J. Clin. Endocr. Metab. 1973;36:965

Nothing to Disclose: IM, CHA

sort_order 2616
Pub # P3-547
Session Information POSTER SESSION: CLINICAL - Adrenal Cases: Insufficiency & Steroid Biosynthesis Disorders (1:30 PM-3:30 PM)
Title Bilateral Adrenal Enlargement Due to Vasculitis
Author String T Tylee, D Trencé
University of Washington, Seattle, WA
Body **Background:** Adrenal enlargement with adrenal insufficiency (AI) is classically associated with infiltrative diseases such as tuberculosis, fungal infection or metastases. We describe a case of bilateral adrenal enlargement due to vasculitis.
Case: A 47 year old female presented to an outside hospital with seven months of intermittent abdominal pain, 50 pound weight loss, nausea and anorexia. Extensive evaluation was unremarkable except for an abdominal CT showing bilaterally enlarged adrenal glands, right 1.6 x 4.5 cm, left 1.7 x 3.2 cm. Her condition continued to worsen with the development of acute renal failure and she was transferred to our hospital for further evaluation. On admission, the patient continued to complain of diffuse abdominal pain. Exam revealed a cachectic female with stable vital signs, weight 33 kg (BMI 16.4), with diffusely tender abdomen. Skin exam was normal without hyperpigmentation. Admission labs included sodium 128 mEq/L, potassium 5.3 mEq/L, and creatinine 2.4 mg/L. Urinalysis showed greater than 100 RBCs. Baseline cortisol was 11.9 mcg/dL. ACTH stimulation test with 250 mcg cosyntropin gave cortisols of 16.0 mcg/dL at 30 minutes and 16.9 mcg/dL at 60 minutes. ACTH was 45 pg/mL. Rheumatology labs revealed positive c-ANCA 1:1024 and anti PR3 2.0. Renal biopsy was consistent with vasculitis.
Conclusion: Our patient had symptoms of AI with unexplained bilateral adrenal enlargement on imaging. Traditional differential diagnoses for AI with adrenal enlargement include infiltrative processes or hemorrhage. She had no evidence on extensive work-up of infiltrative diseases and no evidence of adrenal hemorrhage clinically or on imaging. Renal biopsy led to the diagnosis of systemic vasculitis. Review of the literature describes one prior case report of unexplained bilateral adrenal enlargement on CT, associated with vasculitis (1). Evidence of peri-adrenal arteritis on adrenal biopsy in that case suggested the glands were directly affected by the vasculitis and this was the etiology of the enlarged adrenals viewed on CT. We present that inflammation from the vasculitis in this case led to the enlarged adrenal glands on imaging and our patient's evolving AI. This case demonstrates the importance of considering vasculitis in the differential diagnosis of bilateral adrenal enlargement to ensure prompt diagnosis and appropriate treatment.

(1) Janssen M, et al. Bilateral adrenal enlargement as a first sign of systemic vasculitis. *Netherlands Journal of Medicine* 51 (1997): 146-149.

Disclosures: DT: Stock Owner, Medtronic Minimed; Principal Investigator, Novo Nordisk. Nothing to Disclose: TT

sort_order 2617
Pub # P3-548
Session Information POSTER SESSION: CLINICAL - Adrenal Cases: Insufficiency & Steroid Biosynthesis Disorders (1:30 PM-3:30 PM)
Title A Case of Tan in Winter: Addison Disease in a 44-Year-Old Woman
Author String SV Peechakara, L Olansky
Cleveland Clinic Foundation, Cleveland, OH
Body
Introduction
Primary adrenal insufficiency (AI) or Addison's disease (AD) was first described by Thomas Addison in 1855, a clinical syndrome secondary to failure of adrenal cortex, resulting in deficient glucocorticoids, mineralocorticoids and androgens. The prevalence for AD is 110-144 cases per million, with autoimmune etiology being the most common. Since it is a rare syndrome, there is often a delay in diagnosis which can be fatal.
Clinical case
44 year old female was admitted with severe hyponatremia, hypotension and somnolence. She reported dizziness, nausea and vomiting for four days, weight loss of ten lbs in six months, fatigue, cold intolerance and a tan since summer which she said would not go away. Further questioning revealed salt craving, hair loss, regular menstrual cycle, and no galactorrhea. Past medical history of scoliosis for which she had multiple spine surgeries. Family history non contributory. Not on any medications. Physical exam (PE): HR: 60bpm, BP: 82/38mmHg, BMI: 22, generalized hyperpigmentation especially on the palmar creases and on the surgical scars. Rest of the PE was normal.
Lab: Na: 116mmol/L (132-148), K: 4.2mmol/L(3.5-5), Cl:91mmol/L(98-110), BUN/Creatinine: 6mg/dl/0.49mg/dl (8-25/0.7-1.4), Hb/HCT: 11.8g/dl/33.5%(11.5-15.5/36-46), ACTH stimulation test: peak cortisol at 60 minute :2.3ug/dl, ACTH : 1180pg/ml (8-42), DHEAS :4.4ug/dl(10-221), testosterone: <10(20-70ng/dl), Aldosterone : <2.8ng/dl(4.5-35.4), Renin(upright): 54.2ug/L/hr(0.8-5.8) Thyroid function tests were normal. Brain MRI showed mildly enlarged pituitary gland with deviation of pituitary stalk. Abdominal CT scan revealed normal anatomy of adrenal glands. She was diagnosed with Idiopathic AD. Managed with intravenous hydrocortisone and normal saline. Once stabilized, was started on oral hydrocortisone 40 mg in three divided doses and decreased to 20 mg after a few weeks, 0.1mg of fludrocortisone and DHEAS 25mg daily. At one month follow up, repeat ACTH: 78pg/ml, metabolic panel was normal. Hyperpigmentation and her symptoms completely resolved.
Conclusion
AI should always be considered in patients with hyponatremia. While initial presentations of fatigue, nausea, vomiting as in our patient are non specific, hyperpigmentation is characteristic of AD and high clinical suspicion is warranted. Timely diagnosis will avert a definite catastrophic event which requires increased awareness of the syndrome, especially amongst primary care physicians.

Nothing to Disclose: SVP, LO

sort_order 2618
Pub # P3-549
Session Information POSTER SESSION: CLINICAL - Adrenal Cases: Insufficiency & Steroid Biosynthesis Disorders (1:30 PM-3:30 PM)
Title Acute Secondary Adrenal Insufficiency from Valproic Acid -- A Case Report
Author String S Ishaq, SK Arora
Overton Brooks VA Medical Center, Shreveport, LA
Body
Introduction
Valproic acid is used primarily as an anti-epileptic agent and a mood stabilizer. It is a gamma-aminobutyric acid (GABA) reuptake inhibitor and by increasing GABA, it can potentially suppress corticotrophin releasing hormone (CRH) and cause secondary adrenal insufficiency.
Case Report
63 years old white man with hypertension, diabetes, stage II chronic kidney disease and bipolar disorder was admitted for aggressive behavior and homicidal ideation. He was on valproic acid 1000 mg daily for 6 months with therapeutic plasma level. On day 9th of admission, he developed hypotension, hyponatremia, mild hyperkalemia and worsening renal function, requiring transfer to intensive care unit. Despite intravenous fluids and vasopressors, his blood pressure remained low. Stress dose glucocorticoids were given for suspected acute adrenal insufficiency, which normalized blood pressure and electrolytes within 24 hours. His random cortisol and adrenocorticotropic hormone (ACTH) levels were inappropriately low for degree of stress and hypotension. Plasma aldosterone and renin levels were elevated. A dedicated adrenal CT showed no hemorrhage, infarction, atrophy or calcification. Anti-adrenal and 21-hydroxylase antibodies were absent. A brain MRI did not reveal any abnormality or mass lesion in hypothalamic-pituitary region. Patient was not on steroids, opioids or other drugs known to affect hypothalamic-pituitary-adrenal axis. Of note, patient had an appropriate cortisol response to infection and hypotension induced stress during a hospitalization prior to starting valproic acid. In absence of other causes, valproic acid was the most likely explanation for patient adrenal insufficiency and it was stopped. He was briefly treated with hydrocortisone and has done well with recovery of ACTH level to normal range and appropriate cortisol response to short ACTH stimulation test.
Discussion
We report first case of acute secondary adrenal insufficiency from valproic acid which is widely used in treatment of seizures and bipolar disorder. Valproic acid has been reported to inhibit synthesis and release of CRH in animal studies. An open clinical trial on safety of valproic acid demonstrated secondary adrenal insufficiency as a significant adverse event in one patient. The cortisol lowering effect of valproic acid is rare, however, evaluation of cortisol level may be valuable during long term therapy with valproic acid, particularly in acutely sick patients.

Nothing to Disclose: SI, SKA

sort_order 2619
Pub # P3-550
Session Information POSTER SESSION: CLINICAL - Adrenal Cases: Insufficiency & Steroid Biosynthesis Disorders (1:30 PM-3:30 PM)
Title Using [lsquo]Prolonged[rsquo] Cosyntropin Stimulation Test to Diagnose Secondary Adrenal Insufficiency after a Single Epidural Injection of Triamcinolone Acetonide (Kenalog[reg]) – A Rare Case
Author String Y Feng, N Needleman, T Araki, AM Fleckman
Beth Israel Medical Center, New York, NY; Beth Israel Medical Center, New York, NY
Body
Background
Cosyntropin stimulation tests (CSTs) diagnose primary with a higher sensitivity than secondary adrenal insufficiency (AI)¹. The common method to diagnose AI uses 250ug ACTH with a cortisol cutoff of 18ug/dL in non-stressed patients. Failure to respond does not separate primary from secondary AI. We present a rare case of adrenal suppression following a single epidural triamcinolone acetonide (Kenalog[reg]) injection that was diagnosed using a 'prolonged' CST.
Case Presentation
A 47 year old man with HTN and HIV was diagnosed with diabetes mellitus (DM) and started on sitagliptin 50mg PO daily. Two weeks later he received a single 80mg epidural Kenalog[reg] injection in his right hip for arthritic pain. He presented 10 days later with abdominal pain, nausea, vomiting, and blood glucose > 500 mg/dL; was admitted for pancreatitis and uncontrolled DM; and treated with IV hydration and escalating insulin doses. 48 hours later gastrointestinal symptoms resolved but diabetes remained difficult to control. Morning cortisol level obtained for hyponatremia was undetectable, while vital signs were stable and appetite robust. Cortisol increased from baseline 2 to 4 and 6 ug/dL at 30 and 60 minutes in response to a rapid injection of 250ug ACTH ([ldquo]short [rdquo] CST). The CST was repeated using a 'prolonged' ACTH test. Cosyntropin 250ug in normal saline was infused over six hours. Cortisol values were 1, 14, 20 and 16 ug/dL at 0, 2, 4 and 6 hours respectively. Urinary triamcinolone acetonide level was 4.9 ug/dL (normal < 0.1). ACTH levels at 0 min for both short and prolonged tests were < 2 and 4 ng/L respectively.
Discussion
The blunt response to short CST did not fit with the patient's clinical picture. We hypothesize that our patient's apparent AI was secondary to pituitary suppression from the Kenalog[reg] injection. Initial course following injection was suggestive of glucocorticoid (GC) excess. Systemic effects have been described with topical steroids², rare cases of joint injection³ and in multiple reports of inhaled corticosteroids⁴. Best methods to diagnose AI, and to differentiate primary from secondary AI, remain controversial⁵.
Conclusion
This case demonstrates: 1) the potent and persistent effects of GC absorbed from joint spaces; 2) the inability of a short CST to discriminate primary from secondary AI even after a brief period of pituitary suppression; and 3) the use of a prolonged ACTH infusion for more accurate separation of primary from secondary AI.

1) Dorin RI, Qualls CR, Crapo LM. Diagnosis of adrenal insufficiency. *Ann Intern Med.* 2003 Aug 5; 139 (3): 194-204.
2) Martine Duclos, Michel Guinot, Marina Colsy, Francis Merles, Christophe Baudot, Jean Benoit Corcuff, and Yves Lebouc. High Risk of Adrenal Insufficiency after a Single Articular Steroid Injection in Athletes. *Med Sci Sports Exerc.* 2007 Jul;39(7):1036-43.
3) Schott S, Schnauder G, Müssig K. Secondary adrenal insufficiency after local injections of triamcinolone acetonide. *Dtsch Med Wochenschr.* 2009 Feb; 134(7):298-301. Epub 2009 Feb 5.
4) Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. *Arch Intern Med.* 2000 Sep 11; 160(16):2549-50.
5) Magnotti M, Shimshi M. Diagnosing adrenal insufficiency: which test is best -- the 1-microg or the 250-microg cosyntropin stimulation test? *Endocr Pract* 2008; 14:233-238

Nothing to Disclose: YF, NN, TA, AMF

sort_order 2620
Pub # P3-551
Session Information POSTER SESSION: CLINICAL - Adrenal Cases: Insufficiency & Steroid Biosynthesis Disorders (1:30 PM-3:30 PM)
Title Primary Adrenal Insufficiency Presenting as a Periodic Fever Syndrome
Author String JM Sharretts, LK Nieman
National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD; Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD
Body
Background: Primary adrenal insufficiency (AI) is an uncommon disease that often presents with nonspecific symptoms. Fever is not typical in the absence of underlying infection or inflammation. Clinical case: A previously healthy 18 year-old male presented for endocrine evaluation for a three-year history of relapsing fevers as high as 104 F, lasting 3-5 days, recurring every 4-6 weeks, and without sweats or rigors. Prior evaluation found mild anemia, a weakly positive ANA titer and IgA deficiency. One year ago, he was presumptively diagnosed with PFAPA (periodic fever, aphthous stomatitis, pharyngitis, adenitis). A single oral dose of prednisone 20 mg at the onset of episodes decreased duration of fever to less than 24 hours. Frequency of episodes gradually increased to every 3-4 weeks. He developed severe fatigue, increased sleep requirements, decreased exercise tolerance, and worsening memory and concentration. He dropped out of college. Subclinical hypothyroidism was diagnosed six months ago and treated with levothyroxine 50 mcg daily. One month ago, increased pigmentation was noted. Electrolytes, ESR and CRP were normal at that visit. At our visit, he denied poor appetite, nausea, vomiting, weight loss or salt craving. On exam, he had postural hypotension and shotty cervical adenopathy. Hyperpigmentation was present and most notable on the hand creases, knuckles, and scars. Labs demonstrated hyponatremia, hyperkalemia and hypoglycemia. Serum cortisol was undetectable at baseline (8 am) and following cosyntropin 250 mcg intravenously. Plasma renin was 61 ng/mL/hr (0.6-4.3), ACTH was 1877 pg/mL (0-46) and 21-hydroxylase antibody titer was 15 units/mL (<1). Very long chain fatty acids were normal. TPO and anti-thyroglobulin antibodies were elevated. No other hormone deficiency was found. ESR was 16.0 mm/hr (0.0-25.0) and CRP was 42.10 mg/L (< 3.0) The patient responded to oral hydrocortisone and fludrocortisone replacement. He gained 20 pounds, and experienced improved mood, memory and function. Fevers resolved, and have not recurred at 6 months follow-up. Inflammatory markers returned to normal. Conclusion: Chronic primary AI typically has an insidious onset, with vague symptoms such as fatigue, weakness, weight loss, depression and poor memory. This case illustrates an unusual presentation, with fever as the major manifestation. AI should be considered in the differential diagnosis of periodic fever syndromes.
Nothing to Disclose: JMS, LKN

sort_order 2621
Pub # P3-552
Session Information POSTER SESSION: CLINICAL - Adrenal Cases: Insufficiency & Steroid Biosynthesis Disorders (1:30 PM-3:30 PM)
Title Adrenal Insufficiency after Spontaneous Bilateral Adrenal Hemorrhage during Pregnancy with Spontaneous Recovery
Author String YH Altowaireb, KC Shoukri, JE Silva, P Sherchan
Baystate Medical Center, Springfield, MA
Body **Case:** A 29 years-old female, G2P1, 12-weeks pregnant, presented with a sudden, right sided, throbbing flank pain. An MRI abdomen showed a right sided adrenal lesion without signal intensity to suggest hemorrhage. Biochemical workup suggested the lesion to be non-functional. 2 weeks later, she presented again with a similar pain, but in her left flank area. A Repeat MRI showed bilateral adrenal lesions with signal intensities in both sides suggesting hemorrhage of different onset. The right adrenal hemorrhage was described as occurring a week to several weeks earlier, whereas the left adrenal hemorrhage was felt to be of more recent onset. Workup at that time proved adrenal insufficiency. Secondary hematological and rheumatological causes of adrenal hemorrhage were ruled out. Steroids were required throughout pregnancy and around parturition, which proceeded uneventfully. A year following the initial event, elevated ACTH and high normal Cortisol levels were repeatedly observed after holding her Hydrocortisone dose for at least 24 hours. Cushing syndrome was biochemically excluded. This was interpreted as representing HPA axis recovery. Subsequently, she was successfully weaned off steroids. 2 years following the initial event, she had another pregnancy, but it proceeded uneventfully. No steroids were required, however, she had persistent elevations of ACTH and cortisol levels throughout that pregnancy consistent with HPA axis up-regulation during gestation. Again, Cushing syndrome was biochemically excluded. 4 years following the initial event, ACTH and Cortisol levels have normalized, indicating normalization of the HPA axis.
Discussion: Spontaneous adrenal hemorrhage is defined as a hemorrhage in one or both adrenal glands occurring without predisposing factors or medical conditions (1). Although MRI is useful for showing adrenal lesions, precise onset of adrenal hemorrhage is not always easy to determine if the time course of the patient's illness is unknown (2). Adrenal hemorrhage during pregnancy was previously reported (3,4). Massive CRH production by placenta results in ACTH-mediated increased vascularity and hypertrophy of the adrenal gland, and hence a predisposition for hemorrhage (5,6). Spontaneous recovery from adrenal insufficiency following adrenal hemorrhage is possible since HPA axis up-regulation results in increased ACTH production, leading to physiologic changes that could potentially mount a normal adrenal response.

(1) Vella A, Nippoldt TB, Morris JC 3rd. Adrenal hemorrhage: a 25-year experience at the Mayo Clinic. *Mayo Clin Proc* 2001;76:161-8.
(2) Hoeffel C, Legmann P, Luton JP, Chapuis Y, Fayet-Bonnin P. Spontaneous unilateral adrenal hemorrhage: computerized tomography and magnetic resonance imaging findings in 8 cases. *J Urol* 1995;154:1647-51.
(3) Cardwell MS. Spontaneous adrenal hemorrhage in pregnancy. A case report. *J Reprod Med* 1988;33:233-5.
(4) Spontaneous adrenal hemorrhage during pregnancy: a review of the literature and a case report of successful conservative management. Gavrilova-Jordan L, Edmister WB, Farrell MA, Watson WJ
(5) Peterson WF, Goldzicher J. Adrenal hemorrhage in pregnancy. *Am J Obstet Gynecol* 1953;66:648-653.
(6) GOLAND, R.S. et al. 1998. Biologically active corticotropin-releasing hormone in maternal and fetal plasma during pregnancy. *Am. J. Obstet. Gynecol.* 159: 884-890.

Nothing to Disclose: YHA, KCS, JES, PS

sort_order 2622
Pub # P3-553
Session Information POSTER SESSION: CLINICAL - Adrenal Cases: Insufficiency & Steroid Biosynthesis Disorders (1:30 PM-3:30 PM)
Title A Family with Dominantly Inherited Autoimmune Polyendocrine Syndrome Type 1 (APS-1)
Author String MM Erichsen, T Fiskerstrand, ASB Wolff, AG Myhre, IM Marthinussen-Cuida, ES Husebye
 Haukeland University Hospital, Bergen, Norway; Haukeland University Hospital, Bergen, Norway; University of Bergen, Bergen, Norway; Oslo University Hospital, Oslo, Norway; University of Bergen, Bergen, Norway
Body Autoimmune polyendocrine syndrome type 1 (APS-1) characterized by chronic mucocutaneous candidiasis (CMC), adrenal insufficiency and hypoparathyroidism, is caused by mutations in the autoimmune regulator (*AIRE*) gene. In all but one Italian kindred (Cetani et al, JCEM 86, 4747-52, 2001) the inheritance is reported to be autosomal recessive. We here report a patient with Addison's disease, CMC, diabetes insipidus, pernicious anemia (PA), autoimmune thyroid disease and type 2 diabetes. Presence of two of the three main components of APS-1 led to a positive finding of interferon omega antibodies. Subsequent mutational analysis of *AIRE* revealed a heterozygous base change (c.932G>A) in exon 8 changing a cysteine to a tyrosine [p.Cys311Tyr] in the PHD1 zinc finger domain.
 The patient has 7 children (12-40 yr) with 3 different women. Four children had the same mutation in *AIRE*; three had clinical APS-1 and interferon antibodies and one had only p.Cys311Tyr. None of the two mothers with APS-1 children had *AIRE* mutations.
Individual
AIRE mutation
anti-IFN[omega]-Ab
Clinical manifestations
 Father
 +
 +
 Addison, CMC, HP, PA, thyroid disease
 Daughter 1*
 +
 +
 HP, POF, EH
 Daughter 2***
 +
 +
 Nail dystrophy
 Daughter 3***
 +
 +
 HP, POF, lacrimal gland hypofunction
 Daughter 4***
 -
 -
 -
 Son 1 **
 -
 -
 -
 Son 2 **
 n.a.
 n.a.
 -
 Son 3 ***
 +
 -
 Mother 1
 -
 n.a.
 Mother 2
 n.a.
 n.a.
 Mother 3
 -
 n.a.
 * child of mother 1; ** child of mother 2; *** child of mother 3
 CMC, chronic mucocutaneous candidiasis; HP, hypoparathyroidism; POF, primary ovarian failure; EH, enamel hypoplasia; PA, pernicious anemia; n.a., not analysed
 In conclusion, we report a family with dominantly inherited APS-1 associated with the p.Cys311Tyr mutation in *AIRE*. This particular mutation is previously reported in a patient together with the Finnish major mutation (c.769C>T). The effect of p.Cys311Tyr on *AIRE* function remains to be elucidated.
 Nothing to Disclose: MME, TF, ASBW, AGM, IMM-C, ESH

sort_order 2623
Pub # P3-554
Session Information POSTER SESSION: CLINICAL - Adrenal Cases: Insufficiency & Steroid Biosynthesis Disorders (1:30 PM-3:30 PM)
Title Evaluating Endocrinopathies in POEMS Syndrome: A Case Report
Author String A Gupta, K Doshi, B Hatipoglu, AH Hamrahian, V Makin
Cleveland Clinic, Cleveland, OH; Cleveland Clinic, Cleveland, OH
Body Background: POEMS syndrome is a rare, multi-system syndrome characterized by the presence of polyneuropathy, monoclonal proliferative plasma cell disorder and one or more of the following Castleman's disease, edema, skin changes, elevated VEGF, organomegaly, endocrinopathy, osteosclerotic bone lesions and papilledema.
Case presentation: A 63-year old caucasian male presented to the endocrinology clinic with a 1-year history of progressive LE weakness, recurrent abdominal swelling and a 100 lb weight loss. Physical exam was significant for temporal wasting, generalized skin hyperpigmentation, anasarca and decreased B/L lower extremity motor strength with absent reflexes, pin prick and vibration sense. Diagnostic testing revealed IgA **[lambda]** monoclonal gammopathy, elevated VEGF 623 (31-86 pg/ml) and severe sensorimotor peripheral neuropathy. In light of the above constellation of symptoms, the patient was diagnosed to have POEMS syndrome. A complete endocrine evaluation was initiated, which showed FT4 0.9 (0.6-2 ng/dl), TSH of 8.06 (0.4-5.5 uU/ml), microsomal abs negative, low total and free testosterone of 41 (220-1000 ng/dl) and 7.2 (40-240 pg/ml) respectively, LH 2.9 (1-7 mU/ml), FSH 4.9 (1-10 mU/ml), PTH 9 (10-60 pg/ml), calcium 9.4 (8.5-10.5 mg/dl), PRL 39 (2.8-29.2 [micro]g/ml), HbA1C 5.5%, ACTH 104 (7-69 pg/ml) and a 250 mcg cosyntropin stim test with basal, 30min and 60min cortisol 10.4, 15.1 and 16.1 [micro]g/dl respectively. Imaging of the brain and the abdomen did not reveal any evidence of a pituitary tumor or an adrenal adenoma; and hydrocortisone replacement was started for primary adrenal insufficiency with resultant marked improvement in strength, weight and appetite. Chemotherapy was initiated for the treatment of his monoclonal gammopathy, FSH and LH levels later increased to 12.1 mU/ml and 6.4 mU/ml respectively with a low testosterone level of 146 without treatment, suggesting coexisting primary hypogonadism. A repeat TSH was normal.
Discussion: A thorough endocrine work up initially and then as part of regular follow up is warranted in patients with POEMS syndrome, since new endocrinopathies may arise during the course of the disease. Because of the rarity of the disease, the evolution and clinical course of endocrine disorders with treatment of monoclonal gammopathy is largely unknown and larger studies are needed for the same.

Nothing to Disclose: AG, KD, BH, AHH, VM

sort_order 2624
Pub # P3-555
Session Information POSTER SESSION: CLINICAL - Adrenal Cases: Insufficiency & Steroid Biosynthesis Disorders (1:30 PM-3:30 PM)
Title Prevalence and Incidence of Autoimmune Addison Disease in Sweden -- Using Two Different Nationwide Registers
Author String S Bjornsdottir, A Sundstrom, P Blomqvist, O Kampe, S Bensing
Karolinska Institutet, Stockholm, Sweden; Karolinska Institutet, Stockholm, Sweden; Uppsala University, Uppsala, Sweden
Body
Introduction: The estimated prevalence of Autoimmune Addison's disease (AAD) in Caucasians have varied from 39-140 per million. Recently published data from Norway showed the incidence for AAD patients to be 0.44 per 100,000 per year and the prevalence to be 144 per million. The incidence and prevalence of AAD in Sweden is not known. Sweden and Finland are countries with the highest incidence of type 1 diabetes in the world. Sweden is well known for its many high quality health registries giving unique opportunities to identify individuals with different medical conditions. Here, our aim was to study the prevalence, incidence and other concomitant endocrine diseases in AAD patients using Swedish national register data.
Methods: In a population-based study, we retrieved all patients who had treatment with both glucocorticoids and mineralcorticoids in the Swedish Prescribed Drug Register (SPDR) during the period 2005-2009. We also retrieved patients diagnosed with AAD between 1964 and 2009 from the Swedish Inpatient Register (IPR).
Results: Of 4275 registered patients with AAD in the IPR during the period 1964-2009, 56.9 % were women and 43.1 % were men. The mean age at diagnosis was 53.3 years. During the study period 23.1 % had autoimmune thyroid disease, 9.7 % had type 1 diabetes and, 3.7 % had both type 1 diabetes and autoimmune thyroid disease. Of 1331 patients with more than two dispensing of both glucocorticoids and mineralcorticoids in the SPDR during the period 2005- 2009, 1107 (83.2 %) also had an AAD diagnosis in the IPR. Of 1944 patients with AAD in the IPR and alive in 2009, 837 patients had not received treatment with both glucocorticoids and mineralcorticoids. Of those 236 (28 %) had been prescribed glucocorticoids alone, and 73 (8.7 %) had mineralcorticoids as single medication. 528 (63 %) had not been prescribed either of the two drugs. The incidence of AAD according to the IPR was 1.34 per 100,000 per year (2009). According to the SPDR the prevalence was 105 per million per year (2009). Patients using the combination treatment in the SPDR gave a prevalence of 105 per million per year (2009).
Conclusion: The prevalence and incidence of AAD in Sweden is similar to Norway confirming the rising incidence of AAD.

Nothing to Disclose: SB, AS, PB, OK, SB

sort_order 2625
Pub # P3-556
Session Information POSTER SESSION: CLINICAL - Adrenal Cases: Insufficiency & Steroid Biosynthesis Disorders (1:30 PM-3:30 PM)
Title Opiate-Induced Endocrinopathies -- Are They Reversible?
Author String A Grover, C Becker
Brigham and Women's Hospital, Boston, MA

Body **Introduction:** Opiates are commonly used for pain control in many clinical scenarios. Both short term and chronic use of opiates can result in a variety of hormonal abnormalities, some of which quickly reverse with cessation of the opiate. We describe a young woman with hemiplegic migraines, treated with opiates for pain control, who was found to have secondary adrenal insufficiency, hyperprolactinemia and menstrual irregularity. All of her endocrine issues resolved within a few days of discontinuing opiates.
Clinical Case: A 39-year-old woman was recently diagnosed with hemiplegic migraines, and prescribed oxycodone (20 mg/daily) for symptomatic pain control. Within a few weeks, she was admitted for hypotension and extensive fatigue. Her morning cortisol was noted to be 5 mcg/dL (2.3-19.4) and corresponding ACTH <10 pg/mL (10-60). She had an appropriate cortisol response to intravenous Cosyntropin (250 mcg) stimulation. On further review of systems, she admitted to new onset intermittent galactorrhea and menstrual irregularity and was found to have an elevated prolactin (79 ng/mL 3-28). A brain MRI did not reveal any pituitary abnormalities. During her hospital stay, she was able to stop opiates and begin topiramate with adequate control of her migraines. Two weeks after her hospitalization, her morning cortisol was 16, ACTH 27, prolactin 10, and her hypotension, fatigue and menstrual irregularities had completely resolved.
Clinical Lessons: It is well known that endogenous opioid peptides contribute to the regulation of anterior pituitary hormones. Exogenous opioids act similarly. As observed, opiates can cause central ACTH/adrenal suppression, prolactin elevation, and irregular menses by altering cyclic gonadotropin release and the episodic LH secretory pulses. These effects are transient and reversible as demonstrated in our patient. Given the prevalence of opiate use in patients with pain and malignancies, it is important to recognize the effects on the hypothalamic-pituitary-target organ axis and consider hormonal replacement therapy unless the opiate can be discontinued.

Nothing to Disclose: AG, CB

sort_order 2626
Pub # P3-557
Session Information POSTER SESSION: CLINICAL - Adrenal Cases: Insufficiency & Steroid Biosynthesis Disorders (1:30 PM-3:30 PM)
Title Zinc Toxicity Secondary to Denture Adhesive Misdiagnosed as Adrenoleukodystrophy
Author String A Nuristani, W Almuti, H Mal, R Alsyaqah, MH Horani, O Salim
Good Samaritan Hospital, Phoenix, AZ; Sound Inpatient Physicians, Phoenix, AZ; Alsham Endocrinology, Chandler, AZ; Arizona State University, Phoenix, AZ
Body
Case report: A 53 year old Caucasian male was brought to ED for hypotension, dyspnea and altered mental status. He was admitted to the ICU, and his mental and hemodynamic states improved. The patient's medical history, in addition to hypertension, anemia, and coronary artery disease, was significant for paraplegia and demyelinating disease. He had a very extensive neurological workup as an outpatient. MRI of his brain and spine had revealed widespread white matter disease. He was diagnosed with adrenoleukodystrophy, after serum level of very long chain fatty acids was slightly elevated. Subsequent Molecular genetic testing of *ABCD1* was negative for this condition. Patient carried potential diagnosis of adrenoleukodystrophy for several years as an etiology of his progressive weakness.
His neurological symptoms started about seven years ago with bilateral feet tingling, followed by hyperaesthesia, which ascended to his entire lower extremities and resulted in flaccid paraplegia three years ago. Gradually, he also started to notice upper extremity weakness, with incontinence of urine and stool for the past several weeks. He had been using Poligrip denture adhesive cream for almost nine years. He started using Poligrip cream nine years ago, which correlated with the onset of his symptoms. He had stopped using the gel, which has been recalled by the manufacturer.
Lab tests revealed: Hgb 9.5, low serum copper < 20 (70-175 mcg / DL) , Ceruloplasmin 8 mg /dl (17-57 mg/ dl), zinc level 80 (60-130 mcg/dl),repeated VLCFA came back normal.B12, folic acid , Methylmalonic acid , TSH, anti gliadin antibodies and Cosyntropin stimulation test were all within normal limits.MRI brain and spine showed hyperintense demyelinating lesions.
patient was treated Initially with IV copper Chloride then swiched to PO treatment, the patient reported improved strength in the upper extremities, minimal improvement of sensation in his lower extremities, but was still unable to ambulate.
Unrecognized copper deficiency could present with similar signs and symptoms adrenoleukodystrophy.Animals studies showed that Low copper status affects polyunsaturated fatty acid composition o brain phospholipids (1)
Spinal magnetic resonance imaging (MRI) may show posterior column hyperintensity in both Copper defeciency (2) and Adrenoleukodystrophy patients (3)
Conclusion : Early recognition and treatment of copper deficiency is warranted to prevent irreversible myeloneuropathy.

1. Adv Exp Med Biol. 1989;258:183-95.
2. Neurol Sci. 2009 Dec;30(6):521-4. Epub 2009 Sep 19.
3.Neurology. 2005 May 24;64(10):1739-45.

Nothing to Disclose: AN, WA, HM, RA, MHH, OS

sort_order

2627

Pub #

P3-558

Session Information

POSTER SESSION: CLINICAL - Adrenal Cases: Insufficiency & Steroid Biosynthesis Disorders (1:30 PM-3:30 PM)

Title

Spontaneous Bilateral Adrenal Hemorrhage Causing Primary Hypoadrenalism during Late Pregnancy

Author String

RJ Chauffe, JR Chintaparthi, B Scott, TF Shawl, DA Marchiano, SG Rosen
Pennsylvania Hospital, Philadelphia, PA; Pennsylvania Hospital, Philadelphia, PA; Pennsylvania Hospital, Philadelphia, PA

Body

Spontaneous adrenal hemorrhage is characterized by acute abdominal pain in the absence of prior trauma or anticoagulant therapy. Its occurrence during pregnancy has been attributed to physiological hypervascularity of the adrenal glands, stress, adrenal vein thrombosis, and hypertension. A 22-year-old primigravid female at week thirty-two of gestation presented with two days of diffuse abdominal and left flank pain that was associated with nausea and vomiting. Physical examination was significant for tachycardia and orthostatic hypotension. There was left upper quadrant abdominal tenderness without peritoneal signs or costovertebral angle tenderness. The cervix was closed and thick. Laboratory testing revealed serum levels of sodium and potassium of 136 and 3.4 mM, respectively, and a leukocytosis to 19,100. Maternal abdominal ultrasonography was unremarkable. After 24 hours of persistent pain, abdominal computed tomography revealed bilateral adrenal thickening with adjacent soft tissue stranding and ill-defined margins consistent with bilateral adrenal hemorrhage. Her 5:40 PM serum cortisol concentration was 2.1 mcg/dL (normal range 3.09-16.66 mcg/dL) at which time her plasma ACTH concentration was 432 pg/mL (normal range 6-58 pg/mL). Her serum cortisol level did not increase in response to cosyntropin. Infectious, hematologic, and autoimmune evaluations were negative leading to the diagnosis of bilateral spontaneous adrenal hemorrhage causing acute adrenal insufficiency. Intravenous hydrocortisone was initiated. On hospital day 5, repetitive late decelerations occurred prompting an urgent low transverse caesarean section; a healthy female infant was delivered without complication. After delivery, her tachycardia, orthostatic hypotension, and abdominal and flank pain resolved; she was ultimately discharged on hydrocortisone and fludrocortisone. Although spontaneous adrenal hemorrhage is rare and often not discovered until autopsy, primary hypoadrenalism secondary to bilateral spontaneous adrenal hemorrhage during late pregnancy can be successfully treated with adrenal replacement therapy resulting in a successful pregnancy outcome.

Nothing to Disclose: RJC, JRC, BS, TFS, DAM, SGR

sort_order 2628
Pub # P3-559
Session Information POSTER SESSION: CLINICAL - Adrenal Cases: Insufficiency & Steroid Biosynthesis Disorders (1:30 PM-3:30 PM)
Title Functional Significance of Adrenal Incidentalomas: A Case-Control Study
Author String MK Huayllas, B Netzel, AJ Sai, RR Singh
Universidade Federal de São Paulo, São Paulo, Brazil; Mayo Clinic, Rochester, MN; Creighton University, Omaha, NE
Body
Background: Adrenal Incidentalomas (AI) are defined as adrenal masses > 1cm in diameter identified by MRI/CT during medical workup for unrelated conditions. Most are non-functional, however subclinical Cushing's syndrome is reported in 0 - 20%. The purpose of this study was to evaluate steroidogenesis in patients with AI and to look for differences between bilateral and unilateral tumors and control subjects.
Methods: 75 patients (50 female) with adrenal masses (50 unilateral, 25 bilateral) were seen in University Hospital, Sao Paulo, Brazil. Exclusions were primary aldosteronism, pheochromocytoma, carcinoma, Cushing's syndrome and overt metastasis. Controls were matched for age. BML Computerized tomography and MRI were done in all subjects. Fasting 8AM blood samples were collected a baseline, after ACTH stimulation and after 11PM dexamethasone 1mg. Pregnenolone, 17OH-Pregnenolone, 17OH Progesterone, 11- Deoxycortisol, 21-deoxycortisol, Cortisol, 11-Deoxycorticosterone, Corticosterone, Aldosterone, and Androstenedione were measured by liquid chromatography-tandem mass spectrometry analysis. Statistical analysis used repeated measures model for changes in serum steroids over time (basal vs ACTH vs Dexamethasone; adjusted for confounders).
Results: Combining basal, post ACTH and post Dexamethasone values, serum cortisol was significantly higher in both tumor types versus controls ($p < 0.0001$) and higher in bilateral than unilateral tumors ($p = 0.014$). Serum 11-deoxycortisol was significantly higher at all times in both tumors types versus controls ($p < 0.0001$), bilateral and unilateral tumors were not different from each other ($p = 0.13$). Serum corticosterone was significantly higher in bilateral tumors compared to controls ($p = 0.0006$) and unilateral tumors ($p = 0.003$) but not significantly different between unilateral tumors and controls ($p = 0.08$).
Clinical tests: Post-dexamethasone 11-deoxycortisol exceeded the normal range in 47/72%; corticosterone exceeded normal range in 30/44%; cortisol exceeded normal range in 26/40% of unilateral and bilateral tumors respectively. Post ACTH: 11-deoxycortisol exceeded the normal range in 35/56%; corticosterone exceeded normal range in 22/24%; cortisol exceeded normal range in 30/40% of unilateral and bilateral respectively.
Conclusion: There is high prevalence (30-40%) of subclinical hypercortisolism in AI, more so in bilateral tumors. The clinical significance of these findings needs evaluation in prospective studies.
Nothing to Disclose: MKH, BN, AJS, RRS

sort_order 2629
Pub # P3-560
Session Information POSTER SESSION: CLINICAL - Adrenal Diseases (1:30 PM-3:30 PM)
Title Adrenal Incidentalomas (AI) -- The Most Frequent Adrenal Disorder: Clinical Studies on 2100 Patients Observed at a Single Endocrinological Center
Author String AA Kasperlik-Zaluska, J Slowinska-Szrednicka, E Roslonowska, M Otto, A Cichocki, W Jeske, P Zdunowski, W Zgliczynski
Medical Center of Postgraduate Education, Warsaw, Poland; Medical University of Warsaw, Warsaw, Poland; Center of Oncology, Warsaw, Poland
Body Objective: This study aimed at analyzing data of 2100 patients with AI, concerning clinical features, frequency of adrenal cancer, metastatic lesions, subclinical hormonal hyperfunction and predisposing factors.
Material: 1540 women, 560 men, aged 11-87 yrs, 4% up to 30 yrs, 38% over 60 yrs. The tumors were 1-23 cm sized, 66% up to 3 cm.
Methods: clinical and imaging studies, hormonal determinations, histological and immunocytochemical investigations of 660 tumors removed mainly for oncological and endocrinological purposes.
Results: Hypertension was present in 25% of the patients, obesity in 16%, diabetes mellitus in 5%. Imaging phenotype in the abdominal CT (size, structure, density of the tumors) was the most useful criterium for surgery. Pre-Cushing's syndrome was the most frequent hormonal disorder (5.4%). Chromaffin tumors were diagnosed in 70 patients (3.3%). Adrenal cancer was present in 155 patients (7.4%), other malignant tumors in 16, metastatic lesions in 54 (2.6%). Out of 216 patients treated previously for malignancy in 55 (25%) adrenal metastatic lesions were found. Congenital adrenal hyperplasia (mainly non-classical form) was a rather frequent finding in our group of patients.
Conclusions: 1/ Hypertension was the most frequent clinical feature (25%), however only in a part of these cases (37%) it seemed to be AI-related. 2/ Adrenal malignancy was observed in 11% of the patients; adrenal cancer was three times more frequent than metastatic infiltrations.
3/ Congenital adrenal hyperplasia seemed to be a factor predisposing to AI development.

Sources of Research Support: 501-1-08-13/10 CMKP grant.

Nothing to Disclose: AAK-Z, JS-S, ER, MO, AC, WJ, PZ, WZ

sort_order 2630
Pub # P3-561
Session Information POSTER SESSION: CLINICAL - Adrenal Diseases (1:30 PM-3:30 PM)
Title The Characteristics and Prognosis of Adrenal Incidentaloma in Koreans
Author String JA Lim, EK Kim, JH An, HS Jung, SW Kim, CS Shin, SY Kim
Seoul National University College of Medicine, Seoul, Republic of Korea
Body
Background: The detection rate of adrenal incidentaloma has been increasing. We aimed to investigate the characteristics of patients with adrenal incidentaloma.
Methods: We reviewed the medical records of 387 patients with adrenal mass incidentally detected by CT from March 1999 to March 2010. The clinical, laboratory, and radiological findings were analyzed.
Results: The adrenal masses were detected in the age of 56.4 ± 12.0 years. Of 387 patients, 215 (55.6%) patients were male and 172 (44.4%) were female. The mean size of masses was 2.5 ± 1.7 cm. For the location of the masses, 54.3% were in the left, 41.3% in the right, and 4.4% in both adrenal glands. Of all incidentaloma, 330 (85.3%) cases were nonfunctioning masses, and others were hormone producing ones; pheochromocytoma in 35 (9.0%), cortisol-producing tumor in 15 (3.9%), and aldosterone-producing tumor in 7 (1.8%). Among the nonfunctioning tumors, adenomas were 299 (77.2%), simple cysts were 18 (4.7%), malignancies were 2 (0.5%), miscellaneous was 11 (2.9%). In 236 apparently benign nonfunctioning adenomas which followed-up over 6 months, the size of tumors was increased 0.5cm or more in 12 cases (5.08%). The increment was 0.88 ± 0.55 cm, during mean follow-up period of 23.0 ± 15.8 months. No tumors have changed to hormone producing ones.
Conclusion: Of all adrenal incidentaloma, 85.3% was nonfunctioning and 14.7% was functioning tumors. Pheochromocytoma was the most common functioning adrenal incidentaloma. There was no significant increase in size or change to hormone-producing tumor in nonfunctioning adenomas during 23.0 ± 15.8 months.
Nothing to Disclose: JAL, EKK, JHA, HSJ, SWK, CSS, SYK

sort_order

2631

Pub #

P3-562

Session Information

POSTER SESSION: CLINICAL - Adrenal Diseases (1:30 PM-3:30 PM)

Title

Evaluation of Patients with Adrenal Incidentalomas

Author String

M Bahceci, A Gorgel, P Tutuncuoglu, G Oruk, D Dolek, F Salgur, M Demirpence
Ataturk Training and Research Hospital, Izmir, Turkey

Body

Background and aims: With the widespread use of imaging techniques, adrenal incidentaloma so-called [ldquo]diseases of modern technology[rdquo] will be diagnosed more frequently, but also might put burden on the patient due to insecurity and will have increasing economic consequences for the health system. We aimed to evaluate the patients with adrenal incidentaloma in terms of clinical and radiological features.

Subjects and methods: In this study 67 patients with adrenal incidentaloma were evaluated with CT or MR imaging (14 male, 53 female). As screening tests; Blood pressure, 24 hour urinary fractionated metanephrines and normetanephrines, serum cortisol after dexamethasone suppression (1 mg at 11 PM orally) and serum aldosterone and plasma renin concentration, serum potassium were measured. The patients with serum cortisol > 1.8 [micro]g/dl were investigated with confirmatory high-dose dexamethasone suppression test (8 mg). If serum cortisol concentrations were again not suppressible, subclinical Cushing's syndrome was diagnosed.

Results: Adrenal mass was located on the right side in 30 patients (44,8%), on the left side in 24 patients (35,8%) and bilateral in 13 patients (19,4%). Endocrinological evaluation: Subclinical Cushing's syndrome in 21 patients (31,3%) and pheochromocytoma in 5 cases (7,5%) were determined. In a patient with bilateral pheochromocytoma, neurofibromatosis type-1 was also determined. None of the patients had high dehydroepiandrosterone sulphate (DHEA-S) and hyperaldosteronism. In the 41 patients (61,2%) adrenal masses were non-functional. Radiological evaluation: Mass diameter was [ge]4cm in 15 patients (22,4%) (8 patients with SCS, 5 patients with pheochromocytoma and 2 patients with non-functional incidentaloma). Mass diameter was <4cm in 52 patients (77,6%). All patients with pheochromocytoma, SCS and mass diameter [ge]4 cm, patients underwent surgical intervention. In the histopathological evaluation there were 2 pheochromocytoma, 1 pheochromocytoma+ganglioneuroma, 1 pheochromocytoma+myelolipoma, 5 cortical adenoma and 1 myelolipoma.

Conclusions: Adrenal incidentalomas had female preponderance. This preponderance might be explained by a referral bias or there may be a real female preponderance. Autonomous cortisol secretion by adrenal incidentaloma is higher than previously reported results. Incidentalomas [ge]4 cm. and incidentalomas in male patients may be more hormonal active.

Nothing to Disclose: MB, AG, PT, GO, DD, FS, MD

sort_order 2632
Pub # P3-563
Session Information POSTER SESSION: CLINICAL - Adrenal Diseases (1:30 PM-3:30 PM)
Title Use of Physiological Testing to Identify the Cause of Adrenal Insufficiency in Patients with Thalassemia Major
Author String KE Huang, SD Mittelman, TD Coates, ME Geffner, JC Wood
Children's Hospital Los Angeles, Los Angeles, CA; Children's Hospital Los Angeles, Los Angeles, CA; Children's Hospital Los Angeles, Los Angeles, CA
Body
Background: Thalassemia is one of the most common genetic blood disorders worldwide. With recent improvements in medical therapy, patients with transfusion-dependent thalassemia, i.e., thalassemia major, are living longer. As a result, there is a greater need to address endocrine complications related to chronic iron overload. Adrenal insufficiency (AI), in particular, is important to identify because therapies are available and can be life-saving.
Objectives: The objectives of this study are to determine the prevalence of AI in our population of subjects with thalassemia major; to identify risk factors that predict AI in these individuals; and to localize the origin of the AI within the hypothalamic-pituitary-adrenal (HPA) axis.
Methods: This is a prospective study of individuals with thalassemia major with an enrollment goal of 30 subjects. All subjects enrolled were initially tested for AI using a glucagon stimulation test. Within 4 weeks, those found to have AI (stimulated cortisol <18 mcg/dL) underwent an ovine corticotrophin-releasing hormone (oCRH) stimulation test for confirmatory purposes and to define the physiological basis for the AI.
Results: Eight subjects (8 - 25 years old, 2 male) have been enrolled to date. Of these, 5 had an 8-9 AM cortisol <10 mcg/dL. Three of those 5 failed the glucagon stimulation test despite a drop in glucose of at least 30 mg/dL in all patients. Interestingly, 2 of the 3 subjects who failed the glucagon stimulation test subsequently passed an oCRH stimulation test (cortisol >20 mcg/dL).
Conclusions: We conclude that, in our population of subjects with thalassemia major, 8-9 AM cortisol levels may not be a specific test for the diagnosis of AI. The fact that some subjects who failed the glucagon stimulation test passed the oCRH test indicates that the etiology of AI in our subjects may be hypothalamic in origin. This outcome is novel to the field and of medical significance to this at-risk population.

Nothing to Disclose: KEH, SDM, TDC, MEG, JCW

sort_order 2633
Pub # P3-564
Session Information POSTER SESSION: CLINICAL - Adrenal Diseases (1:30 PM-3:30 PM)
Title Subclinical Cushing Syndrome: How To Predict Post-Surgical Hypoadrenalism
Author String MP Ricciato, V Di Donna, F Ianni, A De Rosa, F Gallo, P Senes, L Castellino, M Raffaelli, CP Lombardi, R Bellantone, A Pontecorvi, SM Corsello
Body Subclinical Cushing's Syndrome (SCS) is a controversial clinical issue, with diagnosis and management still extremely debated. In order to evaluate the role of adrenal scintigraphy (AS), we retrospectively analyzed 33 patients (pts: 23 F, 10 M; mean age 53.3 yrs, range 18-75; mean BMI 28.2 kg/m², range 19.5-37.0) referred to our center since 2004 to 2010 for adrenal [ldquo] incidentalomas[rdquo] and with SCS. SCS was defined by the presence of at least 1 criteria of metabolic syndrome according to ATPIII-NCEP and/or by 2 or more hormonal criteria among: ACTH <10 pg/ml, free urinary cortisol >137 [mu]g/24h, cortisol after 1 mg dex suppression test >18 ng/ml, absence of circadian rhythm. All pts underwent ¹³¹I-19-iodocholesterol AS. 16 pts were submitted to laparoscopic adrenalectomy (group A), 15 pts showing concordant scintigraphic pattern (AS+) and 1 pt showing indeterminate pattern (AS-) because of dimensional criteria; the remaining 17 pts (10 AS+, 7 AS-) underwent medical therapy (group B). All pts were followed-up by clinical evaluation for 32.3 ± 22.1 months. No significant differences in hormonal and metabolic parameters were found at baseline between the two groups and between AS+ and AS- pts. Post-surgical hypoadrenalism (PH) occurred in 14/15 pts AS+ (regardless of hormonal criteria), meanwhile in the only one pt AS- did not. Diagnostic accuracy in predicting PH was 93.7% and 68.7% for AS and hormonal criteria respectively. In group A, after surgery, a significant HDL rise (57.8±15 vs 49.9±15.3 mg/dl, p<0.05) and a reduction of BMI (26.2±3.1 vs 28.5±3.1 kg/m², p<0.001), glycemia (96.5±18.1 vs 110.2±27.6 mg/dl, p<0.001), systolic BP (121.1±11.5 vs 147.3±15.3 mmHg, p<0.001), diastolic BP (79.3±6.5 vs 92.0±7.5 mmHg, p<0.001), were observed in AS+ pts. Moreover, among them, one pt reduced and 3 pts stopped antihypertensive therapy. Even in absence of hormonal criteria of SCS the outcome of pts AS+ of group A showed an improvement of metabolic syndrome parameters. No pts in group B developed overt CS during follow-up, even if AS+ pts worsened glycemic values (p<0.05); AS- pts had a better control of diastolic BP (p<0.05). In conclusion AS allows to diagnose controversial or very early cases of SCS. It represents the gold standard in predicting PH and therefore seems to be the most accurate diagnostic test of SCS. Moreover AS, regardless of therapeutic choice, has a prognostic value in predicting hormonal and metabolic outcome.

Nothing to Disclose: MPR, VDD, FI, ADR, FG, PS, LC, MR, CPL, RB, AP, SMC

sort_order 2634
Pub # P3-565
Session Information POSTER SESSION: CLINICAL - Adrenal Diseases (1:30 PM-3:30 PM)
Title Immunomodulation of New-Onset Addison Disease Using B Lymphocyte Depletion Therapy: Interim Analysis
Author String SHS Pearce, AL Mitchell, S Bennett, P King, S Chandran, S Nag, S Chen, B Rees Smith, B Vaidya, JD Isaacs
Newcastle University, Newcastle upon Tyne, UK; Northumbria Healthcare NHS Trust, North Tyneside, UK; Bishop Auckland General Hospital, Co Durham, UK; James Cook University Hospital, Middlesbrough, UK; RSR Ltd, Cardiff, UK; Royal Devon & Exeter Hospital, Exeter, UK
Body
A new diagnosis of Addison's disease means lifelong dependence on glucocorticoid and mineralocorticoid therapy, with associated complications of osteoporosis and impaired glucose tolerance, as well as the risk of unexpected adrenal crisis. We wished to explore whether immunosuppressive therapy might lead to preservation or improvement in adrenal steroidogenesis in early autoimmune Addison's disease.
We conducted an open-label study (NCT00753597) of B lymphocyte depletion therapy starting within 4 weeks of the first diagnosis of autoimmune Addison's disease in 6 patients (4 female) with a median age of 32yrs (range 18 to 47). Two 1g doses of rituximab were given 14 days apart with 125mg of IV methylprednisolone, followed by tapering oral glucocorticoids until a replacement dose was reached. Adrenal function was tested by ACTH_{1-24}} (tetracosactrin 250ug) stimulation at baseline and then 3 monthly for a year, along with basal plasma ACTH, DHEAS, renin and aldosterone.
At diagnosis the median peak serum cortisol level was 125 nmol/l (range 65 to 235) [4.5 ug/dl; 2.4 to 8.5], with corresponding plasma ACTH of 813 ng/l (72 to >1250). All six patients achieved B lymphocyte depletion (<0.1%), and IgM levels became subnormal in 4 of the 6 patients. Four patients have completed a year of follow up, one patient 8 months and one patient 11 months. Two of the subjects with completed autoantibody measurements had a tenfold reduction in 21-hydroxylase antibody titre over the 12 months of the study. Five of six patients had decline of basal and stimulated serum cortisol, such that peak levels were undetectable (<24 nmol/l [<0.87 ug/dl]) in 3 individuals, or between 24 and 50 nmol/l [0.87-1.81 ug/dl] in 2 patients. However one patient has preservation of adrenal function with a peak stimulated serum cortisol of 229 nmol/l [8.3 ug/dl] eleven months following initial diagnosis.
Although B lymphocyte depletion has immunomodulatory properties in autoimmune Addison's disease, particularly on autoantibody titres, these data suggest that it is not sufficient as a sole therapy to restore adrenal function in most Addison's patients.

Sources of Research Support: MRC (UK) experimental medicine programme.

Nothing to Disclose: SHSP, ALM, SB, PK, SC, SN, SC, BRS, BV, JDI

sort_order 2635
Pub # P3-566
Session Information POSTER SESSION: CLINICAL - Adrenal Diseases (1:30 PM-3:30 PM)
Title Inappropriately [ldquo]Normal[rdrquo] Cortisol Levels in Face of Increased Interleukin-6 Levels in Response to Acute Treadmill Exercise in Patients with Sarcoidosis
Author String G Mastorakos, G Paltoglou, M Greene, I Ilias, A Papamichalopoulos, A Samakovli, E Pouliou, I Fatouros, S Nanas
Medical School, National and Kapodistrian University of Athens, Athens, Greece; Children's Memorial Hospital, Chicago, IL; Elena Hospital, Athens, Greece; Medical School, National and Kapodistrian University of Athens, Athens, Greece; University of Thrace, Komotini, Greece
Body **Background and Aim:** Sarcoidosis is a chronic granulomatous disorder of unknown etiology that fulfills the criteria for an autoimmune disorder. In sarcoidosis, T cells initiate and maintain granuloma formation, through interactions mediated by various cellular and cytokine pathways. Blunted Hypothalamic-Pituitary-Adrenal (HPA) axis responses are associated with enhanced susceptibility to autoimmune inflammatory diseases. To examine the HPA axis of sarcoidosis patients we evaluated its response to a major stimulus, such as acute aerobic treadmill exercise in patients, as well as in healthy volunteers.
Methods: 44 patients with sarcoidosis (27 untreated and 17 under treatment with dexamethasone) and 20 controls were recruited. All subjects undertook cardiopulmonary treadmill exercise testing (CPET) and blood samples were drawn before, at peak and 15 minutes after the CPET, for measurement of ACTH, cortisol, and proinflammatory cytokines interleukin (IL)-1 β , Tumor Necrosis Factor (TNF) and IL-6.
Results: We found that ACTH levels increased significantly at exercise peak in sarcoidosis patients as well as in control subjects. Cortisol levels increased at exercise peak and recovery in the untreated sarcoidosis patients, and at recovery in the control subjects. In treated patients, cortisol levels at recovery were lower than untreated patients and control subjects. Baseline IL-6 levels were higher in untreated and treated sarcoidosis patients as compared to healthy controls, while they also increased from baseline at exercise peak and recovery, in all three groups. At exercise peak and recovery they were higher in the untreated than the dexamethasone treated group. TNF levels were higher in sarcoidosis patients, than controls. Interleukin-1 β increased significantly from baseline to exercise peak, in the control group.
Conclusions: Our findings indicate that the HPA axis of untreated sarcoidosis patients reacts to exercise similarly to healthy control subjects. Even though IL-6 remains a potent stimulator of the HPA axis for sarcoidosis patients the secreted cortisol levels in these patients, are inappropriately similar to those of healthy subjects. This reflects either a dysfunctional IL-6-induced stimulation of the HPA axis or an adaptation of this axis in face of the chronically elevated IL-6 levels in sarcoidosis patients.
Nothing to Disclose: GM, GP, MG, II, AP, AS, EP, IF, SN

sort_order

2636

Pub #

P3-567

Session Information

POSTER SESSION: CLINICAL - Adrenal Diseases (1:30 PM-3:30 PM)

Title

Successful Use of Continuous Subcutaneous Hydrocortisone Infusion after Bilateral Adrenalectomy Secondary to Bilateral Pheochromocytoma

Author String

JR Broussard, N Mitre
Childrens Mercy Hospital and Clinics, Kansas City, MO

Body

Background

Hydrocortisone has been the main drug used to treat adrenal insufficiency in children. Poor absorption due to gastrointestinal problems or poor compliance in the older children makes treatment cumbersome. We describe the use of continuous subcutaneous hydrocortisone infusion in an adolescent patient who had poor compliance and was unable to tolerate long acting preparations due to gastrointestinal side effects.

Clinical Case

A 17 year old male presented with blood pressure of 182/102 and headache. Past medical history was significant for a diagnosis of bilateral pheochromocytoma, status post left adrenalectomy with right cortical-sparing. He was not taking any medications. Work-up showed elevated plasma fractionated metanephrine and right adrenal mass by MRI. Patient underwent completion laparoscopic right adrenalectomy. He was started on hydrocortisone replacement at 10 mg/m²/day and fludrocortisone 0.2 mg daily. He was admitted multiple times for acute adrenal crisis. Poor compliance was suspected. Regimen was changed to dexamethasone with a hydrocortisone equivalent of 15 mg/m²/day. The patient continued to be admitted with adrenal crisis with hyponatremia and dehydration. Resolution of symptoms was achieved with intravenous fluids and hydrocortisone. Last admission showed ACTH of 424 pg/mL (0-46) and renin activity of 32.4 ng/mL/hr (0.5-4.0). Upper endoscopy was performed due to concerns of impaired absorption, showing moderate gastritis. Omeprazole was started. Fludrocortisone was increased to 0.3 mg and NaCl was added. Hydrocortisone by continuous subcutaneous infusion using a Medtronic Minimed insulin pump was initiated. Basal rates of Hydrocortisone sodium succinate 25 mg/mL, were set to mimic endogenous secretion with 4 basal rates delivering 60% of the total daily dose in early morning hours. Stress dosing rates (pattern A in the pump) were set as 3 times the basal dose. The patient remained stable and was followed as an outpatient. He was diagnosed with Von Hippel-Lindau syndrome.

Conclusion

Continuous subcutaneous hydrocortisone infusion is a feasible, well tolerated and safe treatment option in patients not able to tolerate oral preparations. It has the advantage of delivering hydrocortisone more efficiently, can mimic the normal diurnal cortisol rhythm and reduce long-term complications. We propose to consider this form of treatment for selected patients with poor response to conventional therapy.

Nothing to Disclose: JRB, NM

sort_order 2637
Pub # P3-568
Session Information POSTER SESSION: CLINICAL - Adrenal Diseases (1:30 PM-3:30 PM)
Title Evening Salivary Cortisol Concentrations Correlate with Internalizing Symptoms in Healthy Children and Adolescents
Author String P Pervanidou, D Bastaki, K Papanikolaou, E Laios, C Kanaka-Gantenbein, GP Chrousos
Athens University Medical School, Aghia Sophia Children's Hospital, Athens, Greece; Athens University Medical School, Aghia Sophia Children's Hospital, Athens, Greece
Body
Background: The HPA axis is involved in the pathophysiology of anxiety disorders and depression in adults, while fewer data exist in children and adolescents, while recent studies have shown that children with aggressive behavior and ADHD often exhibit hypocortisolism. The majority of data showing relations between HPA dysregulation and emotional-behavioral disorders have been reported in individuals with clinical psychiatric diagnoses, while scarce data exist in community samples of apparently healthy children and adolescents.
Methods: Ninety-nine healthy children and adolescents (57 boys, mean age 10.57 years) and their parents were screened for emotional behavioral disorders using the entire Achenbach System (Child Behavior Checklist) for a variety of internalizing and externalizing symptoms. The children were derived partly from the obesity clinic and partly from other outpatient clinics of our department of Pediatrics. All children were free of current of past psychiatric disorders and had no chronic medical illnesses. Five diurnal salivary samples were obtained to examine cortisol diurnal variation.
Results: T-scores of scale of internalizing symptoms (anxiety, depression, withdrawn behavior, and somatic complaints) correlated significantly with evening (21.00p.m.) salivary cortisol concentration in the entire population (both sexes, entire range of BMI z-scores)(Spearman: $r=0.219$, $p=0.029$). No such relations were noted in T-scores of externalizing symptoms (rule breaking and aggressive behavior).
Conclusions: Evening salivary cortisol concentrations correlated with symptoms of anxiety, depression, withdrawn behavior and somatic complaints (internalizing) in a population of healthy children and adolescents. In contrast, no such relations were found between cortisol concentrations and externalizing symptoms.
Nothing to Disclose: PP, DB, KP, EL, CK-G, GPC

sort_order 2638
Pub # P3-569
Session Information POSTER SESSION: CLINICAL - Adrenal Diseases (1:30 PM-3:30 PM)
Title Salivary Cortisol as a Diagnostic Tool for Hyper- and Hypocortisolism: Improved Screening by an Automated Immunoassay
Author String T Deuschbein, M Broecker-Preuss, J Flitsch, A Jaeger, R Althoff, M Walz, K Mann, S Petersehn
University Hospital of Essen, Essen, Germany, Essen, Germany; University Hospital Hamburg-Eppendorf, Hamburg, Germany; Kliniken Essen-Mitte, Essen, Germany
Body Background: Salivary cortisol is increasingly used to assess patients with suspected hyper- and hypocortisolism. This study established reference ranges for an automated electrochemiluminescence immunoassay (ECLIA).
Methods: 40 patients with confirmed hypercortisolism (12x Cushing's disease, 2x ectopic Cushing's syndrome, 26x adrenal Cushing's syndrome) were compared with 115 healthy subjects and 45 control patients with adrenal masses (18x nonfunctioning adenoma, 15x pheochromocytoma, 12x aldosterone-producing adenoma). Sampling of saliva was performed at 11 pm and at 8 am following low-dose dexamethasone suppression. Receiver operating characteristics (ROC) analysis was used to calculate thresholds with at least 95% sensitivity for hypercortisolism. Besides, 63 patients with proven hypothalamic-pituitary disease (54x sellar masses, 9x hormonal impairment) were enrolled. A peak serum cortisol level below 500 nmol/l during the insulin hypoglycemia test was used to define adrenal insufficiency. Unstimulated saliva samples were collected at 8 am, and ROC analysis was used to establish lower and upper cutoffs with at least 95% specificity for either adrenal insufficiency or adrenal sufficiency. Salivary cortisol measurements were performed with a commercially available ECLIA (Roche, Mannheim, Germany).
Results: An 11 pm salivary cortisol cutoff of 6.06 nmol/l (sens 95%, spec 92%, AUC 0.97) and a dexamethasone-suppressed salivary cortisol cutoff of 2.02 nmol/l (sens 97%, spec 86%, AUC 0.98) were calculated for the diagnosis of hypercortisolism. With respect to the HPA axis, a lower cutoff of 3.21 nmol/l and an upper cutoff of 20.4 nmol/l identified 12 of 31 patients (39%) as adrenal insufficient and 2 of 32 patients (6%) as adrenal sufficient.
Conclusions: The newly established thresholds allowed excellent identification of both hyper- and hypocortisolemic states by an automated immunoassay, which will allow broader use of salivary cortisol as a routine diagnostic tool.
Nothing to Disclose: TD, MB-P, JF, AJ, RA, MW, KM, SP

sort_order 2639
Pub # P3-570
Session Information POSTER SESSION: CLINICAL - Adrenal Diseases (1:30 PM-3:30 PM)
Title Reproducibility of Late-Night Salivary Cortisol Using an Automated Immunoassay System and Performance of One or Two Samples in the Diagnosis of Cushing Syndrome
Author String CMA Carrasco, M Garcia, M Goycoolea, J Cerda, J Bertherat, O Padilla, D Meza, N Wohlk, T Quiroga
Faculty of Medicine, Pontificia Universidad Cat[oaacute]lica de Chile, Santiago, Chile; Faculty of Medicine, Pontificia Universidad Cat[oaacute]lica de Chile, Santiago, Chile; Faculty of Medicine, Pontificia Universidad Cat[oaacute]lica de Chile, Santiago, Chile; Centre de R[ef]erence des Maladies Rares de la Surr[en]ale, H[ocirc]pital Cochin, Paris, France; Hospital del Salvador, Universidad de Chile, Santiago, Chile
Body **Introduction:** International Consensus recommends two samples of late night salivary cortisol (LNSC) as screening test for Cushing's syndrome (CS). However, there are few and contradictory report comparing reproducibility or accuracy of one versus two measurements of LNSC. **Aim:** To evaluate reproducibility of LNSC using automated electrochemiluminescence immunoassay (ECLIA) and compare accuracy of one versus two samples in diagnosing CS. **Subjects and measurements:** We prospectively included 64 healthy volunteers (normal UFC and no drugs or pathologies known to interfere with cortisol axis), 35 patients with suspected CS but normal standard tests, and 15 patients with confirmed CS by standard test and histology. They collected at home UFC (normal value < 106 mcg/g creatinine) and two consecutive LNSC (LNSC1, LNSC2). Range of cortisol assay was 0.018-63.4 mcg/dL, analytical sensitivity 0.018 mcg/dL and functional sensitivity 0.099 mcg/dL. **Results:** CS patients had higher UFC, LNSC1 and LNSC2 than suspected or healthy group (all p<0.001). No differences were found between healthy and suspected group in UFC (median 42.2 mcg/g creatinine vs. 36.2 mcg/g creatinine, p=0.764), LNSC1 (median 0.087 mcg/dL vs. 0.089 mcg/dL, p=0.913) and LNSC2 (median 0.092 mcg/dL vs. 0.089 mcg/dL, p=0.698). To evaluated variability and reproducibility of LNSC, healthy and suspected patients were analyzed together as non-Cushing group (n=99). Mean difference of LNSC1 and LNSC2 among patients of non-Cushing group was +0.003 mcg/dL (range [minus]0.075 to +0.185), while patients with CS had +0.208mcg/dL (range [minus]0.845 to +1.480). Intra individual variability was 12% (0-89%) in non-Cushing group and 46% (4-67%) in the CS group. The AUC of LNSC1 was 0.959 (CI95% 0.904[minus]1.014) with 100% of sensitivity and 58.6% of specificity at a cut-off value of 0.099 mcg/dL. Considering the highest LNSC for each patient, the AUC was 0.992 (CI95% 0.979[minus]1.005), with 100% of sensitivity and 91.9% of specificity using a cut-off value of 0.208 mcg/dL. We found 95% of concordant results in non-Cushing group and 80% in CS group (cut-off value of 0.208 mcg/dL). Considering all patients (n=114), we found that 93% of patients had concordant LNSC. **Conclusion:** Our results suggest that LNSC measured by ECLIA is variable, mainly in CS patients, with reproducibility of 80% between two samples. We found significant improvements in the diagnostic accuracy of LNSC measurement by obtaining two samples and choosing the highest value.
Nothing to Disclose: CMA, MG, MG, JC, JB, OP, DM, NW, TQ

sort_order 2640
Pub # P3-571
Session Information POSTER SESSION: CLINICAL - Adrenal Diseases (1:30 PM-3:30 PM)
Title Dehydroepiandrosterone-Sulfate and Other Parameters of Adrenal Function in Patients with Acute Ischemic Stroke Are Predictive for Outcome
Author String CA Blum, C Mueller, P Schuetz, F Fluri, B Mueller, M Katan, M Christ-Crain
University Hospital, Basel, Switzerland; Department of Emergency Medicine, Boston, MA; Cantonal Hospital, Aarau, Switzerland; University Hospital, Basel, Switzerland
Body
Introduction: Stroke is a devastating event; therefore, rapid evaluation is urgent to detect severity and to guide treatment and rehabilitation. In critical illness and sepsis, adrenal function measured by dehydroepiandrosterone sulfate (DHEAS), dehydroepiandrosterone (DHEA) and cortisol are predictive for outcome. We herein evaluated the predictive value of adrenal function testing in acute ischemic stroke.
Methods: We measured levels of DHEA, DHEAS, cortisol (basal and 30 minutes after stimulation with 1 ug ACTH) on day 1 after admission to the emergency department in the remaining 231 serum samples of a prospective stroke cohort study. The primary endpoint was all-cause mortality after 1 year, the secondary endpoint was functional outcome after 90 days defined as > 2 points in the modified rankin scale (mRS). We calculated logistic regression analysis adjusted for age, gender and co-morbidity using the Charlson Index.
Results: The median National Institute of Health Stroke Scale (NIHSS) on admission was 5 (IQR 2-10). Mortality was 17.0% (38 patients) after one year, and 86 patients (37%) had a bad outcome at day 90. Median baseline DHEA, DHEAS, basal cortisol and delta cortisol were 4.5 nmol/l (IQR 2.7-7.2), 2.4 umol/l (IQR1.3-3.7), 475 nmol/l (IQR 337-608.5), and 257 nmol/l (IQR 152-376), respectively.
In logistic regression analysis adjusted for age, gender and comorbidities, there was no association of DHEA (OR 0.99, 95%CI 0.96- 1.03) or DHEAS (OR 1.10, 95%CI 0.44) with mortality. DHEAS, but not DHEA, was associated with adverse functional outcome (OR 1.23, 95%CI 1.04-1.46). Baseline and stimulated cortisol (per 100 unit increase) were associated with both 1-year mortality (OR 1.41, 95%CI 1.20-1.71 and 1.35, 95%CI 1.15-1.60) and adverse functional outcome (OR 1.38, 95%CI 1.18-1.62 and OR 1.24, 95%CI 1.08-1.43). Delta cortisol increase was not associated with either outcome.
Conclusion: DHEAS predicts functional outcome but not mortality in stroke, while basal and stimulated cortisol are predictive for mortality and functional outcome.
Sources of Research Support: Gottfried and Julia Bangerter-Rhyner-Stiftung (CAB); Foerderungsforschung Schweizerischer Nationalfonds PP00P3_123346/1 (MCC).
Nothing to Disclose: CAB, CM, PS, FF, BM, MK, MC-C

sort_order 2641
Pub # P3-572
Session Information POSTER SESSION: CLINICAL - Adrenal Diseases (1:30 PM-3:30 PM)
Title Evaluation of Adrenocortical and Adrenomedullary Function in Subjects with Non-Classical Adrenal Hyperplasia (NCAH), Classical Adrenal Hyperplasia (CAH), and Heterozygotes Secondary to 21-Hydroxylase Deficiency (21OHD)
Author String B Bali, C Azen, R Samoa, J May, M Karantz, M Geffner
Children's Hospital Los Angeles, Los Angeles, CA; Children's Hospital Los Angeles, Los Angeles, CA
Body **BACKGROUND:** Patients with classical CAH require additional glucocorticoid (GC) coverage during major intercurrent stress to avoid Addisonian crises due to cortisol deficiency. Adrenomedullary function is also impaired in patients with CAH presumably due to lack of in utero intra-adrenal GC. GC are necessary for induction of PNMT, the key enzyme that controls conversion of norepinephrine (NE) to epinephrine (EPI). Recently, partially reduced EPI responses have been reported in patients with GC-treated 21OHD NCAH compared to controls during high-intensity exercise. (1)
OBJECTIVE: To assess adrenocortical and adrenomedullary function of patients with NCAH and CAH secondary to 21OHD and heterozygotes.
METHODS: In 9 subjects with NCAH, 16 with CAH, and 6 heterozygous controls (all biochemically and genetically confirmed), we assessed adrenocortical responsiveness to simulated stress by the serum cortisol (mcg/dL) rise following administration of ovine corticotrophin-releasing hormone (oCRH) and adrenomedullary function from plasma catecholamine (pg/mL) levels. Results are expressed as mean±SD and analyzed by mixed model repeated measures ANOVA or non-parametric Kruskal-Wallis test as appropriate.
RESULTS: Subjects with NCAH had significantly higher mean peak cortisol increases over baseline in response to oCRH than did those with CAH (10.5±6.9 vs 3.2±2.1, p= 0.0038), and both were significantly less than those of heterozygotes (20.2±4.6, p=0.0004 vs CAH and p=0.025 vs NCAH). Mean EPI levels were also significantly different among the 3 groups [CAH 38±19, NCAH 55±29, and heterozygotes 66±25 (p=0.036)], with CAH < NCAH (p=0.041). Mean metanephrine (META) levels were also significantly different among the groups [CAH 26±7.8, NCAH 38.7±17, and heterozygotes 27±6.7(p=0.049)], with CAH < NCAH (p=0.025).
CONCLUSIONS: Subjects with NCAH have higher serum cortisol responses to oCRH and higher EPI and META levels compared to those with CAH, although lower responses than do heterozygotes, which may partially reduce their risk of Addisonian crises during stress. Together, these responses may obviate the need for extra GC during stress in patients with NCAH.
(1) Verma S, et al. *Horm Metab Res* 2010;42:607-612
Sources of Research Support: NIH NCRR GCRC Grant M01 RR00043 and by grants from the CARES Foundation and the David Abell Foundation.
Nothing to Disclose: BB, CA, RS, JM, MK, MG

sort_order

2642

Pub #

P3-573

Session Information

POSTER SESSION: CLINICAL - Adrenal Diseases (1:30 PM-3:30 PM)

Title

Clinical Features and Laboratory Findings in Patients with ACTH-Independent Macronodular Adrenal Hyperplasia (AIMAH)

Author String

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Hospital das Clinicas, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

Body

Background: AIMAH is a rare cause of endogenous Cushing's syndrome. The oversecretion of cortisol in this disease is the result of an increased number of adrenocortical cells rather than more efficient steroidogenesis, as enzymatic pathways have been shown to be compromised. **Objective:** The aim of this study was to delineate clinical features and laboratory findings (cortisol and androgen secretion) in AIMAH. **Methods:** A retrospective review was performed for relevant clinical and laboratory data on patients with AIMAH followed up at Hospital das Clinicas, Faculdade de Medicina da Universidade de Sao Paulo (Brazil) between March 1980 to January 2011. **Results:** 10 patients (9 F and 1 M) were diagnosed with AIMAH. The mean age at the diagnosis was 48.8 ±10.5 yrs (33 to 70). The clinical features of Cushing's syndrome in these patients were as follow (% prevalence): weight gain (80%), overweight (50%), obesity (0%), blood hypertension (80%), diabetes (30%), hyperlipidemia (70%), moon face (30%), plethora (40%), buffalo hump (70%), striae (10%), bruising (80%), acne (10%) and hirsutism (0%). All patients exhibited suppressed plasma ACTH levels and abnormal 1-mg overnight dexamethasone suppression test (plasma cortisol > 1.8[μg/dL]). Midnight salivary cortisol was determined in six patients, demonstrating values above the normal range. Four individuals exhibited normal 24-h urinary cortisol at the initial evaluation. In eight patients, serum DHEAS levels were below the normal range for age and, in the other two, the levels were just above the lower limit. Serum testosterone and androstenedione levels were in the lower half of the normal range. Eight patients underwent screening tests for aberrant hormone receptors, the most frequent cortisol response was found after upright posture (2/7 patients) and after the administration of vasopressin (2/5) and metoclopramide (2/7); in two patients, cortisol secretion was not regulated by any hormone other than ACTH. **Conclusions:** Hypercortisolism in AIMAH is frequently mild and generally associated with low androgen levels. Many clinical features of Cushing's syndrome (overweight, obesity, moon face, plethora, striae, acne and hirsutism) were far less prevalent in these patients. We speculate that adrenal androgen biosynthesis is usually disrupted, since DHEAS levels were below the normal range in most cases.

(1) Lacroix A et al. Best Pract Res Clin Endocrinol Metab 2009; 23(2):245-259 (2) Hsiao HP et al. J Clin Endocrinol Metab 2009; 94(8):2930-2937

Nothing to Disclose: GAA, BBM, AML, LOL, MQA, MCBVF

sort_order 2643
Pub # P3-574
Session Information POSTER SESSION: CLINICAL - Adrenal Diseases (1:30 PM-3:30 PM)
Title Laparoscopic vs. Open Abdominal Surgery: Marked Differences in Cortisol and Catecholamine Responses Dependent on Size and Severity of Abdominal Wall Trauma
Author String E Zoumakis, A Krikri, V Alexopoulos, P Katsaronis, E Balafas, G Kouraklis, PE Karayannacos, GP Chrousos, G Skalkeas
Biomedical Research Foundation, Academy of Athens, Athens, Greece; Athens University Medical School, Aghia Sophia Children's Hospital, Athens, Greece; Athens University Medical School, Laiko General Hospital, Athens, Greece
Body Surgical stress is a composite emotional and physical stress, with the latter depending on the extent of the surgical abdominal wall and/or visceral trauma and the concurrent activation of the immune and inflammatory reaction. Before, during and after surgery, activation of the systemic sympathetic/adrenomedullary nervous systems and the hypothalamic-pituitary-adrenal (HPA) axis allow the body to adjust and preserve homeostasis. Even though the extent of visceral surgical trauma is similar in laparoscopic and the corresponding open surgery, the former has advantages over open surgery including a smaller abdominal wall trauma, reduced operating time, rapid mobilization, early oral feeding, decreased hospital stay and cost, as well as a decreased catabolic reaction, less pain and lower need for analgesics. We compared laparoscopic cholecystectomy and unilateral adrenalectomy to the corresponding open surgeries in a controlled experiment in 20 adult pigs. Identical anesthesia was administered. Blood samples were taken at the same time, one day before surgery, immediately before incision, every 15 minutes during surgery, right after closing the wound and on the first postoperative morning.
Circulating epinephrine and norepinephrine concentrations were significantly lower in both cholecystectomies and adrenalectomies during laparoscopic than during open surgery. This was far more impressive in adrenalectomies, where catecholamines were up to 40 times higher during open surgery. On day 1 after surgery no significant differences in catecholamine levels were observed in both cholecystectomy and adrenalectomy.
Cortisol levels were significantly lower in laparoscopic than in open adrenalectomies both during surgery and on postoperative day one, while no major differences in cortisol levels were observed between laparoscopic and open cholecystectomies.
Our results indicate that laparoscopic surgery has a much smaller stimulatory effect on the stress system than open surgery and that this difference is accentuated as the surgical abdominal wall trauma increases. The increased and prolonged HPA axis response associated with extensive damage of the abdominal wall in open surgeries may contribute to the prolonged catabolism in the postoperative course following major open surgeries.

Nothing to Disclose: EZ, AK, VA, PK, EB, GK, PEK, GPC, GS

sort_order 2644
Pub # P3-575
Session Information POSTER SESSION: CLINICAL - Adrenal Diseases (1:30 PM-3:30 PM)
Title Adrenal Cortical Hyperplasia with Hemorrhage Presenting as Unilateral Adrenal Mass in a Patient with History of Prostate Cancer
Author String MS Sivanandy
Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA
Body
INTRODUCTION:
Adrenal cortical hyperplasia is less common and may or may not be associated with hormonal hypersecretion. This case report is about a patient with history of prostate cancer who presented with a heterogeneous adrenal mass. CASE REPORT:
A 73-year-old man with a history of prostate cancer, status post external beam radiation, was found to have an elevated creatinine, had renal ultrasound that showed a 3-cm hypoechoic mass in the right adrenal gland. Past Medical History: Prostate cancer s/p external beam radiation therapy, hypertension, hearing loss right ear, right adrenal mass.
Allergies: Penicillin. Medications: Amlodipine, atenolol, hydrochlorothiazide, lisinopril, lovastatin, doxazosin, aspirin, Lipitor.
Family History: No family history of adrenal or pituitary disease. Social History: quit smoking a year ago, no alcohol.
Physical Examination: well-appearing, well-nourished, very pleasant middle-aged man, not in acute distress, oriented x3. Vital Signs: BP 135/73; weight 200 pounds. Pulse 69, regular. HEENT: Eyes; comea normal. Sclerae anicteric. Neck: Thyroid, normal in size and consistency. Cardiovascular: Regular rhythm, normal heart sounds. Respiratory: Normal breath sounds heard bilaterally. GI: Abdomen soft, no mass palpable. Skin: No rashes, no bruising. Neurological: No tremor.
Laboratory Data: Plasma aldosterone 7, plasma renin 2.1, DHEAS 27, 24-hour urinary cortisol 5.5, 24-hour fractionated metanephrine 19, normetanephrines 29, 24-hour urinary creatinine 1.31.
CT abdomen: 4 cm heterogeneous mass in the right adrenal gland with persistent enhancement on the 15-minute delayed images and no features of benign adenoma.
CT number histogram: no convincing evidence of fat foci
Surgery: Laparoscopic right adrenalectomy
Surgical pathology: Adrenal cortical hyperplasia with hematoma and organization
Management: Patient had laparoscopic adrenalectomy and surgical pathology was reported as adrenal cortical hyperplasia with hematoma and organization.
DISCUSSION: Unilateral adrenal cortical hyperplasia though less common, can be associated with hemorrhage and can present as heterogeneous mass with delayed enhancement raising the suspicion of primary adrenocortical cancer or metastasis especially in patients with history of other primary malignancies thus causing a diagnostic and therapeutic challenge.

Nothing to Disclose: MSS

sort_order

2645

Pub #

P3-576

Session Information

POSTER SESSION: BASIC/TRANSLATIONAL/CLINICAL - Thyroid Gland Development & Function (1:30 PM-3:30 PM)

Title

Dominant Protein Interactions between Mutant and Wild-Type Thyroglobulin

Author String

X Wang, P Arvan
University of Michigan, Ann Arbor, MI

Body

Congenital hypothyroidism with homozygous mutation in the *Tgn* gene (encoding thyroglobulin, Tg) is a rare cause of thyroid dyshomogenosis; in non-consanguineous marriage, hypothyroid patients with compound heterozygosity is more common. A vastly larger population of individuals are simple heterozygotes who are unaffected carriers of the gene encoding this autosomal recessive disease. Such patients co-express one mutant and one wild-type allele. We have recently shown that recombinant mutant rdw-Tg (from hypothyroid rodents) can cross-dimerize with wild-type Tg. In this study, we have expressed epitope-tagged wild-type or rdw Tg. Like their untagged counterparts, either 3xMyc- or GFP-tagged mutant Tg cannot be secreted, although wild-type Tg3xMyc can rescue secretion of co-expressed rdw-TgGFP and the two proteins co-precipitate (1). However, we now find that when rdw-TgGFP is in molar excess, the mutant [ldquo]wins[rdquo] and inhibits secretion of co-expressed wild-type Tg3xMyc. Which partner contains which epitope tag is irrelevant, as we find that both untagged or 3xMyc-tagged rdw-Tg are capable of inhibiting secretion of co-expressed wild-type TgGFP. The effects are not an artifact of promoter competition, because expression of wild-type Tg3xMyc cannot inhibit secretion of co-expressed wild-type TgGFP. Using a series of increasing ratios of rdw-TgGFP, progressive inhibition of secretion of co-expressed wild-type Tg3xMyc is observed. Surprisingly, the secretion of rdw-TgGFP is partially rescued even in the same samples in which secretion of wild-type Tg3xMyc secretion is inhibited. We conclude that for misfolded Tg mutants, cross-dimerization between mutant and wild-type Tg proteins can lead to bi-directional consequences: rescuing the mutant or blocking the wild-type protein (or both). It is likely that such bi-directional interactions may occur in the thyrocytes of heterozygous individuals bearing mutations that cause congenital hypothyroidism with defective Tg.

(1) Wang X et al., J Biol Chem 2010; 285:17564

Nothing to Disclose: XW, PA

sort_order

2646

Pub #

P3-577

Session Information

POSTER SESSION: BASIC/TRANSLATIONAL/CLINICAL - Thyroid Gland Development & Function (1:30 PM-3:30 PM)

Title

Congenital Hypothyroidism with Mutant Thyroglobulin-Induced Thyroid Cell Death

Author String

A Kellogg, X Wang, Y Zhang, D Larkin, RJ Koenig, WH Olds, P Arvan
University of Michigan, Ann Arbor, MI; Yale University, New Haven, CT; University of Miami, Miami, FL

Body

Congenital hypothyroidism is the most frequent congenital endocrinopathy, and a statistical genetics analysis has suggested that 8q24 (the site of the human *Tgn* gene encoding thyroglobulin) is linked to autosomal recessive hypothyroidism even in the absence of goiter (1). All clinically-relevant thyroglobulin (Tg) coding sequence mutants appear to be imperfect proteins that are impaired in export from the endoplasmic reticulum (ER). As for animal models of the disease, *cog/cog* mice suffer from congenital hypothyroidism with stunted growth and other defects, decreased serum thyroxine and increased TSH, and a large goiter -- all caused by Tg misfolding as a consequence of a missense mutation in the cholinesterase-like domain of Tg. Thyrocytes of *cog/cog* mice exhibit a distended ER with activation of the unfolded protein response (UPR). A similar model, *rdw/rdw* rats, also exhibit stunted growth, a distended thyrocyte ER with UPR activation, decreased serum thyroxine and increased serum TSH, all from a nearby Tg missense mutation in the same domain as that of the *cog* mutation -- but they do not develop a goiter. Recent studies show that wild-type Tg rescues ER export of co-expressed rdw-Tg (2), but to understand the absence of goiter in homozygotes that make no wild-type Tg, we engineered mice expressing (from a *Tgn* promoter) a *rdw-Tg-3xMyc* transgene selectively in the thyroid, as judged by qPCR, anti-myc Western blotting and immunofluorescence. The transgenic animals (with two wild-type *Tgn* alleles) had no grossly abnormal phenotype, and could grow a normal-sized goiter when hypothyroidism was induced with propylthiouracil. However, when expressed in a *cog/cog* background (that lacks any wild-type Tg), these hypothyroid "congenital goiter" transgenic mice could not grow a goiter. Such *cog/cog* transgenic animals had markedly increased Ki-67 staining in thyrocytes consistent with thyrocyte proliferation as seen in other *cog/cog* mice. Remarkably, however, the *cog/cog* transgenic mice exhibited extensive TUNEL-positive cells across the thyroid gland. These data strongly suggest that the rdw-Tg3xMyc transgene product is proteotoxic, causing cell death in thyrocytes that lack co-expressed wild-type Tg. However, in thyrocytes co-expressing wild-type Tg, the cells are rescued from proteotoxicity, such that ongoing thyrocyte proliferation allows for thyroid goitrogenesis.

(1) Ahlbom et al. 2002 Hum Genet 110:145

(2) Wang et al., 2010 J Biol Chem 285:17564

Nothing to Disclose: AK, XW, YZ, DL, RJK, WHO, PA

sort_order 2647
Pub # P3-578
Session Information POSTER SESSION: BASIC/TRANSLATIONAL/CLINICAL - Thyroid Gland Development & Function (1:30 PM-3:30 PM)
Title Zebra-Fishing To Obtain New Insights into Vertebrate Thyroid Development
Author String P Porazzi, N Tiso, T de Filippis, F Marelli, F Benato, F Argenton, L Persani
Universit[agrave] degli Studi di Milano, Milano, Italy; University of Padova, Padova, Italy; IRCCS Istituto Auxologico Italiano, Milano, Italy
Body The thyroid follicular cells originate from the ventral floor of the anterior foregut and, during development, follow some conserved morphogenetic steps such as their re-localization in the anterior neck region, the organization into follicular structures and the proliferation and functional differentiation. Alterations in these initial events lead to congenital hypothyroidism (CH), a frequent endocrine disorder that, in 85% of the cases, is the result of disturbed thyroid organogenesis, a condition known as thyroid dysgenesis (TD). The etiology of TD is still poorly understood, as only few cases are associated with mutations of known thyroidal transcription factors, suggesting that other unknown mechanisms play a role during thyroid organogenesis.
A comparative gene expression analysis allowed us to identify new TSH-sensitive genes. Several genes, belonging to Notch pathway, which is involved in multi-organ development, were down-regulated by TSH treatment. Therefore, we focused our attention on these genes as novel candidates that might contribute to thyroid organogenesis. To functionally characterize the role of these novel candidates, we took advantage of the vertebrate model zebrafish. We have recapitulated the main steps of zebrafish embryonic thyroid development by whole mount in situ hybridization (nkx2.1a, pax2a, tg and slc5a5) or immunohistochemistry techniques to assess zebrafish thyroid hormone production (T4). We have then analyzed the expression of our candidate genes in combination with thyroid specific markers at different time-points during development. In case of a co-expression in the thyroid primordium, we have further investigated their role analyzing the thyroid phenotype with different approaches: morpholino knock-down or over-expression strategies, and, when available, analysis of mutant zebrafish lines. In some of these conditions, thyroid development was severely impaired. The combination of these different techniques allowed us to dissect the contributions of Notch-related genes to thyroid development.
Nothing to Disclose: PP, NT, TdF, FM, FB, FA, LP

sort_order

2648

Pub #

P3-579

Session Information

POSTER SESSION: BASIC/TRANSLATIONAL/CLINICAL - Thyroid Gland Development & Function (1:30 PM-3:30 PM)

Title

Significance of Transient Receptor Potential Canonical 2 (TRPC2) in the Regulation of Rat Thyroid FRTL-5 Cell Proliferation and Migration

Author String

P Sukumaran, C Lof, K Tornquist

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Body

Mammalian transient receptor potential (TRP) channels are widely expressed and function in many physiologically important processes. They are non-selective cation channels, and are considered putative receptor- and store-operated cation channels that play a fundamental role in the regulation of cellular Ca^{2+} homeostasis. Differences in the expression pattern or mutations of the channels have implications for diseases. In the present study we have studied the significance of the TRPC2 channel in the regulation of rat thyroid FRTL-5 cell proliferation and migration. To investigate the physiological importance of the channel, we developed stable TRPC2 (shTRPC2) knock-down cells using shRNA. In shTRPC2 cells, the ATP-evoked entry of calcium was significantly decreased, implicating an important role of TRPC2 in FRTL-5 function. Furthermore, in the shTRPC2 cells, proliferation was decreased due to a prolonged G1/S cell cycle phase. This was due to an upregulation of the tumor suppressor p53 and the cyclin-dependant kinase inhibitors p27 and p21. In addition, cell migration and cell adhesion was also attenuated in shTRPC2 cells. In control cells, the potent TRPC channel blocker 2-APB had similar effects on both migration and on the ATP evoked calcium response as knock-down of TRPC2. Sphingosine 1-phosphate induced a three-fold increase in migration in control cells, but not in the shTRPC2 cells. In conclusion, TRPC2 is a major regulator of rat thyroid cell function.

Sources of Research Support: Academy of Finland, the Sigrid Juselius Foundation, the Centre of Excellence in Cell Stress and Molecular Ageing, Magnus Ehrnrooth's Foundation, and the Receptor Research Program ([Aring]bo Akademi University and University of Turku).

Nothing to Disclose: PS, CL, KT

sort_order 2649
Pub # P3-580
Session Information POSTER SESSION: BASIC/TRANSLATIONAL/CLINICAL - Thyroid Gland Development & Function (1:30 PM-3:30 PM)
Title Transient Receptor Potential Canonical 2 (TRPC2) Regulates the Expression of the Thyroid-Stimulating Hormone Receptor and the Secretion of Thyroglobulin in Rat Thyroid FRTL-5 Cells
Author String C Lof, P Sukumaran, T Viitanen, M Vainio, K Kemppainen, J Nasman, I Pulli, K Tornquist
[Aring]bo Akademi University, Turku, Finland; [Aring]bo Akademi University, Turku, Finland; Minerva Foundation Institute for Medical Research, Helsinki, Finland; University of Turku, Turku, Finland
Body Transient receptor potential (TRP) cation channels are widely expressed and function in many physiologically important processes. Perturbations in the expression or mutations of the channels have implications for diseases. Many thyroid disorders, as excessive growth or disturbed thyroid hormone production, can be a result of dysregulated thyroid-stimulating hormone (TSH) signaling. The potential functions of canonical TRP (TRPC) channels in thyroid cells have not been elucidated. In the present study we have investigated which TRPCs are expressed in rat thyroid FRTL-5 cells. We found that only TRPC2 was expressed in FRTL-5 cells. To investigate the physiological importance of the channel, we developed stable TRPC2 knock-down cells using shRNA (shTRPC2). In these cells, the ATP-evoked entry of calcium was significantly decreased. Electrophysiological measurements also revealed decreased currents in shTRPC2 cells. The secretion of thyroglobulin was decreased in shTRPC2 cells, probably due to improper folding and glycosylation of the protein. Interestingly, the expression of thyroid-stimulating hormone receptor (TSHR) was enhanced in the shTRPC2 cells. Accordingly, TSH-evoked cAMP production was increased in shTRPC2 cells. Furthermore, the phosphorylation of extracellular signal-regulated kinase 1/2 (Erk1/2) was increased in shTRPC2 cells. By expressing a constitutively active mitogen-activated protein kinase kinase 1 (MEK1) construct in FRTL-5 cells, we show that the MEK/Erk1/2 pathway positively regulates the expression of the TSHR in FRTL-5 cells. In conclusion, TRPC2 is a major regulator of rat thyroid cell function.

Nothing to Disclose: CL, PS, TV, MV, KK, JN, IP, KT

sort_order 2650
Pub # P3-581
Session Information POSTER SESSION: BASIC/TRANSLATIONAL/CLINICAL - Thyroid Gland Development & Function (1:30 PM-3:30 PM)
Title Effects of Estrogen on Sodium/Iodide-Symporter and Thyroid Peroxidase Gene Expression in Female Rats
Author String G Ceresini, M Lane, GP Ceda, I Merchenthaler
University of Parma, Parma, Italy; University of Maryland, Baltimore, MD
Body **Introduction:** Estrogen receptors have been demonstrated in thyroid tissue. However, the role of estrogens in thyroid function is still poorly understood. We evaluated the effects of estrogen (17 β -estradiol: E2) in female rats on Sodium/Iodide- Symporter (NIS) and Thyroid Peroxidase (TPO). **Materials and Methods:** The expression of NIS and TPO in thyroid tissue was performed with RT-PCR utilizing ovariectomized (OVX) OVX+E2-treated adult SD. For PCR amplification of rat NIS and TPO the following sense and antisense primers were used: for NIS, 5'-TCT TCC TGG CCT GTG CCT ACA-3' and 5'GCC CGA GTC CAT TCC AGA ACT-3'; for TPO, 5'- GCA CCT TGG ATC TGG CAT CAC-3' and 5'-TGT GGG AAG GTC TCC CTC CAT-3'. RNeasy Mini Kit (Quiagen) was used to isolate total RNA following the manufacturer's directions. The RNA was eluted and the optical density was obtained using a spectrophotometer. **RT reaction:** Using the OD's, 1 microgram of total RNA was made into cDNA in the first strand RT reaction of the PCR. The procedure (Invitrogen) was followed using the random hexamers to produce the cDNA utilized in the PCR reaction. **PCR Reaction:** All samples were run for quantification utilizing Real Time-PCR in a LightCycler machine from Roche Applied Science. The RT-PCR used SYBR Green in the PCR and the fluorescence from each sample was measured continuously in every cycle during PCR, and plotted against cycle number. Absolute quantification was possible by comparing the genes (NIS and TPO) to standard curves for those genes along with a housekeeping gene which in this experiment was 18S. A ratio between the fluorescent measurements obtained with either NIS or TPO and that obtained with 18S in the same reaction was calculated. **Results:** A significant decrease in NIS mRNA expression was found in OVX+E2 rats as compared with OVX rats (7.91 \pm 1.74 U vs 3.47 \pm 0.58 U in OVX vs OVX+E2 rats, P<0.01). Also TPO mRNA expression was lower in OVX+ E2 rats as compared to OVX rats, although the difference did not reach the statistical significance (33.93 \pm 8.2 vs 22.77 \pm 6.52 in OVX vs OVX+E2 rats, P= 0.1). **Conclusions:** Our data demonstrate that, in female rats, estrogen deprivation induces an up-regulation of both NIS and TPO genes, which, for NIS, reaches the statistical significance. Estrogen treatment on the contrary, reduces the expression of both genes. Through this mechanism, estrogen deprivation in menopausal and aged women may have important influences on thyroid physiology.

Nothing to Disclose: GC, ML, GC, IM

sort_order 2651
Pub # P3-582
Session Information POSTER SESSION: BASIC/TRANSLATIONAL/CLINICAL - Thyroid Gland Development & Function (1:30 PM-3:30 PM)
Title The Effect of Chronic Exposure to Carbendazyme on Thyroid Function and Morphology of Rats
Author String C Marcisz, B Urbaniak-Lampart, K Kita, TJ Irzyniec, M Marcisz-Orzel
Medical University of Silesia, Tychy, Poland; Institute of Industrial Organic Chemistry, Pszczyna, Poland; Medical University of Silesia, Katowice, Poland; Hospital of the Ministry of Interior and Administration, Katowice, Poland
Body
Introduction: Carbendazyme (Cbd) is a synthetic fungicide belonging to benzimidazol derivatives. In experimental animals may cause morphological changes in the thyroid gland and the increase its weight. There are only several reports concerning the effects of carbendazyme on thyroid hormones of the experimental animals. Furthermore the results proved to be incoherent.
Aim: The purpose of the study was to examine the morphology and the function of the rats' thyroid gland during and after 24 months of exposure to Cbd.
Material and methods: Eighty male and female rats divided into 4 groups. Cbd was administered with feeding stuff at the doses: 5 mg/kg body weight (bw)/d-group 1, 125 mg/kg bw/d-group 2, 125 mg/kg bw/d-group 3. Control group (CG) didn't receive Cbd. The thyroid and pituitary glands were weighted, their histopathology was examined and the plasma concentrations of FT3, FT4 and TSH were assessed.
Results: Two years exposure to Cbd caused the increase the thyroid weight but significant only in females receiving the highest dose of Cbd. Furthermore, we observed the decrease of pituitary weight in the exposed animals as compare to CG, but significant only in females groups 1 and 2 and males from group 3. Hyperplasia, adenoma or carcinoma were present in the thyroid and pituitary glands in all examined groups. However morphological changes in thyroid and pituitary glands proved to be dependent on the sex: in thyroid glands mainly in males and in the pituitary mostly in females. In the male rats the increase FT3 and decrease TSH levels were observed in the group 3 but no significant differences were found in all groups in FT4 levels. In the female rats, the FT3 level was gradually but significantly decreasing in the group 2 and 3. The negative correlations between TSH and FT4 in all examined groups were found.
Conclusions: 1. Two years exposure of the rats to 125 mg/kg bw/day of Cbd increases the thyroid gland weight of females and decreases the pituitary gland weight of males. 2. The histopathological changes in the thyroid and pituitary glands of rats seem to be independent of the chronic exposure to Cbd, however they are reliant on the sex: in males are predominant in thyroid, in females in pituitary glands. 3. Cbd applied to the rats for 2 years at the dose of 125 mg/kg bw/day tends to stimulate the thyroid function in males and has the opposite effect in females. 4. The chronic exposure of rats to Cbd does not disturb the pituitary-thyroid feedback.

Nothing to Disclose: CM, BU-L, KK, TJI, MM-O

sort_order 2652
Pub # P3-583
Session Information POSTER SESSION: BASIC/TRANSLATIONAL/CLINICAL - Thyroid Gland Development & Function (1:30 PM-3:30 PM)
Title Thyroid Function Tests during Pregnancy: Should There Be Specific Normal Ranges According to Gestational Age?
Author String L Bondaz, K Mourabit Amari, SJ Weisnagel, Y Giguere, M-C Dube, M-C Denis
Centre Hospitalier Universitaire de Québec, Québec City, Canada; Centre Hospitalier Universitaire de Québec, Québec City, Canada; Centre Hospitalier Universitaire de Québec, Research Center, Québec City, Canada; Centre Hospitalier Universitaire de Québec, Research Center, Québec City, Canada; Centre Hospitalier Universitaire de Québec, Québec City, Canada; Centre Hospitalier Universitaire de Québec, Research Center, Québec City, Canada
Body
Abnormal thyroid function in pregnant women is associated with adverse outcomes. Pregnancy related physiologic changes complicate the interpretation of thyroid function test results and may justify the need to characterize gestational age specific reference ranges.
Our study aimed to establish reference intervals according to gestational age. Secondary goals were to assess the impact of auto-immunity and β -HCG levels on thyroid function tests during pregnancy. This cross-sectional study included 524 women evaluated at the Centre M[grave]re-Enfant of the Centre Hospitalier Universitaire de Québec at different stages of pregnancy defined by gestational age in weeks (T1: [9-13], T2: [14-28], T3: [29-36]). The patients were anonymously tested for TSH, free T4 (FT4), total T3 (TT3), anti-TPO antibodies and β -HCG using the Roche Modular system. Women with increased anti-TPO antibodies (>34 kIU/L) were excluded in order to determine a reference range based on the distribution of values (2.5th to 97.5th percentile). These pregnant reference ranges were compared to the non-pregnant normal values validated in our center (TSH: [0.25-5.0 mIU/L], FT4: [12-22 pmol/L] and TT3: [1.3-3.1 nmol/L]). TSH and FT4 distributions were determined to be log normal and statistical analysis was performed accordingly. Means for TSH were significantly different between every group ($p[le]0.0112$). The reference ranges were: T1: 0.46-4.3, T2: 0.45-4.5, T3: 0.68-5.2 mIU/L. FT4 values decreased throughout pregnancy and the distribution was narrower compared to non-pregnant women. Means of normalized FT4 differed statistically between each group ($p<0.0001$) and were: T1: 10.3-17.7, T2: 9.3-16.0, T3: 8.0-16.7 pmol/L. TT3 was higher in pregnancy than in non-pregnancy and in T3 compared to T1 and T2. Reference ranges for TT3 were: T1: 1.8-3.6, T2: 1.8-3.7, T3: 1.6-4.1 nmol/L.
Women with the highest values of β -HCG ($>95\%$, $n=10$) in T1 had TSH levels that were lower than other women (0.89 vs 1.38, $p=0.022$). Prevalence of high anti-TPO was 10.6% (8.3-13.6%, CI 95% and was associated with higher values of TSH in T1 and T2 ($p<0.05$), but not with higher FT4 levels.
Our results support the relevance of gestational age specific reference ranges for thyroid function tests in pregnancy and underline the impact of auto-immunity and β -HCG levels on the interpretation of thyroid function tests in this setting. This justifies the establishment of a specific testing algorithm in pregnant women.

Nothing to Disclose: LB, KMA, SJW, YG, M-CD, M-CD

sort_order 2653
Pub # P3-584
Session Information POSTER SESSION: BASIC/TRANSLATIONAL/CLINICAL - Thyroid Gland Development & Function (1:30 PM-3:30 PM)
Title Reference Intervals for Thyroid Hormone Function in the Second Trimester in Pregnant Filipino Women
Author String JN Hamin, PC Patal, CA Jimeno, LT Acampado, MAL Abrahan
University of the Philippines - Philippine General Hospital, Manila, Philippines
Body
Background: Interpretation of thyroid function tests during pregnancy needs trimester-related reference intervals from pregnant populations due to the physiologic changes seen during pregnancy. These changes are most pronounced in the 1st trimester, but additional changes occur in both the 2nd and 3rd trimesters. In an unpublished data in the first trimester specific reference interval among pregnant Filipino women noted the following reference values: TSH 0.014-3.84 pmol/L (NV 0.25-4 pmol/L); FT4 10.44-21.58 pmol/L (NV 11.5-23 pmol/L); and FT3 2.4-5.82 pmol/L (NV 2.5-5.8 pmol/L) among TPOAb negative patients. If the non-pregnant TSH reference range was applied to the study participants, 21 patients (18%) will be misclassified to have subclinical hyperthyroidism. Special attention should be focused on establishing what is normal thyroid function in pregnancy to avoid misclassification, overtreatment, undertreatment and consequent untoward effects to the unborn.
Objective: To establish the second-trimester-specific reference intervals for thyroid function tests in pregnant Filipino women.
Design, setting and participants: Two hundred (200) healthy pregnant Filipino women (16-20 weeks' gestation) attending a tertiary center were recruited. Levels of serum thyrotropin (TSH) were measured using IRMA while free thyroxines (FT4), free triiodothyronine (FT3), thyroid peroxidase antibodies (TPOAb) were measured by radioimmunoassay method.
Main outcome measures: Reference intervals based on 2.5th and 97.5th percentiles for TSH, FT4 and FT3 among TPOAb negative pregnant patients.
Results: Among the 200 pregnant Filipino women recruited, 192 (96%) were TPO antibody negative while 8 (4%) had positive titers. Thyroid function tests did not differ significantly between the two groups. The 2.5th and 95th percentiles values were used to determine the reference ranges for FT3, FT4 and TSH during the second trimester of pregnancy as follows: TSH = 1.53 ± pmol/L; FT4 = 13.30 ± 4.2 pmol/L and FT3 = 3.90 ± 2 pmol/L.
Conclusions: Reference ranges of FT3, FT4 and TSH have been established for pregnant Filipino women using in the second trimester using the 2.5th and 95th percentiles. In our study population, the levels of TSH increases as pregnancy duration increases. On the other hand, negative relationship was observed in the FT4 levels. FT4 level decreases while pregnancy duration increases. On the other hand, no statistically significant change in the level of FT3 noted throughout the gestation.

Sources of Research Support: Philippine Society of Endocrinology and Metabolism.

Nothing to Disclose: JNH, PCP, CAJ, LTA, MALA

sort_order 2654
Pub # P3-585
Session Information POSTER SESSION: BASIC/TRANSLATIONAL/CLINICAL - Thyroid Gland Development & Function (1:30 PM-3:30 PM)
Title Selenium's Changes in Pregnancy and Its Relationship with Thyroid Autoimmunity
Author String M Alexiou, I Ilias, K Markou, I Mamali, M Nicopoulou, M Alevizaki, E Koukkou
E Venizelou Hospital, Athens, Greece; University of Patras, Rion, Patras, Greece; University of Athens, Alexandra Hospital, Athens, Greece
Body **Introduction:** Selenium (Se) is a key component of iodinases; changes in the availability of Se has been reported to affect thyroid autoimmunity (expressed by thyroid autoantibodies). More particularly, in subjects with higher levels of Se the titer of antithyroid peroxidase antibodies (a-TPO) is lower. Pregnancy is a state that has profound effects on thyroid function and autoimmunity
Aim: To assess Se levels in pregnancy and its relationship with thyroid function and autoimmunity in pregnant women residing in Athens, Greece.
Methods: We studied prospectively 136 euthyroid women in uncomplicated singleton pregnancies (mean age±SD: 29.8±4.7 years) in each trimester and 2 months postpartum. Blood was collected for thyrotropin (TSH), free thyroxine and triiodothyronine (FT4 and FT3, respectively) and a-TPO and urine was collected for Se and iodine (I). Changes of the measured parameters were assessed over each trimester and postpartum; thyroid parameters were assessed also vis-à-vis Se levels (with the Kruskal-Wallis' and Spearman's test, respectively).
Results: TSH and a-TPO did not show appreciable changes, whereas FT4 and FT3 showed a gradual drop as the pregnancy advanced and increased postpartum. Urine Se dropped by the third trimester and remained to approximately the same levels postpartum. Weak correlations were observed among Se and FT4 and FT3 (both $r=0.20$, $r^2=0.04$, $p=0.001$) and Se and I ($r=0.21$, $r^2=0.04$, $p=0.0005$). No differences of Se levels by a-TPO were observed.
Conclusion: Se levels drop by the end of pregnancy; changes in Se levels are associated with slight changes in thyroid function, but not with thyroid autoimmunity.
Nothing to Disclose: MA, II, KM, IM, MN, MA, EK

sort_order 2655
Pub # P3-586
Session Information POSTER SESSION: BASIC/TRANSLATIONAL/CLINICAL - Thyroid Gland Development & Function (1:30 PM-3:30 PM)
Title Na⁺/I⁻ Symporter and Type 3 Iodothyronine Deiodinase Expression in Term Placenta
Author String M Akturk, A Sargin, N Danisman, S Erkek, U Buyukkagnci, E Unlu, U Tazebay
Faculty of Medicine, Gazi University, Ankara, Turkey; Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara, Turkey; Bilkent University, Ankara, Turkey; Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara, Turkey; Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara, Turkey
Body
Background and Aim: Placental type 3 iodothyronin deiodinase (D3) is thought to protect the fetus from the elevated maternal thyroid hormones. Na⁺/I⁻ symporter (NIS) is a plasma membrane glycoprotein that takes role in active iodine uptake. The purpose of this study is to establish any relationship between placental D3, NIS expressions and maternal thyroid, selenium, iodine status. Subjects and Methods: Placental tissues were collected from normal pregnant women immediately after elective cesarean delivery. NIS and D3 expression levels were investigated with total mRNA RT-PCR method in the maternal side of placental tissue samples from forty-nine healthy pregnant women at term. NIS and DIII expression levels were quantified by normalization to TATA-binding protein expression (a house-keeping gene for placenta) levels. We measured thyroid hormone parameters, serum selenium, spot urinary iodine excretion, fasting blood glucose in the pregnant women and also thyroid volumes which were assessed by ultrasonography.
Results: Mean age of the women was 31.08±5.33 year. Median TSH levels and urine iodine excretion were 2.06 (1.5) microIU/mL and 143 (269) microg/L, respectively. Serum selenium level was 66±26.5 microg/L. Ratio of D3/NIS expression was 2.9. When divided into two groups based on the TSH levels of the women (<2.5, and [ge]2.5 microIU/mL), placental D3 expression was slightly decreased in the TSH [ge]2.5 group compared with the TSH<2.5 group, but there was no statistically significant difference between the two groups (p=0.1). Placental NIS expressions were positively correlated with maternal Thyroxine Binding Globulin (TBG) levels (r=0.3, p=0.04) and placental D3 expressions were positively correlated with preoperative maternal fasting blood glucose levels (r=0.4, p=0.006).
Conclusion: D3 and NIS are widely expressed in term placenta. Maternal TBG, which is increased in pregnancy, might have a role in the arrangement of placental NIS expression. Consequently, it might affect iodine transmission from mother to fetus, although it needs further investigation. Moreover, further studies are needed to clarify the relationship between maternal glucose levels and placental D3 levels.
Sources of Research Support: This project (106S229/SBAG-3475) was supported by TUBITAK (Scientific and Technical Research Council of Turkey).
Nothing to Disclose: MA, AS, ND, SE, UB, EU, UT

sort_order 2656
Pub # P3-587
Session Information POSTER SESSION: BASIC/TRANSLATIONAL/CLINICAL - Thyroid Gland Development & Function (1:30 PM-3:30 PM)
Title Iodothyronine Deiodinase 1 Polymorphisms Are Associated with Body Height
Author String GLLER, S Guillemaere, H De Naeyer, S Vandewalle, YEC Taes, J-M Kaufman
Universitary Hospital of Ghent, Ghent, Belgium
Body
Introduction:
Thyroid hormone concentrations are genetically determined and exert pleiotropic effects in the body. Especially Iodothyronine Deiodinases have been associated with circulating thyroid hormones (Deiodinase 1: rs 11206244 and rs 2235544) or body composition (Deiodinase 2: rs 225014).
Methods:
We investigated the effects of these 3 SNPs on thyroid hormone concentrations and body composition in young healthy euthyroid men. A total of 677 healthy male siblings aged 25-45 yrs were recruited in this study. Total (TT3, TT4) and free (FT3,FT4) thyroid hormones were determined using immunoassays and SNPs using a Taqman Genotyping SNP assay.
Results:
Two SNPs in Deiodinase 1 were associated with thyroid hormone concentrations. Subjects with a T-allele for rs 11206244 displayed higher concentrations of FT4 and reverse T3 (rT3) and lower FT3/FT4 and TT3/rT3 ratios, in agreement with a lower Deiodinase 1 activity. A higher Deiodinase 1 activity was observed in subjects with a C-allele for rs 2235544, with higher concentrations of FT3, higher ratios of FT3/FT4, TT3/TT4 and TT3/rT3 and lower concentrations of rT3. No associations between rs 225014 and thyroid hormone concentrations were observed. A positive relation was seen between the T-allele of rs 11206244 and body height (2 cm difference between categories, p=0.009). Other anthropometric parameters (armspan, calf height, sitting and sternum height) were also higher in these carriers. We observed a negative association between the C-allele of rs 2235544 and body height (1.8 cm difference between categories, p=0.02) and armspan. Rs 225014 in Deiodinase 2 was not associated with height (parameters). FT4 and TT4, but not FT3 and TT3, were also associated with height in this population. When we added thyroid hormone concentrations (FT4 and TT4) to the model, the associations between height and the 2 SNPs remained significant.
Conclusion:
Deiodinase 1 polymorphisms are associated with thyroid hormone levels but also with body height and anthropometric parameters.
Nothing to Disclose: GLLER, SG, HDN, SV, YECT, J-MK

sort_order 2657
Pub # P3-588
Session Information POSTER SESSION: BASIC/TRANSLATIONAL/CLINICAL - Thyroid Gland Development & Function (1:30 PM-3:30 PM)
Title Underestimation of (Long-Term) Effect of Thyroid Function on Morbidity and Mortality Due to Intraindividual Variation
Author String A Van de Ven, R Netea, F Sweep, R Peeters, M Medici, A Hofman, A Hermus, T Visser, M den Heijer
Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands; Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands; Erasmus University Medical Center, Rotterdam, Netherlands; Erasmus University Medical Center, Rotterdam, Netherlands; Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands
Body
Introduction
Thyroid dysfunction is associated with several diseases, such as atrial fibrillation and cardiovascular disease, and mortality. Due to intraindividual variation of TSH and FT₄ levels, the association between thyroid function and disease or mortality rates might be underestimated in studies based on one single measurement of TSH and/or FT₄. This kind of bias is called regression dilution bias. The aim of this study was to examine the intraindividual variability of TSH and FT₄ measurements several years apart in different study cohorts and to determine the magnitude of the underestimation of the association between thyroid function and disease rates in population-based studies using only one measurement.
Methods
We used a pair of measurements of TSH and FT₄ in subjects of the Nijmegen Biomedical Study (NBS) and the Rotterdam Study (RS) with an interval of 2-4 years to calculate the regression dilution ratio (RDR) with a nonparametric method (Macmahon's method). Based on the first measurement, subjects were divided in TSH and FT₄ quintiles. The initial range (R₁) was defined as the difference between the means of the top and bottom quintiles of the TSH or FT₄ value. Secondly, the mean values of TSH or FT₄ of the second measurement were calculated per quintile, still using the initial, baseline measurements for subdividing the subjects into the quintiles. The ratio of the two ranges provided an estimate of the regression dilution ratio (RDR). In addition, we assessed the correlation coefficient between the first and second measurements (i.e. the self-correlation) as another (parametric) method to estimate the RDR. Correction for regression dilution bias involves dividing the estimated disease association by the RDR. (1-2)
Results
Using the Macmahon's method, RDRs of serum TSH in the NBS and the RS were respectively 0.74 and 0.78. The RDRs of serum TSH were similar for women and men, 0.75 and 0.74 respectively in the NBS and 0.80 and 0.77 in the RS. The RDRs of serum TSH in participants, excluded from the previous analysis because of known thyroid disease, were 0.42 in the NBS and 0.52 in the RS. The RDR of serum FT₄ in subjects of the NBS was 0.77. Estimation of the RDR by the self-correlation method gave similar results.
Conclusion
The relationship between thyroid function and diseases is underestimated by studies using only one measurement. The real association will be about 33% higher for studies with a follow-up time of 2-4 years.
Nothing to Disclose: AVdV, RN, FS, RP, MM, AH, AH, TV, MdH

sort_order 2658
Pub # P3-589
Session Information POSTER SESSION: BASIC/TRANSLATIONAL/CLINICAL - Thyroid Gland Development & Function (1:30 PM-3:30 PM)
Title Brown Fat Metabolism but Not Perfusion Is Enhanced in Hyperthyroid Patients
Author String M Lahesmaa, J Orava, M Soimio, JC Hannukainen, T Noponen, C Schalin-Jantti, KA Virtanen, P Nuutila
University of Turku, Turku, Finland; University of Turku, Turku, Finland; Helsinki University Hospital, Helsinki, Finland
Body
Introduction: Cold exposure has been shown to activate brown adipose tissue (BAT) metabolism in adult humans. Recent studies demonstrated that thyroid hormones play an important role in the development and function of BAT. The aim of this study was to investigate the effects of hyperthyroidism on glucose metabolism and perfusion of BAT.
Design and methods: Ten overtly hyperthyroid patients (9 with Graves' disease) and ten healthy volunteers were recruited. Thyroid, BAT and skeletal muscle glucose uptake (GU) and perfusion were measured using ¹⁸F-FDG- and ¹⁵O-H₂O-PET in baseline conditions. All subjects underwent MRI and CT scans for localisation of supraclavicular BAT. Indirect calorimetry was used to measure energy expenditure.
Results: Compared to euthyroid subjects, GU was 3-fold higher in BAT (3.4 ± 2.7 vs. 1.0 ± 0.5 [μ]mol/100g/min, $p < 0.05$) and in skeletal muscle (2.2 ± 0.6 vs. 0.7 ± 0.2 [μ]mol/100g/min, $p < 0.001$), but only 50% higher in thyroid gland (4.1 ± 1.3 vs. 2.6 ± 1.3 [μ]mol/100g/min, $p < 0.05$) in hyperthyroid patients. No difference between the groups was observed in perfusion of BAT, while hyperthyroidism was associated with enhanced muscle perfusion. Energy expenditure was increased five-fold in hyperthyroid patients with significantly higher use of lipids as energy substrate compared to healthy subjects (1173 ± 348 vs. 770 ± 224 kcal/d, $p < 0.01$).
In conclusion, hyperthyroidism increased glucose metabolism in human BAT even more than in the thyroid gland and independently of tissue perfusion. These results show that in hyperthyroidism human BAT is also metabolically activated, independently of cold exposure. This hormone-driven activation of human BAT is likely mediated via simultaneous enhanced sympathetic tone and activation of the enzyme type 2 deiodinase.

Nothing to Disclose: ML, JO, MS, JCH, TN, CS-J, KAV, PN

sort_order 2659
Pub # P3-590
Session Information POSTER SESSION: BASIC/TRANSLATIONAL/CLINICAL - Thyroid Gland Development & Function (1:30 PM-3:30 PM)
Title The Effect of Treatment of Hyperthyroidism on Body Composition and Its Correlation with Ghrelin Levels
Author String ECK Yeoh, CF Sum, SC Lim, KC Lim, LJ Ong, LC Lim
Khoo Teck Puat Hospital, Singapore; Khoo Teck Puat Hospital, Singapore; Khoo Teck Puat Hospital, Singapore; Jurong General Hospital, Singapore
Body
Background
Disturbances in thyroid function are associated with changes in body composition, energy expenditure and food intake with weight loss a key feature of hyperthyroidism. Ghrelin, an orexigenic hormone, is associated with food intake and energy homeostasis. This study aims to observe the relationship between the treatment of hyperthyroidism, changes in body composition and its correlation with ghrelin levels. We hypothesise that ghrelin levels will increase with restoration of euthyroidism and that the degree of thyroid hormone elevation may predict weight gain.
Methods
Ten Patients (mean age 42, age range 21 -75) with Graves' hyperthyroidism had their free thyroxine (fT4), thyroid stimulating hormone (TSH) and total tri-iodothyronine (T3) measured. Their body weight, fat mass (FM), fat free mass (FFM) and ghrelin levels were measured before and after treatment.
Results
Mean levels of fT4 and T3 were 48.3 (range 29.7-100 pmol/L) (NR 11.8 -24.6) and 5.21 (range 2.90- 9.78 nmol/L) (NR 1.60-2.60) respectively. TSH ranged from < 0.005-0.013 mIU/L (NR 0.270-4.20). Mean treatment duration to euthyroidism was 118 days. Nine patients gained weight, mean weight gain 3.3 kg (range 0.9-9.1 kg). Mean changes in FM and FFM were 1.87 ± 1.73 kg and 1.43 ± 1.98 kg respectively. Linear regression analysis showed a positive correlation between the level of T3 and weight gain (p=0.031). Ghrelin levels increased during the course of treatment, mean ghrelin levels were 17.17 pg/ml (range 11.01-27.57 pg/ml) and 35.47 pg/ml (range 13.31-95.16 pg/ml) at hyperthyroidism and euthyroidism respectively; mean change 18.3 ± 26.31 pg/ml. This rise in ghrelin levels post-treatment reached near-significance (p=0.051) and was found to be significantly associated with pre-treatment and post-treatment FM (p=0.003 and 0.007 respectively). There was no correlation observed between ghrelin levels, weight change and FFM.
Conclusion
In hyperthyroidism, ghrelin levels increased upon achieving euthyroidism. This rise in ghrelin was associated with an increase in fat mass. Baseline T3 may be a useful predictor of weight gain.

Sources of Research Support: National Medical Research Council Grant.

Nothing to Disclose: ECKY, CFS, SCL, KCL, LJO, LCL

sort_order 2660
Pub # P3-591
Session Information POSTER SESSION: BASIC/TRANSLATIONAL/CLINICAL - Thyroid Gland Development & Function (1:30 PM-3:30 PM)
Title Higher Requirement for Levothyroxine Replacement Therapy in Adult Patients with Congenital Hypothyroidism and Thyroid Agenesis than in Adult Patients with Postsurgical Hypothyroidism
Author String B Bagattini, L Montanelli, M De Servi, C Di Cosmo, M Ciampi, A Pinchera, P Vitti, M Tonacchera
University of Pisa, Pisa, Italy
Body
Introduction: Levothyroxine (LT4) is commonly employed to correct hormone deficiency in children affected by congenital hypothyroidism (CH) and in patients with iatrogenic hypothyroidism.
Objective: To compare the daily weight-based dosage of the replacement therapy with LT4 in adult patients affected by CH due to thyroid agenesis and adult patients with thyroid nodular or cancer diseases treated with total thyroidectomy.
Study group and methods: 28 patients (19 females and 9 males) aged 18 to 26 years were studied. Group A: 12 adult patients (mean age 19.9 yr) with congenital hypothyroidism due to thyroid agenesis treated with LT4 since the first days of life; Group B: 16 adult patients (mean age 22.8 yr) with hypothyroidism for total thyroidectomy (8 patients previously affected by nodular disease and 8 affected by thyroid carcinoma with clinical and biochemical remission). Serum free thyroid hormones, thyroglobulin (TG), antithyroglobulin and antithyroperoxidase antibodies and thyrotropin concentration were measured in all patients, and patients' weight and LT4 dosage requirement were evaluated. At the time of the observation all patients presented serum free thyroid hormones within the normal range and values of serum TSH between 0.3 and 3 uIU/ml.
Results: All patients had undetectable TG and antithyroid antibodies. Patients in group A showed values of serum TSH significantly higher with respect to patients in Group B ($p<0.01$); Group A: median = 1.70 [micro]IU/ml; Group B: median = 0.70 [micro]IU/ml). The daily weight-based dosage of the replacement therapy with LT4 in Group A patients was significantly higher with respect to Group B patients ($p<0.05$; Group A: mean = 2.03 [micro]g/Kg, SD = 0.29; Group B: media = 1.69 [micro]g/Kg, SD = 0.29).
Conclusions: Group A patients showed a daily LT4 dose/Kg higher than Group B patients even though presenting higher serum TSH values. The different requirement of replacement therapy in patients with congenital thyroid agenesis and iatrogenic hypothyroidism could be explained by a lack of thyroid hormones since fetal life in CH, which could determine a different setpoint of the hypothalamus-pituitary-thyroid axis.
Nothing to Disclose: BB, LM, MDS, CDC, MC, AP, PV, MT

sort_order 2661
Pub # P3-592
Session Information POSTER SESSION: BASIC/TRANSLATIONAL/CLINICAL - Thyroid Gland Development & Function (1:30 PM-3:30 PM)
Title Free Thyroxine Levels in Euthyroid Subjects Are Negatively Associated with Insulin Resistance
Author String MHC Gurgel, CMM Ponte, PP Mendes, SS de Mesquita, G Aragao, Jr, G Paiva, RM Montenegro, MV Mota, D Forte, RM Montenegro, Jr
Federal University of Ceará, Fortaleza, Brazil
Body **Background and Aims:** The physiological role of thyroid hormones on insulin sensitivity in euthyroid subjects as well as the consequences of insulin resistance on thyroid function are still poorly understood. Thus this study was proposed to evaluate the relationship between insulin resistance determined by homeostasis model assessment (HOMA-IR), and thyroid function in a sample of Brazilian euthyroid individuals. **Subjects and Methods:** This was a cross-sectional study conducted from March 2009 to January 2010 which included 267 euthyroid subjects (mean age of 34.5±11.2 years-old, 68.5% female). Thyroid stimulating hormone (TSH), free thyroxine (FT4), anti-thyroid antibodies (anti-thyroglobulin and anti-thyroperoxidase), fasting glucose and insulin levels, HOMA-IR, and thyroid ultrasound were assessed. The subjects were grouped into tertiles according to increasing levels of HOMA-IR (group 1: [Delta] 0,23 - 1,32; group 2: [Delta] 1,33 - 2,32; group 3: [Delta] 2,33 - 8,50). Mann-Whitney test was performed to compare means of TSH and FT4 in each tertile (significance level of 5%, p <0.05, SPSS^[acrc]). **Results:** Among those 267 euthyroid evaluated (mean age of 34.5±11.2 years-old), 183 (68.5%) were female. The mean HOMA-IR of the total sample was 2.11±1.45. TSH levels (mIU/mL) were not statistically different among HOMA-IR tertiles (1.65±0.90 vs. 1.68±0.80 vs. 1.74±0.80, p>0.05), while the FT4 (ng/dL) values were progressively lower with increasing HOMA-IR, reaching statistically significant difference between the average first and last tertiles (1.23±0.20 vs. 1.21±0.16 vs. 1.15±0.20, p <0.001). **Conclusions:** As previously demonstrated in other populations, those findings of FT4 negatively associated with insulin resistance in Brazilian euthyroid subjects may suggest an increased risk of metabolic syndrome in individuals with low normal thyroid function, or a possible adaptive response to the former condition.
Nothing to Disclose: MHCG, CMMP, PPM, SSdM, GA, GP, RMM, MVM, DF, RMM

sort_order 2662
Pub # P3-593
Session Information POSTER SESSION: BASIC/TRANSLATIONAL/CLINICAL - Thyroid Gland Development & Function (1:30 PM-3:30 PM)
Title Changes in Acid-Labile Subunit and Insulin-Like Growth Factor 1 in Hyperthyroidism after Medical Treatment
Author String KA Al-Shoumer, NS Vasanthy, SI Abalkhail
Faculty of Medicine, Kuwait University, Jabriya, Kuwait; Mubarak Al-Kabeer Hospital, Jabriya, Kuwait
Body
INTRODUCTION:
Hyperthyroidism is often associated with altered body weight. Insulin-like growth axis and its mediators have been reported to be altered in various conditions associated with weight changes. There is no consensus on the changes of components of insulin-like growth factor axis in patients with hyperthyroidism after medical therapy.
SUBJECTS & METHODS:
This study aimed to assess the changes in insulin-like growth factor 1 (IGF-1) and Acid-Labile Subunit (ALS) before and after medical treatment of hyperthyroidism. We studied 29 hyperthyroid patients (matched with 32 normal controls) before and after medical therapy with the antithyroid drug carbimazole.
RESULTS:
Untreated hyperthyroid patients had significantly lower IGF-1 ($P=0.007$) and ALS ($P=0.012$) than controls. In the patients, after 6 months of medical therapy with carbimazole and attainment of euthyroidism, levels of IGF-1 and ALS increased significantly (compared to baseline levels, $P=0.046$, $P=0.006$, respectively), and reached concentrations similar to those of control subjects. Both IGF-1 and ALS demonstrated strong negative correlations with free T3 ($P=0.001$, $P=0.05$), whereas only IGF-1 correlated negatively with free T4 ($P=0.005$)
CONCLUSION:
This study demonstrated low levels of IGF-1 and ALS in untreated hyperthyroidism. Both levels are normalized after medical therapy and correlated negatively to levels of thyroid hormones. It is thus possible that IGF-1 and ALS levels could be useful in monitoring treatment as markers of response to therapy in hyperthyroidism.
Nothing to Disclose: KAA-S, NSV, SIA

sort_order 2663
Pub # P3-594
Session Information POSTER SESSION: BASIC/TRANSLATIONAL/CLINICAL - Thyroid Gland Development & Function (1:30 PM-3:30 PM)
Title Vitamin D Receptor Gene (*VDR*) Polymorphisms Are Not Associated with Autoimmune Thyroid Disease Risk in Turner Syndrome Patients
Author String B Bianco, ITdN Verreschi, KC Oliveira, AD Guedes, CP Barbosa, MVN Lipay
Universidade Federal de São Paulo, São Paulo, Brazil; Faculdade de Medicina do ABC, Santo André, Brazil
Body **BACKGROUND/AIM:** Individuals with Turner Syndrome (TS) clearly have increased risk for autoimmune diseases. The most common autoimmune disorders appear to be thyroid abnormalities. The etiology of the autoimmune thyroid is not very clear, however, genetic susceptibility is thought to play a critical role. The vitamin D receptor (VDR) has been demonstrated to be able to carry out modulation of the immune response. The function of the *VDR* gene is influenced by several genetic polymorphisms which are associated with a susceptibility to a range of autoimmune diseases. Thus, we have hypothesized a possible relationship between thyroid abnormalities and the *VDR* polymorphisms in TS patients.
METHODS OF STUDY: Case-control study that included 101 Brazilian women with TS (aged 4.8 to 55.5 years) and a control group consisting of 133 healthy fertile women (mean age: 39.7 + 3.2y) without a history of autoimmune diseases. In TS group, 21.8% (n=22) had thyroid abnormalities as Grave[acute]s disease and Hashimoto's thyroiditis. Detection of *VDR* polymorphisms (*Apal*, *TaqI*, *FokI* and *BmsI*) was performed using TaqMan real time PCR. The chi-square was used to compare allele and genotype frequencies between groups and to estimate the Hardy-Weinberg equilibrium. The association between the combined genotypes of *VDR* gene polymorphisms was assessed by haplotype analysis. A *p*-value < 0.05 was considered statistically significant.
RESULTS: We found relatively similar *VDR* polymorphisms genotype and allele frequencies in cases and controls, even only considering the patients with thyroid abnormalities. We did not observe any associations between polymorphisms in *Apal*, *TaqI*, *FokI* and *BmsI* and thyroid abnormalities in TS patients. Haplotype analysis showed that none of the *VDR* haplotypes were associated to thyroid diseases in TS patients. Statistical analysis showed that the genotype distribution in TS and control groups was in Hardy-Weinberg equilibrium for all polymorphisms studied.
CONCLUSION: To our knowledge, this is the first study that associated *VDR* polymorphisms and thyroid abnormalities in TS. The results showed no association between *VDR* gene polymorphisms and thyroid abnormalities in Brazilian TS patients tested.

Sources of Research Support: CAPES for granting student Bianca Bianco a post-doctor scholarship. Grants No. 2009/05250-0 from FAPESP.

Nothing to Disclose: BB, ITdNV, KCO, ADG, CPB, MVNL.

sort_order 2664
Pub # P3-595
Session Information POSTER SESSION: BASIC/TRANSLATIONAL/CLINICAL - Thyroid Gland Development & Function (1:30 PM-3:30 PM)
Title Topical Thyroid Hormone Accelerates Wound Healing in Diabetic Mice
Author String K Choong, JD Safer
Boston University Medical Center, Boston, MA
Body
Background: Wound healing is impaired in diabetes. This may be attributed to multiple causes including impairments in keratinocyte and fibroblast proliferation, altered cytokine levels and growth factor levels, and impairment in angiogenesis. Thyroid hormone is a major regulator of skin homeostasis and has been shown to have stimulatory effects on skin cell growth through keratinocyte and fibroblast proliferation. Topical administration of the T3 hormone analog, TRIAC, increases dermal thickness and restores collagen levels in glucocorticoid-induced skin thinning. In vivo, wound closure has been accelerated in wounds treated with topical T3. Local skin manipulation by thyroid hormone may prove a novel and cost-effective strategy for the treatment of cutaneous pathology; particularly in the multi-dimensional approach to diabetic wound management.
Objective: To examine the role of topical thyroid hormone as an adjunctive treatment modality in the management of diabetic wounds and to assess the mechanisms involved by which thyroid hormone modulates wound healing.
Methodology: The db/db mouse is a well-accepted diabetic mouse model for the study of wound healing. In a pilot experiment, 6 db/db male mice, aged 8 weeks, were purchased. On day 1, two wounds, one on each side of the midline, were created on the shaved dorsum of each mouse using a sterile 6 cm punch biopsy tool. Each mouse was its own control; the wounds on one side of each mouse were treated with placebo cream while the remaining wounds were treated with the cream containing triiodothyronine. Digital photographs were taken daily from Day 1 to Day 14 for wound area assessment and for comparisons of wound closure rate.
Result: Administration of topical thyroid hormone accelerated wound closure by 15-20% in the T3 treated wounds relative to placebo. Topical T3 administration achieved complete wound closure 24-48 hours earlier than placebo-treated wounds.
Conclusion: Previously, we demonstrated that topical T3 accelerated wound healing in non-diabetic mice. In this preliminary study, an improvement in both wound area size and in wound closure rate was appreciated. We attribute at least part of the acceleration to enhanced skin cell proliferation.
Nothing to Disclose: KC, JDS

sort_order 2665
Pub # P3-596
Session Information POSTER SESSION: BASIC/TRANSLATIONAL/CLINICAL - Thyroid Gland Development & Function (1:30 PM-3:30 PM)
Title Therapeutic Effect of Quercetin in an *In Vitro* Model of Graves Ophthalmopathy
Author String HJ Lee, JS Yoon, SH Choi, SY Lee, EJ Lee
Yonsei University College of Medicine, Seoul, Korea; Yonsei University College of Medicine, Seoul, Korea; Yonsei University College of Medicine, Seoul, Korea; Northwestern University Feinberg School of Medicine, Chicago, IL
Body Management of Graves' ophthalmopathy (GO) is challenging, as no reliable, specific and safe medical therapeutic agents have yet been developed. We investigated the therapeutic effect of quercetin in an *in vitro* model of GO, targeting pathways of inflammation, aberrant accumulation of extracellular matrix macromolecules, and adipose tissue expansion. The inhibitory effects of quercetin on IL-1 β -induced proinflammatory molecule gene expression and on hyaluronan production induced by IL-1 β or TNF- α were determined by semiquantitative RT-PCR and hyaluronan ELISA. To evaluate the antiadipogenic activity of quercetin, confluent fibroblasts were subjected to a differentiation protocol including adipogenic supplements and peroxisome proliferator-activated receptor gamma (PPAR γ) agonist for 10 days, and exposed to quercetin during differentiation. Differentiated cells were stained with Oil Red O and the expression of PPAR γ and CCAAT-enhancer-binding proteins (C/EBP) α and β was determined by western blot. Quercetin significantly attenuated IL-1 β -induced increases in intercellular adhesion molecule-1, IL-6 and IL-8 mRNA, and IL-6 and IL-8 protein. Increased hyaluronan production induced by IL-1 β or TNF- α was suppressed by quercetin in a dose- and time-dependent manner. Treatment with quercetin during the process of adipocyte differentiation inhibited accumulation of intracytoplasmic lipid droplets stained with Oil Red O and resulted in a dose-dependent decrease in expression of PPAR γ , C/EBP α , and C/EBP β proteins. In conclusion, this inhibition of inflammation, hyaluronan production, and adipogenesis by the natural plant product quercetin provides the basis for further study of the potential use of quercetin in the treatment of GO.
Nothing to Disclose: HJL, JSY, SHC, SYL, EJJ

sort_order 2666
Pub # P3-597
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)
Title Effects of Prolonged Discontinuation of L-Thyroxine Replacement in a Child with Congenital Hypothyroidism
Author String RA Kubicky, E Weiner, B Carlson, F De Luca
St Christopher's Hospital for Children, Philadelphia, PA; St Christopher's Hospital for Children, Philadelphia, PA; Drexel University College of Medicine, Philadelphia, PA
Body
Background: When diagnosed through neonatal screening and treated promptly and adequately, infants with Congenital Hypothyroidism (CH) experience normal physical growth and neurological development. Here we present a 3-year old boy diagnosed with CH, with subsequent poor compliance to L-thyroxine replacement.
Case report: JD is a 2 11/12 year old male, born in Mexico and diagnosed by neonatal screening with CH. He was then treated with L-thyroxine for ~ 1 year, until his mother lost her insurance coverage. At age 2 [frac12] yrs he immigrated with his family to the United States, and a few months later presented to St. Christopher's Hospital for Children's (SCHC) Emergency Department.
Upon physical examination (PE), JD was able to sit and crawl but could not stand or walk. His weight and length were less than the 3rd percentile (statural length of an 8 [frac12] month old). The rest of his PE was significant for coarse facial features, macroglossia, a small umbilical hernia, and dry skin. His thyroid was not palpable. The TSH was very elevated (1620 mIU/L) and the free T4 and thyroglobulin undetectable. His prolactin level was mildly elevated (27.9 ng/mL). On the day of presentation, JD was placed on L-thyroxine (50 meg daily).
When evaluated at SCHC Endocrinology clinic 2 weeks later, his mother reported increased activity and alertness. In addition, his constipation had improved and he was less sleepy. A thyroid ultrasound revealed thyroid hypoplasia. Upon evaluation by a pediatric neurologist, he was found at the 18-month old level for personal/social, fine motor/adaptive and language skills; his gross motor skills were at a 12-month old level (by Denver scale). His muscle tone was mildly but symmetrically decreased in all extremities, and his deep tendon reflexes were decreased.
6 weeks after presentation, the TSH was markedly decreased (5.20 mIU/L), while both free T4 and prolactin had normalized (1.41 ng/dL and 10.1 ng/mL, respectively).
After 4 months of treatment, JD was able to pull to stand and walk a few steps; his free T4 and TSH were normal (1.5 ng/dL and 2.84 mIU/L, respectively). Conclusions: Since neonatal screening for congenital hypothyroidism has been introduced, early L-thyroxine replacement has virtually eliminated hypothyroidism-related growth failure and severe neurological impairment. This case emphasizes the importance of a consistent adherence to treatment in preventing such complications, especially in infancy and early childhood.

Nothing to Disclose: RAK, EW, BC, FDL

sort_order 2667
Pub # P3-598
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)
Title Severe Hypothyroidism with Superimposed Coumadin Toxicity: Is That Right?
Author String ND Kuhadiya, P Yarra, S Dutta, R Khanal, J Matta, V Lala
Mount Sinai (Jersey City) Medical Center, Jersey City, NJ
Body Patients with hypothyroidism are relatively refractory to the hypoprothrombinemic effects of coumadin because the clearance of coagulator factors is slowed. Therefore it may take higher doses of coumadin for long time to maintain adequate anticoagulation in comparison to euthyroid patients. We present a case of severe hypothyroidism with over anticoagulation on low doses of coumadin. 75-year-old Egyptian male with past medical history of prosthetic aortic and mechanical valve on 5 mg of coumadin therapy presented to a nearby hospital with complaints of throat pain, hoarseness of voice and worsening difficulty breathing since 3 days. He was transferred to Jersey City Medical Center (JCMC) after intubation and mechanical ventilation for acute respiratory failure. His vital signs were as follows: Temperature: 98.7F, Pulse: 42/minute, BP: 78/35 mm Hg. Physical exam revealed diffuse neck swelling with red and bluish discoloration in addition to blood clots at the floor of the mouth. Enhanced CT scan of the neck showed diffuse subcutaneous and parapharyngeal soft tissue swelling along with pharyngeal and laryngeal wall edema. International Normalized Ratio (INR) was 18.76 on presentation to nearby hospital for which he received fresh frozen plasma (FFP) and Vitamin K. INR at JCMC was 2.44, which was again reversed with FFP and vitamin K. Thyroid Stimulating Hormone (TSH) was 52.30 mIU/L (0.46-4.68) with a free thyroxine of 0.55 ng/dl (0.78-2.19) and blood sugar of 96 mg/dl. His thyroglobulin antibodies were 295 IU/ml (0-40). The patient was treated with Intravenous (IV) levothyroxine (75 ug/day) and IV hydrocortisone for 4 days which resulted in reversibility of airway obstruction and diffuse pharyngeal, parapharyngeal and laryngeal swelling. He was extubated after 2 days. He received oral levothyroxine (75 ug daily) after 4 days and discharged after 7 days on same dose. On day 2, his TSH was 43.10 mIU/L while that on discharge after 7 days was 22.9 mIU/ml. He continued to receive coumadin therapy from second day due to risk of prosthetic mitral valve thrombosis. In severe hypothyroidism, high doses of coumadin are required to maintain therapeutic INR due to decreased hepatic clearance of clotting factors. This patient had supratherapeutic INR on relatively low doses of coumadin, which is not well understood. We alert the clinicians to closely monitor for fluctuant INR levels in all patients with hypothyroidism on coumadin therapy.

Nothing to Disclose: NDK, PY, SD, RK, JM, VL

sort_order 2668
Pub # P3-599
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)
Title Subclinical Hypothyroidism and Pregnancy
Author String C Duranceau, G Houde, L Takser, N Abdelouahab, M-F Langlois
Universite de Sherbrooke, Sherbrooke, Canada; Universite de Sherbrooke, Sherbrooke, Canada
Body
BACKGROUND
It is well known that overt hypothyroidism is prejudicial to the fetus and the outcome of pregnancy. Studies tend to demonstrate that subclinical hypothyroidism as well can induce prematurity.
OBJECTIVES
1) To determine the prevalence of subclinical hypothyroidism in our population of pregnant woman in the area of Sherbrooke, Quebec, Canada.
2) To determine the proportion of pregnant women with subclinical hypothyroidism who are treated with levothyroxine, and who achieve a TSH value below 2,5 mIU/L.
METHODS
We evaluated 389 women without known thyroid disorder and with uncomplicated pregnancy who were enrolled prospectively from September 2007 until December 2008. TSH and anti-thyroid peroxidase antibody were measured between the 3rd and 28th week of pregnancy, and at delivery. A questionnaire filled at the time of delivery and review of medical records allowed us to identify the women who were supplemented with levothyroxine during their pregnancy.
RESULTS
Mean age was 28 years old (range 18-40), 27% had a familial history of dysthyroidism. The prevalence of subclinical hypothyroidism, defined as TSH >2,5 mIU/L with normal free T3 (3,3-5,3 pmol/L) and normal free T4 (11,7-18,5 nmol/L), was 7,5% (29/389 women). The prevalence falls to 1,5% (6 women/389) when a TSH cutoff of >3,5 is used. Five women were treated with levothyroxine and all achieved a value of TSH <2,5 during their pregnancy. Four out of these 5 women had a TSH >3,5 at the time of screening, and 3 out of 5 had positive anti-TPO antibodies. Two women with a TSH >3,5 were not treated and they normalised their TSH during the second trimester. Of interest, 38% (11/29) of the women with a TSH >2,5 had positive anti-TPO antibodies, compared to 13,6% (49/359) of the women with a value of TSH <2,5.
CONCLUSIONS
The prevalence of subclinical hypothyroidism in our population is consistent with the literature and raise from 1,5 to 7,5 % as defined with a TSH from 3,5 to 2,5 mIU/L. (1-2) Only 17% were treated with levothyroxine, and all normalised their TSH below 2,5 mIU/L.

(1) Endocrine Society, JCEM 2007; p. 12
(2) Oken et al., JCEM 2009; (94)2:497-503

Nothing to Disclose: CD, GH, LT, NA, M-FL

sort_order 2669
Pub # P3-600
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)
Title Central Obesity in Primary Hypothyroidism: Improvement Following Adequate L-Thyroxine Replacement
Author String U Kabadi
VA Central Iowa Health Care System, Des Moines, IA; University of Iowa, Iowa City, IA
Body Weight gain is a prominent manifestation of Primary Hypothyroidism (Hypo T). Moreover, achieving euthyroid state with L-Thyroxine (LT4) induces a decline in body weight in most subjects. However, the characteristic fat distribution is not well documented. Therefore, occurrence of central obesity was assessed by determination of waist:hip ratio (WHR) in 55 men with ages 39 to 84 years at diagnosis of primary hypothyroidism established by subnormal Free T4 and elevated TSH concentrations and again after their normalization by LT4 replacement. Subjects with concurrent diagnosis of Diabetes Mellitus were excluded. The subjects were divided into 3 groups according to Body Mass Indices (BMI-kg/m²). I-20 men with BMI <25; II-BMI 25-30; III-BMI>30. Fifteen euthyroid men matched for age and BMI in each group participated as controls. WHR were 0.92±0.01 in Hypo T I and 0.88±0.01 in N I; 0.96±0.02 in Hypo T II and 0.92±0.02 in NII; and 1.02±0.03 in Hypo T III and 0.98 ±0.02 in N III (p <0.01 for all individual groups vs N). WHR declined on attaining euthyroidism in all groups; I, 0.89±0.01; II, 0.93 ±0.02; III, 0.98±0.02 (p < 0.01 vs pre treatment for all groups). WHR for all Hypo T collectively (0.97±0.03) was significantly higher (p < 0.01) than all N (0.92±0.02) and declined significantly (p < 0.01) on achieving euthyroidism (0.93±0.02). Therefore, central obesity is a characteristic clinical manifestation of primary hypothyroidism in men with a significant improvement on achieving euthyroid state irrespective of initial body weight or its change following L-Thyroxine replacement.
Nothing to Disclose: UK

sort_order 2670
Pub # P3-601
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)
Title The Effect of Hormon Replacement Treatment on Hearing Function in Hypothyroid Patients
Author String A Tatlipinar, I Kartal, H Gozu, T Gokceer
Haydarpasa Numune Research and Training Hospital, Istanbul, Turkey; Haydarpasa Numune Research and Training Hospital, Istanbul, Turkey
Body **Background:** Although it is well known that congenital hypothyroidism causes physiologic, morphologic and developmental abnormalities of the auditory system, there is not enough study that investigates correlation between acquired hypothyroidism and hearing impairment. There is not also enough studies related with effect of hormone replacement treatment on hearing functions in hypothyroid patients.
Methods: Hearing thresholds were estimated by the pure tone audiometry (PTA) of fifty hypothyroid patients. The patients were given levothyroxine (0.05-0.2mg/dl) and its dosage was gradually increased until they were euthyroid. PTA was repeated when they were euthyroid.
Results: The audiometry of patients revealed that there was statistically significant hearing improvement at 250 Hz and 8000 Hz. There was also statistically significant negative correlation between the severity of hypothyroidism and hearing gain ($p<0,05$). The patients with lower free T4 and higher TSH levels have lower pure tone average improvement.
Conclusion: Thyroid homon replacement treatment hardly improves hearing disorders in severe hypothyroidism.
Nothing to Disclose: AT, IK, HG, TG

sort_order 2671
Pub # P3-602
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)
Title The Predicting Factors for Spontaneous Course, Prognosis, and Benefit of Treatment in Subclinical Hypothyroidism
Author String M Lee, S Hwang, O Kwon, EJ Lee
Institute of Endocrine Research, Yonsei University College of Medicine, Seoul, Korea
Body
Background
Subclinical hypothyroidism is common in clinical practice. The necessity for further evaluation and benefit of treatment, however, have not been clearly established.
Methods
We reviewed the medical records of Korean patients who visited our endocrinology clinic from January 2008 to May 2010.
Results
In observation group(131), only TSH level was different with statistical significance(P-value=0.034) between two subgroups. In spontaneously improved subjects of observation group, neither TPOAb nor TgAb titer was decreased during follow-up period significantly, showing only decreasing trend. And of the lipid profile, triglyceride level shows significant difference during follow-up(p-value < 0.01). In synthroid supplement group, TPOAb titer and triglyceride level were decreased during follow-up period significantly (p-value = 0.011, p-value < 0.01, respectively). Plasma Selenium concentration and TSH showed a weak but significant correlation($\gamma=0.342$, p-value <0.01). Diffuse thyroiditis on US was associated with lower FT4 level and higher TPOAb titer in newly-diagnosed subclinical hypothyroidism patients(p-value =0.039, p-value < 0.01, respectively). However, presence of diffuse and/or focal thyroiditis on US did not affect spontaneous course and prognosis of subclinical hypothyroidism.
Conclusions
In subclinical hypothyroidism, TSH level can be a predicting factor for spontaneous course and prognosis. Triglyceride level, no other lipid profile, was lowered as TSH level normalized during observation in spontaneously improved patients. Levothyroxine supplement brought decreased TPOAb titer and triglyceride level, but benefit of treatment do not seem to be apparent with this. Plasma selenium concentration and TSH showed a weak but significant positive correlation in newly-diagnosed subclinical hypothyroidism patients, so we could not find the unfavorable effect of selenium insufficiency in subclinical hypothyroidism. Thus it seems that selenium supplement as subclinical hypothyroidism management cannot be considered at present, at least in Korean subjects. And further study about the potential role of selenium in the pathogenesis of subclinical hypothyroidism is needed. The existence of diffuse thyroiditis on US was associated with lower FT4 level and higher TPOAb titer at initial presentation. However, findings of diffuse and/or focal thyroiditis on US did not affect spontaneous course and prognosis of subclinical hypothyroidism.
Nothing to Disclose: ML, SH, OK, EJJ

sort_order 2672
Pub # P3-603
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)
Title Iodine Status during Pregnancy in a City in Eastern India
Author String A Shaw, S Ghosh, A Majumdar, S Chatterjee
University of Calcutta, Kolkata, India; Vivekananda Institute of Medical Sciences, Kolkata, India
Body It is well recognized that Iodine requirement rises during pregnancy. Urinary iodine excretion is a good guide to short term iodine intake. A urinary iodine excretion of 200 mcg/l has been accepted as a marker of adequate iodine intake in pregnancy.
In this study 237 women in various stages of pregnancy, not known to have thyroid disease or taking any iodine containing medication and attending the antenatal clinic of the hospital had their urinary iodine excretion measured. A social history was taken. Control data was obtained from 59 non pregnant age matched females and 56 males. Urinary iodine was measured by the ammonium persulfate method.
Of the 237 subjects, 91 (38.3%) had urinary iodine excretion of 200 mcg/l or more; 78 (32.9%) had excretion rates of 99 mcg/l or less indicating iodine deficiency. 47 (79.6%) female controls and 41 (73 %) male controls were iodine replete. Sixty-five of the iodine deficient mothers had delivery in the hospital. There was no significant difference in term delivery, birth weight, Cesarean section rates, Apgar scores or stay in the NICU. However 21 (32.3%) of the babies were reported to have respiratory distress on chart review compared to 11 out of 108 (10.1%) babies who were delivered on the same days as the babies of iodine deficient mothers. There was no incidence of neonatal hypothyroidism.
The study was conducted in the city of Kolkata in Eastern India which is approximately 50 km from the sea and is considered an iodine replete area. India follows a policy of iodine supplementation in table salt and 75 % to 100 % of the subjects studied used branded salt which delivered a minimum of 15 ppm of iodine. Our data suggests that much higher levels of iodine supplementation are necessary to achieve adequate levels in pregnancy.
The study design did not permit iodine supplementation to the subjects. However, on the advice of our Ethics Committee, the data was made available to the treating obstetricians as soon as possible.
Nothing to Disclose: AS, SG, AM, SC

sort_order 2673
Pub # P3-604
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)
Title Diabetic Nephropathy with Macroproteinuria Could Be a Cause of Subclinical Hypothyroidism in Japanese Populations
Author String S Izawa, K Matsuzawa, K Sumi, H Shiochi, Y Fujioka, N Yamamoto, H Kinoshita, T Ohkura, H Ohkura, A Yoshida, S-i Taniguchi, C Shigemasa
Tottori University Faculty of Medicine, Yonago, Japan; Tottori University Graduate School of Medicine, Yonago, Japan; Tottori University Faculty of Medicine, Yonago, Japan
Body **Background:** The prevalence of subclinical hypothyroidism (SCH) is higher in older individuals, women, individuals with positive anti-thyroid peroxidase antibody, and individuals with iodine-rich diet. Adding to the direct toxicity or immunologic alterations of iodine-rich diet, urinary loss of thyroid hormones may lead to low free thyroid hormones unless their production are increased under the feedback influence of TSH in nephrotic patients. Furthermore, loss of albumin and thyroxin-binding globulin may reduce the binding capacity for thyroid hormones. To evaluate SCH associated with renal functions, diabetic nephropathy (DN) could be one of the reliable models.
Patients and Methods: All patients were recruited from October 2008 to September 2010. Patients with malignant tumor, acute infection, thyroid disease, and medication associated with drug-induced thyroid disease were excluded. Ninety-five patients (male: female =56: 39, mean age 61.5±14.8) were included to this trial. They had no restriction of iodine-rich diet. We studied the correlation of thyroid function tests (TSH, free T₃, and free T₄) and renal functions, which included daily proteinuria, urinary albumin-creatinine ratio (Alb/Cr), estimated GFR (eGFR), and serum creatinine (sCr), when they started the diabetic education program for inpatients.
Results: DN was classified into 4 grades (Grade 1: no manifestation, Grade 2: microproteinuria, Grade 3: macroproteinuria, Grade 4: macroproteinuria with elevated serum creatinine). Forty-nine patients with Grade 1, 19 of Grade 2, 21 of Grade 3, and 6 of Grade 4 were included. No significant differences were observed in age, sex, BMI, HbA1c, fasting plasma glucose, TSH and free T₄. However, free T₃ of Grade 3 and 4 were significantly lower than that of Grade 1 (p<0.001). Also TSH had significant positive correlation to daily proteinuria (p=0.001) and Alb/Cr (p=0.012). Free T₃ (p=0.003) and Free T₄ (p=0.014) had significant negative correlation to daily proteinuria. No significant correlations were observed between thyroid function tests and others (eGFR and sCr).
Discussions: Though Japanese iodine intake is reported as 544[μg]/day (range 361-1023), the limitation of our study is that iodine metabolism is not precisely evaluated. Further study with dietary intake and urinary excretion of iodine is needed. However, this is the first report for the association of SCH and DN, and macroproteinuria could increase the risk of SCH in Japanese populations.
Nothing to Disclose: SI, KM, KS, HS, YF, NY, HK, TO, HO, AY, S-IT, CS

sort_order 2674
Pub # P3-605
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)
Title Persistent Subclinical Hypothyroidism and Cardiovascular Risk in the Elderly: The Cardiovascular Health Study
Author String KA Hyland, AM Arnold, JS Lee, AR Cappola
University of Pennsylvania School of Medicine, Philadelphia, PA; University of Washington, Seattle, WA; University of California, Davis, CA
Body
Background: Use of a single set of thyroid function tests to define subclinical hypothyroidism may lead to significant misclassification over time and could influence the findings from longitudinal studies. We sought to assess the risks of coronary heart disease (CHD) and congestive heart failure (CHF) in older adults with persistent subclinical hypothyroidism.
Methods: All analyses were performed using data from US community-dwelling men and women aged 65 and over who were enrolled in the Cardiovascular Health Study and not taking thyroid hormone preparations. The 10-year incidence of CHD and CHF were compared between persistent subclinical hypothyroid and persistent euthyroid groups, adjusting for age, sex, race, and thyroid hormone initiation. Two sets of analyses were performed. In the first set of analyses, subclinical hypothyroidism was defined at the first set of thyroid function tests and updated over time, with up to three additional thyroid function tests over a 7 year period (time varying exposure), using data from 681 people who were subclinically hypothyroid and 4183 people who were euthyroid at their first thyroid function test. Additional analyses were performed after stratifying the subclinical hypothyroidism group by maximum TSH of 4.5-6.99 mU/L, 7.0-9.99 mU/L, or 10-19.99 mU/L. In the second set of analyses, persistent (n=129) and transient subclinical hypothyroidism (n=208) were defined by two tests performed two years apart and compared to persistent euthyroidism (n=2302) (fixed exposure).
Results: In the time varying exposure analyses, there was no difference in CHD risk between the subclinically hypothyroid and euthyroid groups, overall (HR 1.13; 95% CI 0.94-1.36) or by TSH strata, nor of CHF, overall (HR 1.04; 95%CI 0.86-1.25) or by TSH strata. Findings were similar in the fixed exposure analyses, with no association between persistent (HR 1.28; 95% CI 0.95-1.73) or transient (HR 1.15; 95% CI 0.79-1.67) subclinical hypothyroidism and incident CHD or of persistent (HR 0.87; 95% CI 0.63-1.19) or transient (HR 1.17; 95% CI 0.84-1.63) subclinical hypothyroidism and incident CHF.
Conclusions: Our data do not support increased risk of CVD or CHF in older adults with persistent subclinical hypothyroidism.

Sources of Research Support: R01 AG032317 to ARC.

Nothing to Disclose: KAH, AMA, JSL, ARC

sort_order 2675
Pub # P3-606
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)
Title Increased Postprandial Apolipoprotein B48 Levels in Subclinical and Overt Hypothyroidism
Author String ANM McGowan, WM Widdowson, G Boran, J Gibney
Body The Adelaide and Meath Hospital Incorporating the National Children's Hospital, Tallaght, Ireland; The Adelaide and Meath Hospital Incorporating the National Children's Hospital, Tallaght, Ireland
Postprandial lipaemia and inflammation are implicated in the development of atherosclerosis and intestinally-derived lipoproteins contribute to these processes. Patients with overt, and possibly also those with subclinical hypothyroidism are at increased risk of atherosclerosis. Whether postprandial lipoproteins contribute to atherosclerosis in hypothyroidism is not known. Subjects (statin-na[ive]) with overt hypothyroidism (n=11), subclinical hypothyroidism (SCH, n=11) and age, gender and BMI-matched controls (n=26) were studied under fasting conditions and at 2, 4, 6 and 8 hours following a mixed meal. Anthropomorphic measurements and biochemical variables were measured. Levels of apolipoprotein (apo)B48 which is specific for intestinally-derived lipoproteins were measured using a novel ELISA.
LDL cholesterol levels did not change postprandially and were greater ($p<0.05$) in overtly hypothyroid subjects compared to controls and SCH subjects at all time points. Triglyceride levels increased postprandially in all groups, peaking at the 4-hour timepoint and did not differ between groups.
Under fasting conditions, apoB48 levels did not differ between groups. ApoB48 levels increased postprandially in the control group, peaking at the 2-hour time-point. Levels also increased in the overtly hypothyroid group but remained significantly elevated for six hours postprandially and were significantly greater than control subjects at the 2-hour (26.29mcg/ml versus 15.53mcg/ml, $p<0.01$) 4-hour (25.32mcg/ml versus 14.92mcg/ml, $p<0.05$) and 6-hour time-points (21.75mcg/ml versus 12.95mcg/ml, $p<0.05$). In SCH subjects, peak apoB48 levels occurred 4-hours postprandially and at this time-point were significantly greater than controls (24.57mcg/ml versus 14.92mcg/ml, $p<0.05$). TSH levels in all groups correlated with apoB48 levels, most strongly with 2-hour levels ($r=0.416$, $p=0.006$).
A delayed postprandial peak in apoB48 levels occurring in overt and less markedly in subclinically hypothyroid subjects is a novel finding and possibly reflects delayed clearance of intestinally-derive lipoprotein particles. These particles are atherogenic and therefore these observations require further investigation.
Nothing to Disclose: ANMM, WMW, GB, JG

sort_order 2676
Pub # P3-607
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)
Title Treatment of a Patient's Hypothyroidism Complicated by Lipodystrophy
Author String A Dothard, C Tapiador
East Tennessee Children's Hospital, Knoxville, TN
Body Background: In most cases, hypothyroidism is easily treated using a thyroid hormone replacement medication, levothyroxine. However, in this case, treatment with thyroid hormone replacement may have been complicated by another condition, lipodystrophy.
Case: A now sixteen year old Caucasian female underwent radioiodine treatment for Grave's disease in November 2003. In June 2004, the patient appeared muscular with prominent veins in her extremities. She had marked abdominal distension, which later was confirmed as hepatomegaly with diffuse fatty infiltration. Laboratory tests at the time showed markedly elevated triglycerides (1754 mg/dl), mildly high fasting cholesterol (216 mg/dl), low HDL (14 mg/dl), low leptin (2 ng/ml) and elevated free fatty acids (1.16 mmol/L). She was diagnosed with acquired lipodystrophy. These tests also showed elevated TSH (89.51 [mu]IU/ml) with low free T4 (0.12 ng/dl). Consequently, she was diagnosed with post-ablation hypothyroidism and started on 50 mg of levothyroxine (brand name). Treatment of the patient's hypothyroidism became difficult, as her TSH levels were unresponsive to increased dosages of levothyroxine. Between June 2004 and November 2009, the patients levothyroxine dosage was increased from 50 mg to 300 mg (her weight increased from 43.1 kg to 66.2 kg), yet her TSH level was never controlled for any acceptable length of time. In January 2009, the patient was prescribed pioglitazone to improve insulin sensitivity. While the patient was taking pioglitazone, her TSH levels began to markedly decrease and remained within the acceptable range. However, after the patient was taken off pioglitazone, her TSH rose to levels (33.7-88.0 [mu]IU/ml) well above the normal range even with an increased levothyroxine dosage of 350 mg. Conclusion: A patient's hypothyroidism complicated by lipodystrophy seems to respond to a combined therapy of a PPAR- γ agonist and levothyroxine. PPAR- γ agonists have been shown to improve the condition of those with lipodystrophy, but it also may play a role in increasing the efficacy of thyroid hormone replacement in those with both lipodystrophy and hypothyroidism.
Nothing to Disclose: AD, CT

sort_order

2677

Pub #

P3-608

Session Information

POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)

Title

Iodine Deficiency in a Euthyroid Male in Iodine Replete United States

Author String

JD Maier, JC Ford, SL Ryan
Louisiana State University Health Sciences Center, Shreveport, LA; Overton Brooks VA Medical Center, Shreveport, LA

Body

Background: Manifestations of iodine deficiency are rarely seen in iodine replete regions in the United States since iodine was incorporated into table salt in 1924¹. Iodine deficiency in the United States can be associated with pregnancy, lactation, and salt restriction^{2,3}. Recent data from NHANES III show falling urinary iodine concentrations⁴. Residents of Louisiana have a typically high consumption of crustaceans, both crawfish and shrimp. Crawfish, a fresh water crustacean, contains a low level of iodine, 0.9 mg/kg⁵. **Clinical Case:** A 50 year old male with history of heavy tobacco and alcohol use presented with complaints of a 22 lb weight loss, insomnia, fatigue, progressive dyspnea. He denied other symptoms of thyroid dysfunction. He denied prior thyroid disease, radiation exposure, viral illness, or use of goiterogens, and had no significant family history of thyroid disease. He reported that he used iodized table salt, albeit sparingly and did not eat shellfish other than crawfish. Physical exam revealed a BMI of 18.2. Thyroid was slightly enlarged without nodules. Testing revealed a TSH 1.05 mIU/mL (normal 0.34-5.60 mIU/mL), FT4 0.97 ng/dL (n 0.61-1.12 ng/dL) and FT3 3.00 pg/ml (n 2.5-3.9 pg/ml). Complete metabolic panel, CBC, sedimentation rate, B12, folate, and workup for malabsorption were normal. Thyroid I-123 uptake and scan was abnormal with 2-hour uptake 22.2% (n 6-18%) and at 23 hours 79.5% (n 10-30%). Repeat uptake and scan demonstrated similar results. Scan revealed an enlarged thyroid, with homogeneous pattern of isotope distribution. 24-hour urine iodine was undetectable (n 0.01-0.8 mg/L). He was given SSKI 1 drop in 6 oz. water weekly for 4 weeks. Repeat 24 hour urine iodine was still low via a different assay, 78 ug/spec (n 100-460 ug/spec). He received additional liquid iodine supplementation, and in the interim had a CT scan of the chest, receiving 100 ml of Visipaque 320(32 gms organified iodine). Repeat 24-hour urine iodine improved to 227 ug/24 hours. His goiter had resolved and repeat I-123 uptake and scan confirmed return to normal size with a homogenous pattern of distribution. Uptakes returned to normal with 4-hour uptake of 9% (n 6-18%) and 24-hour uptake of 21% (n 10-30%). Serum TSH, FT4 and FT3 remained normal through this period. **Conclusion:** The possibility of iodine deficiency should be considered in individuals presenting with goiter, normal TSH and FT4 and discordant thyroid uptake and scan.

(1) Zimmermann MB, J of Nutr. 2008; 138(11):2060-2763.

(2) Becker DV et al., Thyroid. 2006; 16(10):949-951.

(3) Tayie FA and Jourdan K. Am J of Hyperten.2010; 23(10):1095-1102.

(4) Caldwell KL et al., Thyroid. 2005; 15(7):692-9.

(5) Sidwell V.D. 1981 Chemical and Nutritional Composition of Finfishes, Whales, Crustaceans, Mollusks, and their Products. NOAA Technical Memorandum NMFS F/SEC-11, NMFS Charleston, U.S. Department of Commerce. Washington, DC, USA.

Nothing to Disclose: JDM, JCF, SLR

sort_order 2678
Pub # P3-609
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)
Title The Coexistence of a Novel Inactivating Thyrotropin Receptor Gene Mutation with Two Thyroid Peroxidase Mutations: A Genotype-Phenotype Correlation
Author String C Sriprapradang, Y Tenenbaum-Rakover, M Weiss, MS Barkoff, O Admoni, D Kawthar, G Caltabiano, L Pardo, AM Dumitrescu, S Refetoff
University of Chicago, Chicago, IL; University of Chicago, Chicago, IL; HaEmk Medical Center, Afula, Israel; Technion Faculty of Medicine, Haifa, Israel; Clalit Health Service, Buaina, Israel; Universitat Autònoma de Barcelona, Bellaterra, Spain
Body
Background: *TSH receptor (TSHR)* and *thyroid peroxidase (TPO)* gene mutations occur independently. This is the first report of their coexistence in the same individuals.
Objectives: To evaluate the genotype-phenotype correlations when mutations in both genes are present alone or together in the same individual.
Patients and Methods: Thirty subjects from an extended Arab kindred, living in Northern Israel, underwent clinical and molecular studies and the mutant TSHRs were analyzed *in vitro*.
Results: A novel *TSHR* gene mutation was identified, involving four nucleotides at three sites on the same allele, c.267G>T (L89L), c.269/270AG>CT (Q90P), and c.790C>T (P264S). These cosegregated in all individuals harboring a *TSHR* mutation. In addition we identified two known *TPO* gene mutations (G493S and R540X). Heterozygotes for the *TSHR* mutation had mild hyperthyrotropinemia. The coexistence of a *TPO* gene mutation in one allele in addition to the *TSHR* mutation did not magnify the hyperthyrotropinemia. Homozygotes for the *TSHR* gene mutations and a compound heterozygote for the *TPO* mutations presented frank hypothyroidism. *In vitro* studies showed increasing loss of function for Q90P < P264S < Q90P/P264S *TSHR* mutants; the latter being that expressed in the subjects under investigation. Since over the past 20 years investigators have used two variant *TSHR* expression vectors differing in one amino acid at codon 87, we tested them alone and in the presence of the Q90P *TSHR* mutant located in their proximity. The V87 and L87 variants were functionally identical but their structure and function were different in the presence of the Q90P mutation. Loss of function of Q90P was more severe in the presence of V87. The reason for this difference was found in the three dimensional structure of the molecule.
Conclusions: *TSHR* and *TPO* gene mutations were identified alone and together in individuals of a consanguineous kindred. Homozygotes for the *TSHR* mutations and compound heterozygote for the *TPO* mutations were hypothyroid. The mild hyperthyrotropinemia of heterozygotes with the *TSHR* mutations was not aggravated by the coexistence of a *TPO* defect in one allele.
Sources of Research Support: In part by Award Numbers R37DK15070, T32DK007011, P60DK20595 from the National Institute of Diabetes and Digestive and Kidney Diseases and 5M01RR04999.
Disclosures: SR: Academic Associate, Quest Diagnostics. Nothing to Disclose: CS, YT-R, MW, MSB, OA, DK, GC, LP, AMD

sort_order 2679
Pub # P3-610
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)
Title New Heterozygous Mutations in Thyroglobulin Gene in Patients with Congenital Hypothyroidism
Author String ES Brust, CB Beltrao, T Watanabe, MC Chammas, S Marui
Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil; Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil
Body Congenital hypothyroidism due to dysmorphogenesis is an autosomal recessive inherited disorder often characterized by congenital goiter. Mutations in thyroid peroxidase (TPO) and thyroglobulin (TG) are the most frequent and studied in dysmorphogenesis.
Up to date, more than 50 different mutations have been identified in the human TG gene contributing to understand the mechanism of this large glycoprotein involved in thyroid hormone synthesis. Affected patients present primary hypothyroidism associated to eutopic thyroid gland or goiter and low serum TG levels. **OBJECTIVE:** Search for mutations in TG gene in patients with dysmorphogenesis due to clinical-hormonal suspected TG deficiency. **MATERIAL AND METHODS:** From 41 patients with primary congenital hypothyroidism evaluated at APAE-Sao Caetano, we selected 6 patients (2 males) with probably TG deficiency: goiter or normal position and thyroid volume at ultrasound and low to normal serum TG levels (IFMA). DNA was extracted from peripheral leukocytes and TG was amplified by PCR and directly automatic sequenced. **RESULTS:** The patients[acute] mean age was 5.2 years-old (3-8.6), whose TG ranged from 1 to 53 ng/dL (mean 24.9±21.9). All presented normal NaClO4 and audiometric tests, excluding TPO/DUOX2 and Pendrin deficiencies. We found a previously described A277X mutation (1) and three novels mutations: p.430fsX465 (insC at 1345-1346), D1748del (delGAT at 5299-5301) and R767X (C>T at 2359). All mutations were absent in 200 alleles from controls with normal thyroid function. All mutations were in heterozygous state and lead to truncated protein or loss of helix region. Two patients had no detected mutation in TG gene, including coding region and exons-introns boundaries. **CONCLUSIONS:** We found mutations in heterozygous state in patients with dysmorphogenesis due to suspected TG deficiency in spite of autosomal recessive disorder. We speculate that all here described mutations lead to truncated or severe abnormal protein, consequently one allele is sufficient to provoke congenital hypothyroidism.

(1)Gutnisky VJ et al, J. Clin. Endocrinol. Metab. 2004; 89: 646.

Sources of Research Support: FAPESP 06/05800-1 and 08/04786-0.

Nothing to Disclose: ESB, CBB, TW, MCC, SM

sort_order

2680

Pub #

P3-611

Session Information

POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)

Title

Ogilvie Syndrome in a Patient with Myxedema Coma

Author String

N Kotwal, U Yanamandra, AS Menon, V Nair
Armed Forces Medical College, Pune, India

Body

Background: Ogilvie's syndrome also known as acute colonic pseudo obstruction [ACPO], presents as massive colonic dilatation without a mechanical cause, usually in critically ill patients due to imbalanced sympathetic and parasympathetic activity. The initial therapy remains conservative with supportive measures and correction of metabolic, infectious or pharmacologic factors followed by neostigmine and decompressive colonoscopy. Surgery is reserved for patients with clinical deterioration or with evidence of colonic ischemia or perforation.

Clinical case: We describe a 60 yr old lady who presented with fever, altered sensorium, obstipation and abdominal distension. Investigations showed the patient to have hyponatremia (Na^+ of 122Meq/L) with metabolic encephalopathy. ECG revealed junctional rhythm. She, in addition, had colonic pseudo-obstruction proven by imaging (Abdominal radiograph revealed gas filled loops of large intestine, later confirmed on CECT abdomen where colon was distended with maximum cecal diameter of 12 cm). The patient was managed conservatively with electrolyte replacement and later with decompressive colonoscopy with no improvement in her condition. Thyroid profile was suggestive of primary hypothyroidism (T3 - 0.37 ng/ml (0.6 - 1.8), T4 - 1.6 mcg/dl (5.6 -13.7), TSH - 341.57 IU/L (0.35 - 5.5)). Anti TPO antibodies were high. On starting thyroxine colonic motility was restored with no distended bowel loops on abdominal radiograph and ECG reverted to sinus rhythm.

Conclusion: The case is illustrative of the need to consider hypothyroidism, a common endocrine disorder, in the differential diagnosis of non obstructive intestinal obstruction. This differential is very crucial, as neostigmine and surgery which are prime modalities of management in ACPO are contraindicated in hypothyroidism. If laparotomy is performed on the patient with ileus, the complications of myxedema coma and death may follow. Chronic pseudo-obstruction has been described in hypothyroidism. [1] But, hypothyroidism de-novo presenting as acute colonic pseudo-obstruction (Ogilvie's syndrome) has not yet been reported in literature. Possible mechanism of hypomotility in hypothyroidism is autonomic neuropathy and altered impulse transmission at myoneural junction, intestinal ischemia, intestinal myopathy and GAG Deposition [2].

[1] Abbasi AA, Douglass AC, Bissell GW, Chen Y: Myxedema ileus: a form of intestinal pseudoobstruction. JAMA 1975;234:181-3.

[2] Dunet AL, Bastenie PA: Intestinal disorders in hypothyroidism: clinical and manometric study. Am J Dig Dis 1971;16:723-7.

Nothing to Disclose: NK, UY, ASM, VN

sort_order

2681

Pub #

P3-612

Session Information

POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)

Title

Cardiac Involvement in Short-Term Overt Hypothyroidism

Author String

S dellaCasa, B Altieri, A Capozzi, F Pennestri, G Perotti, A Pontecorvi
Patologia Speciale e Semeiotica Medica, Roma, Italy; Cardiologia, Roma, Italy; UOC Medicina Nucleare, Roma, Italy

Body

It is well known thyroid hormones have important effects on cardiovascular system. Chronic hypothyroidism is associated with well recognized cardiac dysfunctions; however, the effects of acute hypothyroidism on cardiovascular system are less studied. The aim of this study was to investigate the effect of acute hypothyroidism on cardiac function after short-term LT4-withdrawal. We studied 10 patients (9F/1M; mean age 43±9 DS) affected by differentiated thyroid cancer (DCT) treated with total thyroidectomy, at two time points: on TSH-suppressive thyroxine replacement therapy, and 6 weeks after thyroid hormone withdrawal for radioiodine ablative treatment. Patients were not affected by cardiovascular disease or treated with any drugs acting on cardiovascular system. We measured serum FT3, FT4 and TSH, levels and performed electrocardiography (ECG) and echocardiography (EcoCG) to measure left atrial (LA) and left ventricular (LV) size and systolic and diastolic function. In acute hypothyroidism, the ECG showed a significant prolongation of QT interval (438 ± 30 ms vs 402 ± 19 ms; $p=0.007$) and an inversion of T wave with normal heart rate. The EcoCG revealed a significant decrease in LA volume (37 ± 8 mm³ vs 47 ± 13 mm³; $p=0.031$), LV systolic volume (25 ± 6 mm³ vs 30 ± 8 mm³; $p=0.029$) and LV diastolic volume (61 ± 12 mm³ vs 77 ± 18 mm³; $p=0.003$). We found also an increase of Left Pre-Ejection Period (LPEP) (107 ± 14 vs 82 ± 14 ; $p=0.002$), LPEP /LVET ratio (Weissler index) (0.35 ± 0.08 vs 0.27 ± 0.06 ; $p=0.004$) and TEI index (0.57 ± 0.11 vs 0.40 ± 0.14 ; $p=0.009$) in acute hypothyroidism. All these parameters indicates an impairment of left ventricular function. No changes were observed in M-mode measurements (LA diameter, LV systolic and diastolic diameter), ejection fraction, and diastolic function index (Dt, E/A, E/E') after thyroid hormone withdrawal. Our study confirmed thyroid hormones withdrawal produces important cardiac dysfunction. We also found a significant left atrial and left ventricular volume reduction. This last observation, to our knowledge, was never described before. Therefore, to avoid cardiac, even transient damage after LT4-withdrawal in selected cases, rhTSH should be an alternative therapy for patients waiting for radioiodine ablative treatment.

Nothing to Disclose: Sd, BA, AC, FP, GP, AP

sort_order 2682
Pub # P3-613
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)
Title Three Japanese Cases with Iodine-Induced Hypothyroidism: Transient Free-T3 [ldquo]Overshoot[rdquo] Elevation after Iodine Restriction
Author String K Takeshima, K Hamamatsu, M Notu, H Murabe, N Murakami, T Yokota
Kurashiki Central Hospital, Kurashiki, Japan
Body **Introduction:** Exposure to excess iodine can cause hypothyroidism, often seen in an iodine sufficient area, where people prefer iodine-rich food such as Laminaria (Kombu). We report three cases of reversible iodine-induced hypothyroidism with transient free-T3 "overshoot" elevation after iodine restriction.
Case 1: A 66-year-old man admitted for foggy head. He spoke slowly and his skin was dry. He preferred Kombu very much. Laboratory data showed free T3 (fT3) 2.1 pg/ml (RI: 1.7-3.7 pg/ml), free T4 (fT4) 0.29 ng/dl (RI: 0.75-1.75 ng/dl), TSH 166 mcU/ml (RI: 0.35-4.0 mU/ml). Antithyroid antibody was positive and TSH binding inhibiting immunoglobulin (TBII) was negative. I-123 scan on day 10 revealed diffuse thyroid RAIU (55.4% at 24-hour) (RI: 10-35 %). After 8 days of iodine restriction, his thyroid function recovered with fT3 elevation, fT3 4.3 pg/ml, fT4 0.77 ng/dl, TSH 30.1 mcU/ml, followed euthyroid on day 88.
Case 2: A 72-year-old woman admitted for fatigue and slurred speech. She preferred the root of Laminaria (Nekombu). Laboratory data showed fT3 1.8 pg/ml, fT4 0.20 ng/dl, TSH 69.3 mcU/ml. Antithyroid antibody and TBII were negative. I-123 scan on day 17 revealed diffuse thyroid RAIU (62.3% at 24-hour). After 16 days of iodine restriction, her thyroid function recovered with fT3 elevation, fT3 4.0 pg/ml, fT4 0.63 ng/dl, TSH 23.3 mcU/ml, followed euthyroid on day 42.
Case 3: A 70-year-old man referred for myalgia and abnormal liver function tests. He preferred Kombu very much. Laboratory data showed fT3 2.1 pg/ml, fT4 0.35 ng/dl, TSH 45.1 mcU/ml. Antithyroid antibody and TBII were negative. I-123 scan on day 12 revealed diffuse thyroid RAIU (49.7% at 24-hour). After 10 days of iodine restriction, his thyroid function recovered with fT3 elevation, fT3 4.0 pg/ml, fT4 0.79 ng/dl, TSH 10.1 mcU/ml, followed euthyroid on day 22.
Discussion: T3 is converted from T4 by both types 1 and 2 deiodinases (D1 and D2) in human. Excess iodine ingestion leads to the decrease in thyroid hormone synthesis, followed by the activation of positive feedback for TSH. In peripheral tissue, deiodinase accelerate conversion of T4 to T3. In iodine-induced hypothyroidism, as the thyroid function may recover rapidly by the iodine restriction, a time lag occurred before the sufficient activation of negative feedback for TSH and D2 to T3, which may have contributed to the overshoot phenomenon.

Nothing to Disclose: KT, KH, MN, HM, NM, TY

sort_order

2683

Pub #

P3-614

Session Information

POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)

Title

Iodine Status and Thyroid Function of Boston-Area Vegetarians and Vegans

Author String

AM Leung, A LaMar, X He, LE Braverman, EN Pearce
Boston Medical Center, Boston, MA; Boston University, Boston, MA

Body

Context: Adequate dietary iodine is required for normal thyroid function. Pregnant and lactating women are particularly susceptible to iodine deficiency, as developing infants rely solely on maternal iodine intake for thyroid hormone synthesis and normal neurodevelopment. The iodine status and thyroid function of U.S. vegetarians (users of plant-based diets, eggs, and milk; abstain from meat, poultry, fish, and shellfish) and vegans (non-consumers of all animal products) have not been previously studied. Exposures to two environmental inhibitors of thyroid iodine uptake, perchlorate (ClO₄ present ubiquitously) and thiocyanate (SCN, a cigarette smoke metabolite and present in some foods) among vegetarians and vegans may additionally decrease available iodine and be associated with mild hypothyroidism.

Methods: Urinary iodine, ClO₄, SCN, and cotinine (a cigarette smoke-specific metabolite) and serum thyroid function were cross-sectionally measured in 141 Boston-area adults (78 vegetarians, 67% women, 30.8 [mean age] ± 10.6 [SD] years, duration of diet: 11.3 ± 11.7 years; and 63 vegans, 69% women, 36.6 ± 13.2 years, duration of diet: 5.6 ± 5.7 years). One vegan kelp-user was excluded due to an extremely elevated urinary iodine level. Subjects were also asked to estimate their ingestion of common iodine, SCN, and isoflavone (which may inhibit thyroid peroxidase)-containing foods.

Results: Median urinary iodine concentration of vegans (78.5 [μg/L; range, 6.8-964.7 [μg/L]) was lower than vegetarians (147.0 [μg/L; 9.3-778.6 [μg/L]) (p<0.01). Urine cotinine revealed 6 recent smokers/group (>500 ng/mL). Median urinary SCN concentration of vegans (630 [μg/L; 108-3085 [μg/L]) was higher than vegetarians (341 [μg/L; 31-1963 [μg/L]) (p<0.01). Excluding the 12 smokers, this difference persisted (vegans: 576 [μg/L, 108-2563 [μg/L; vegetarians: 321 [μg/L, 31-1698 [μg/L; p<0.01). There were no between-group differences in urinary ClO₄ levels (p=0.75), TSH (p=0.46), and FT4 (p=0.77). Urinary iodine, ClO₄, and SCN levels were not associated with TSH (p=0.59) or FT4 (p=0.14), even when adjusted for age, gender, country of birth, diet type, diet compliance, salt type use, smoking, and isoflavone consumption.

Conclusions: U.S. vegetarians are iodine sufficient. U.S. vegans may be at risk for low iodine intake, and vegan women of childbearing age should supplement with 150 [micro]g iodine daily. Environmental ClO₄ and SCN exposures are not associated with thyroid dysfunction in these groups.

Sources of Research Support: Boston University Building Interdisciplinary Research Careers in Women's Health (BIRCWH) grant, K12-HD43444.

Nothing to Disclose: AML, AL, XH, LEB, ENP

sort_order 2684
Pub # P3-615
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)
Title "Tight Control" of the TSH Target Range for Thyroxine Replacement in Primary Hypothyroidism: How Tight Is Too Tight?
Author String D Shah, P Sridhar, K Raghunathan, V Balakrishnan, C Barsano
Captain James A Lovell Federal Health Care Center, North Chicago, IL; Chicago Medical School, North Chicago, IL
Body Recommended TSH target ranges ("TR") for thyroxine (T4) replacement in primary hypothyroidism have progressively narrowed and remain controversial. Although physiologically sound, some TR's may be too narrow for practical use. We have determined the percentages of TSH values ("%OUT") that would be expected to fall outside of increasingly narrow TR's (ranging from 5.0-0.3 mU/L to 0.3-0.3 mU/L) because of clinically insignificant physiologic variations, infrequent patient non-compliance, and unavoidable technical reasons (e.g. interassay variation). Forty-two series of stable, consecutive TSH levels obtained from 27 generally compliant patients were studied. To be regarded as [stable] each series had to be (a) on the same dosage of T4, (b) preceded by 2 consecutive TSH levels within the range of 3.0-0.3 mU/L on the same dose of T4, (c) derived from a patient who had already been on T4 for at least 1 year, and (d) no longer than 3 years in duration. Each series contained from 4 to 10 TSH levels at least 1 month apart. Deviations were calculated as the plus or minus difference (in mU/L) from the mean TSH within the series. The 245 deviations were pooled for analysis.
The distribution of deviations (sd = ±0.67 mU/L) was not "Normal" but skewed toward higher TSH values (Skewness = 0.643). Using a standard natural-logarithmic transformation of the deviations the distribution was rendered nearly "Normal" (Skewness = 0.066). Given this Normalized distribution the following %OUT's could be calculated for progressively narrowed TR's: UPPER LEVEL OF TR(%OUT)*: 5.0(3.6%), 4.5(4.9%), 4.0(6.9%), 3.5(9.8%), 3.0(14.3%), 2.5(21.1%), 2.0(31.1%), 1.5(45.3%), 1.0(64.5%), 0.5(88.9%), 0.3(99.9%). [*Calculated for TR's using a Lower TR Level of 0.3 mU/L and when the mean TSH levels are mid-target range. Were the mean TSH levels to approach the Upper or Lower limits of the TR, the %OUT's would increase.] As an empirical test of the method, in 35 series from 24 patients treated to maintain a TR of 3.0-0.3 mU/L, the observed %OUT was 15.2%, very close to the projected estimate of 14.3%.
CONCLUSION: Though subject to clinical judgment, if "practical" implies that clinically insignificant excursions outside of a selected TSH target range should occur no more than perhaps 20-25% of the time (i.e. %OUT <20-25%), the upper limit of a TSH target range should be no lower than 3.0 to 2.5 mU/L and the mean TSH level should be maintained at approximately mid-target range.
Nothing to Disclose: DS, PS, KR, VB, CB

sort_order 2685
Pub # P3-616
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)
Title Hypothyroidism with Very Low Free T₃/Free T₄ Ratio May Represent Decreased Peripheral Conversion of T₄ to T₃: Case Report and Differential Diagnosis
Author String A Goldberg, R Tirona, U Schwarz, RB Kim, SHM Van Uum
Schulich School of Medicine and Dentistry, University of Western Ontario, London, Canada
Body Background: Clinically symptomatic hypothyroidism in the context of increased TSH and elevated free thyroxine (T₄) but decreased triiodothyronine (T₃) production is rare (1). We present a case of decreased extra-thyroidal T₃ production and review the potential underlying pathophysiological mechanisms.
Clinical Case: A 36-year old female presented with hypothyroidism and pituitary hyperplasia. Hypothyroidism was diagnosed at age 24, after her third pregnancy, and levothyroxine (LT₄) was started. The clinical symptoms and TSH did not normalize on increasing doses of levothyroxine. At age 34 she underwent a total thyroidectomy to relieve compressive symptoms of a goiter. She had a family history significant for thyroid dysfunction in her maternal grandmother and 3 aunts, two of whom required thyroidectomy. Headaches triggered a CT of her head and then a dedicated sella MRI scan showing significant pituitary hyperplasia, but not an adenoma. The LT₄ dose was increased to 0.5 mcg daily and she was referred to endocrinology.
In endocrinology clinic, she appeared to be clinically hypothyroid. Laboratory testing indicated an extremely elevated TSH (52.6 mIU/L; range=0.27-4.20), but her free T₄ levels were high (75.5 pmol/L; range=11-22) ruling out non-compliance or malabsorption of LT₄. Her free T₃ was normal at 6.2 pmol/L (range=3.0-6.5), resulting in decrease free T₃/free T₄ ratio. Her reverse T₃ was within normal range.
The decreased free T₃/free T₄ ratio in a post-thyroidectomy patient suggests decreased peripheral conversion of T₄ to T₃, or increased clearance of T₃. Abnormal conversion may result from deiodinase (D) type 1 and type 2 deficiency or perhaps abnormal uptake of T₄ into D1 or D2 containing tissues. Increased type 3 deiodinase is unlikely because of the normal rT₃ level. In this patient, sequencing of the coding region of D1 and D2 genes did not reveal any mutations of previously described polymorphisms. We propose to sequence T₃ transporter genes, and planned to test her response to T₃ administration, but the patient was lost to follow-up.
Conclusion: This post-thyroidectomy patient exhibits a very low free T₃/free T₄ ratio and high TSH, suggesting hypothyroidism most likely caused by decreased conversion of T₄ to T₃. In this report, we discuss a diagnostic approach to the potential mechanisms of abnormal free T₃/free T₄ ratio.

(1) Jansen et al., Lancet. 1982; 2(8303):849

Nothing to Disclose: AG, RT, US, RBK, SHMVU

sort_order 2686
Pub # P3-617
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)
Title Subclinical Hypothyroidism, Weight, and Body Composition in the Elderly: The Cardiovascular Health Study
Author String MC Garin, AM Arnold, JS Lee, AR Cappola
University of Pennsylvania School of Medicine, Philadelphia, PA; University of Washington, Seattle, WA; University of California, Davis, CA
Body **Background:** Subclinical hypothyroidism is common in the elderly, yet its relationship with weight status is unknown. We examined the relationship between subclinical hypothyroidism and 1) body composition and 2) weight change over a six year period in an older population.
Methods: All analyses were performed using data from US community-dwelling men and women aged 65 and over who were enrolled in the Cardiovascular Health Study and not taking thyroid hormone preparations. We included 421 women and 260 men with subclinical hypothyroidism and 2303 women and 1880 men with euthyroidism in cross-sectional linear regression analyses of weight and BMI. Lean body mass and fat mass by DXA were available in a subset of 637 women and 533 men with euthyroidism and 73 women and 51 men with subclinical hypothyroidism. We subsequently performed longitudinal GEE analyses of the relationship between subclinical hypothyroidism and weight change over 6 years of follow-up in 1970 women and 1458 men. All models were adjusted for age and race and stratified by sex.
Results: In cross-sectional analyses, women with subclinical hypothyroidism were 1.58 kg heavier with a 0.58 kg/m² higher BMI than their euthyroid counterparts (p=0.03 for each), whereas there was no weight or BMI difference in men (-0.22 kg, p=0.79; +0.12 kg/m², p=0.64, respectively). In linear models, a one mU/L higher TSH level within the normal or subclinical hypothyroid range was associated with a 0.36 kg higher weight in women only (p=0.003). There were no associations between subclinical hypothyroidism and total lean body or fat mass, in either women or men (all p=ns). The average annual weight change was -0.38 kg in this older population and did not differ between subclinically hypothyroid and euthyroid individuals (p=0.64 for women and p=0.57 for men).
Conclusions: Older women with subclinical hypothyroidism weigh slightly more than their euthyroid counterparts, with no difference between subclinically hypothyroid and euthyroid groups in weight change over time and no associations between subclinical hypothyroidism and weight or body composition in men. These data do not support a clinically significant impact of subclinical hypothyroidism on weight status in the elderly.

Sources of Research Support: R01 AG032317 to ARC.

Nothing to Disclose: MCG, AMA, JSL, ARC

sort_order 2687
Pub # P3-618
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)
Title Lenalidomide-Exacerbated Hypothyroidism: A Case Report
Author String LE Trask, A Bauman, RJ Comi
Dartmouth Hitchcock Medical Center, Lebanon, NH; VA Medical Center, White River Junction, VT
Body
Background:
Lenalidomide is a novel immune modulatory drug used in multiple myeloma as well as other hematologic malignancies. Hypothyroidism has been well-described as a side effect of thalidomide, a less potent analogue of lenalidomide. As the number of patients receiving lenalidomide for longer periods of time increases, hypothyroidism is becoming recognized as an important associated adverse event. We report a case of primary hypothyroidism that was markedly exacerbated by the use of lenalidomide.
Clinical Case:
An 87 year-old man with IgG kappa multiple myeloma since 2003 was begun on lenalidomide and dexamethasone for relapsing disease. He had previously been receiving melphalan and zoledronic acid. At the time of treatment with lenalidomide, he carried a previous diagnosis of primary hypothyroidism that had been diagnosed 8 months prior. His thyroid function tests prior to lenalidomide therapy showed a TSH of 4.17mIU/ml while on 75 mcg per day of levothyroxine. Two months later his TSH had risen to 64.73 mIU/ml. Malabsorption was ruled out with thyroxine absorption testing. He was noted to be compliant with taking his medication. His dose of levothyroxine was increased to 125 mcg daily. After treatment, the TSH returned to near normal range requiring one more slight dose adjustment. Although dexamethasone has been associated with lowering TSH, his TSH actually rose while on the dexamethasone and lenalidomide. He then had correction of both his FT4 and TSH with increasing his levothyroxine dose.
Conclusion:
It is now increasingly recognized that lenalidomide increases the risk of thyroid dysfunction. Lenalidomide also appears to worsen thyroid dysfunction in pre-existing hypothyroidism. Based on this case and other cases in the literature, we recommend close monitoring of thyroid function in hypothyroid patients who are begun on lenalidomide.
Nothing to Disclose: LET, AB, RJC

sort_order 2688
Pub # P3-619
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)
Title Subclinical Hypothyroidism Is Associated with Increased Prevalence of Fatigue: Re-Analysis of the Whickham Data
Author String AC Madathil, SHS Pearce, MPJ Vanderpump, S Razvi, JU Weaver
Gateshead Health NHS Foundation Trust, Gateshead, UK; Royal Victoria Infirmary and Newcastle University, Newcastle upon Tyne, UK; Newcastle University, Newcastle upon Tyne, UK; Royal Free Hampstead NHS Trust, London, UK
Body
Background
Subclinical hypothyroidism (SCH) is a common endocrine condition. Clinicians face the problem of attributing symptoms such as fatigue to the diagnosis of SCH because previous studies have shown conflicting results with respect to prevalence of fatigue in this condition. Some of these studies might have selection bias where individuals were recruited from clinic based centres. So, we need more population based studies looking at the prevalence of fatigue in SCH.
Objective
To assess the prevalence of fatigue in people with SCH identified in Whickham study.
Methodology
The Whickham study was a population survey of thyroid disease conducted in England. The fatigue was reported as a yes or no response. We analysed the prevalence of fatigue in the SCH group (TSH 6-15mIU/L and normal total T4 levels) and compared with euthyroid controls. Individuals on medications interfering with thyroid function were excluded. A binary logistic regression analysis was performed with fatigue as dependent variable, and age, thyroid status, diabetes mellitus, body mass index, smoking, hypertension, ischaemic heart disease and cerebro-vascular disease as the co-variables. Additionally, we analysed fatigue in relation to serum TSH as a continuous variable after combining both groups and adjusting for other variables as above.
Results
There were 2357 euthyroid people (mean age 46 years and 51% females) and 121 people with SCH (mean age 51.4 years and 72% females). The median TSH were 2.0 mIU/L and 7.2 mIU/L in euthyroid and SCH group, respectively. The fatigue was reported 27.3% (n=33) in SCH group compared to 18.8% (n=461) in euthyroid controls (p=0.02). The multivariate adjusted odds ratio of fatigue for females and males was 1.81 (95% CI 1.12-2.92, p=0.01) and 0.98 (0.37-2.62, p=0.97) respectively. For each unit increase in serum TSH, the risk of fatigue was increased by 5% (0.4-9.5%, p=0.03).
Discussion and conclusion
The data shows that fatigue is more commonly reported in SCH than in euthyroid individuals. This is particularly more significant in women, even after correction for age and co-morbidities. A rise in serum TSH was associated with increased risk of fatigue. This was a population study where individuals were unaware of their thyroid status at the time of symptom assessment, unlike previously published highly selected cohort studies. Our data supports those of previous work showing that fatigue is a clinical manifestation of SCH.

Nothing to Disclose: ACM, SHSP, MPJV, SR, JUW

sort_order 2689
Pub # P3-620
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)
Title Absence of TSH Receptor (*TSHR*) Gene Mutations in Severe Permanent Congenital Hypothyroidism Due to Apparent Athyreosis
Author String P Scaglia, L Gruneiro-Papendieck, P Papendieck, L Prieto, HM Domene, A Chiesa
Ricardo Gutierrez Buenos Aires Children's Hospital, Buenos Aires, Argentina; CONICET, Buenos Aires, Argentina; Fundacion de Endocrinologia Infantil, Buenos Aires, Argentina
Body Resistance to TSH is a syndrome of reduced sensitivity to TSH, associated with molecular defects hampering the adequate transmission of the TSH stimulatory signal into the thyroid cells. The phenotype covers a wide spectrum of thyroid abnormalities going from mild hyperthyrotropinemia to severe congenital hypothyroidism (CH) with thyroid hypoplasia.
Apparent athyreosis defined as negative ⁹⁹Tc thyroid scan uptake with hypoplastic thyroid on ultrasound or detectable TG levels represents 7% of permanent CH detected in our neonatal screening program and 30% of those preliminarily classified as athyreotic.
In order to search for mutations in *TSHR* gene, we retrospectively selected 19 CH patients (15 girls) with apparent athyreosis detected by the neonatal screening at a median age of 21 days (R:9-50) and confirmed as permanent CH with TSH >100 mU/l, median (range) T4: 1.0 [mu]g/dl (0.4-5.6) FT4: 0.2 ng/dl (0.11-0.64) T3: 57 ng/dl (19-109) TG: 34 ng/ml (1.8-81.5), negative antithyroperoxidase (ATPO) and anti-thyroglobulin (ATG) antibodies, absence of thyroid image in a ⁹⁹Tc scan, presence of a normally located hypoplastic thyroid gland on ultrasound and/or detectable serum TG. ⁹⁹Tc thyroid scan and ultrasound were performed in the neonatal period and serum TSH, T4, FT4 and T3 were measured by EQLIA, ATPO and ATG antibodies by ICMA and TG by IFMA. The whole coding sequence of *TSHR* gene (exons 1 to 10) and intronic flanking regions were amplified by PCR from genomic DNA and automatically sequenced.
Thirteen out of the 19 CH selected patients had negative ⁹⁹Tc thyroid scan, positive ultrasound and median TG 32 ng/ml (1.8-65). The remaining 6 had negative ⁹⁹Tc thyroid scan and ultrasound and TG levels of 45 ng/ml (6.8-81).
Results: Analysis of *TSHR* gene sequence revealed 4 different SNPs in heterozygous state in 9 patients: 1 P52T (rs 2234919), 4 N187N (rs2075179), 2 D727E (rs1991517), 1 D727E / N187N and 1 D727E A459A (rs 113951800). No novel mutation or gene variants previously described to be associated with CH were found.
Conclusion: *TSHR* gene mutations appear to be uncommon in severe permanent CH with apparent athyreosis in our population. Although a functional effect of *TSHR* polymorphisms could not be ruled out, previous studies of SNPs does not support this hypothesis. Other potential defect may include genes involved in TSH signaling and defects in *NIS* gene.
Nothing to Disclose: PS, LG-P, PP, LP, HMD, AC

sort_order 2690
Pub # P3-621
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)
Title Effective Treatment of Hypothyroidism with Intravenous Infusion of Levothyroxine in a Patient with Multidrug Resistance
Author String T Yoshida, Y Hirota, H Yokoo, S Higuchi, I Sakuma, H Nagano, E Imada, N Hashimoto, S Suzuki, T Mayama, K Suyama, T Tanaka, K Nakasa, K Yokote, I Tatsuno
Chiba University Hospital, Chiba, Japan; Chiba University Hospital, Chiba, Japan
Body
Introduction
Multidrug resistance (MDR) is characterized by a cross-resistance among structurally and mechanistically diverse agents, and recognized as a major obstacle for successful treatment of cancers, bacterial and viral infections and others. However, MDR associated with autoimmune hypothyroidism (Hashimoto's thyroiditis) has not yet been documented.
Patient
A 79-year-old woman was diagnosed as autoimmune hypothyroidism (Hashimoto's thyroiditis) in 2006, combined with idiopathic thrombocytopenic purpura (ITP) and hypertension. Treatment was started with levothyroxine sodium tablets, but even daily dose of 600 [mu]g (17.6 [mu]g/kg body weight) levothyroxine was not effective (TSH level was 81.425 [mu]IU/ml, and Free T4 was below 0.40 ng/dl). Other orally administered drugs, such as 5 kinds of anti-hypertensive agents or daily dose of over 20 mg prednisolone were also ineffective, and she was admitted to our hospital due to congestive heart failure and cerebellar hemorrhage. Although the first-line treatment of surgical removal of cerebellar hematoma was not applicable because of severe thrombocytopenia (platelet count, 4000 /[mu]l), she was almost fully recovered by intravenous infusion of drugs including levothyroxine, prednisolone, and nicardipine, about 1 month after the admission.
Methods and Results
ATP-binding cassette (ABC) transporter P-glycoprotein is known to contribute MDR, and its involvement was tested. Flow cytometric analysis of efflux transporter function revealed accelerated drug extrusion in the patients' peripheral blood mononuclear cells, but mRNA expression of ABCB1, which encodes P-glycoprotein, was not increased in the patient's leukocytes.
Conclusion
Our findings suggest a possible association between poor oral bioavailability and accelerated transporter function, although further studies are still needed to determine the pathophysiology of this disease.

Nothing to Disclose: TY, YH, HY, SH, IS, HN, EI, NH, SS, TM, KS, TT, KN, KY, IT

sort_order 2691
Pub # P3-622
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)
Title High Iodine Content of Korean Seaweed Soups: A Health Risk for Lactating Women and Their Infants?
Author String SS Rhee, LE Braverman, X He, EN Pearce
Boston Medical Center, Boston, MA
Body
Context: Dietary iodine requirements increase during pregnancy and lactation due to increased maternal thyroid hormone production, increased maternal renal iodine excretion, fetal and neonatal iodine requirements, and loss of iodine in breast milk during lactation. The World Health Organization (WHO) recommends 250[micro]g/day of iodine intake during pregnancy and lactation, while the Institute of Medicine (IOM) recommends 220[micro]g/day of iodine intake during pregnancy and 290[micro]g/day during lactation. Seaweed in various preparations is an integral part of Korean food culture. In particular, the majority of Korean and many Korean-American women consume seaweed soup on a daily basis during the early postpartum period. Studies of the iodine content in the breast milk of Korean lactating mothers have demonstrated that iodine content in human milk correlates strongly with the frequency and quantity of seaweed soup consumption. However, the actual iodine content of this seaweed soup has not previously been reported.
Objective: The aim of this study was to measure the average iodine content in traditional Korean seaweed soup.
Methods: We selected 10 brands of commercially available dried seaweed purchased in the United States. 1oz of each brand was used to produce traditional Korean seaweed soup (1oz seaweed, 6cups water, beef, soy sauce, sesame oil). The iodine concentration of the dried seaweed and seaweed soup broths were measured spectrophotometrically. In total, the iodine concentrations of 10 samples of seaweed and 10 samples of seaweed soup broth were measured.
Results: The average iodine content of the dried seaweed was 359±254 [micro]g/gm. The average iodine content of seaweed broth was 1.95±0.8 [micro]g/mL (mean±SD), with 1 bowl (240mL) of broth containing an average of at least 470±201 [micro]g of iodine.
Conclusion: Depending on quantity and frequency of seaweed soup intake, postpartum women who consume Korean seaweed soup may have daily iodine intakes and produce breastmilk that exceed the tolerable upper limit of daily intake as recommended by WHO (500[micro]g/day for lactating women and >180 [micro]g/day for infants). Iodine-induced hypothyroidism and iodine-induced thyrotoxicosis are both potential adverse effects of excess iodine consumption. Further studies should be carried out in the U.S. to evaluate the potential adverse effects of high dietary iodine consumption on thyroid function in breastfeeding Korean-American women and their infants.

Nothing to Disclose: SSR, LEB, XH, ENP

sort_order 2692
Pub # P3-623
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)
Title Levothyroxine Dosing after Total Thyroidectomy: Efficacy and Barriers to Achieving Euthyroidism
Author String AE Reiher, S Schaefer, H Chen, RS Sippel
University of Wisconsin-Madison, Madison, WI; University of Wisconsin-Madison, Madison, WI
Body
Introduction:
After a total thyroidectomy, levothyroxine replacement is typically started at 1.6 mcg/kg body weight per day. Adjustments in dose are based on TSH values. Our study investigated the efficacy of starting patients on a weight-based dose of levothyroxine after total thyroidectomy, potential barriers to achieving euthyroidism, and how long it takes to achieve euthyroidism post-operatively.
Methods:
A retrospective review was performed using our institution's surgical database. Inclusion criteria included total thyroidectomy, benign final pathology, and follow-up labs available at post-operative follow-up. Normal TSH was defined as 0.45 to 4.5 uIU/mL.
Results:
115 patients met inclusion criteria. Average age at time of thyroidectomy was 51 years, and 83.5% of patients were female. 35 patients (30.4%) achieved euthyroidism at 6-8 week follow-up, with an average 1.49 mcg/kg/day levothyroxine dosing. Of the 80 patients that were not euthyroid at 6-8 weeks, it took an average of 6.7 months to achieve euthyroidism. For patients with an initially elevated post-operative TSH (N=33, 41.3%), the average starting levothyroxine dose post-operatively was 1.54 mcg/kg/day, and euthyroidism was ultimately achieved with an average dose of 2.03 mcg/kg/day. For those patients with a below-normal TSH post-operatively (N=47, 58.8%), the average starting levothyroxine dose post-operatively was 1.62 mcg/kg/day, and euthyroidism was ultimately achieved with an average dose of 1.37 mcg/kg/day. Autoimmune disease was more common in patients with an elevated TSH at initial post-operative follow-up than those with a below-normal TSH post-operatively (46% vs 26%, p=0.058). Body-mass-index (BMI) > 35.0 was associated with initial overdosing of levothyroxine (p=0.006), and BMI < 25.0 was associated with initial under dosing of levothyroxine (p<0.001).
Conclusions:
The current weight based method for thyroid hormone dosing is suboptimal with only 30.4% of patients achieving euthyroidism at 6-week follow-up. Normal BMI and autoimmunity were both associated with initial under dosing of thyroid hormone and high BMI was associated with initial overdosing. These factors should be considered when choosing an initial starting dose of levothyroxine after a total thyroidectomy, and patients should be counseled that it may take several months to determine their optimal levothyroxine dose.

Nothing to Disclose: AER, SS, HC, RSS

sort_order 2693
Pub # P3-624
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)
Title Intravenous Levothyroxine Drip as an Initial Treatment of Myxedema in a High-Risk Cardiac Patient
Author String H Zainah, H Mahmud, H Brooks
University of Pittsburgh Medical Center Presbyterian Shadyside, Pittsburgh, PA; University of Pittsburgh Medical Center Presbyterian, Pittsburgh, PA
Body
Background: Myxedema coma is a rare endocrine emergency. Treatment with thyroid hormone is crucial, but the initial type of replacement (levothyroxine (T4), T3, or both) and dosing remain controversial due to the rarity of cases and lack of randomized controlled trials. Expert opinion recommends intravenous bolus T4 therapy (200-400[mu]g), with lower doses in the elderly due to risk of myocardial infarction (MI) and atrial fibrillation (afib). We present an alternative therapy of intravenous T4 infusion at a rate of 12.5[mu]g/hour as opposed to a bolus in an elderly patient presenting with myxedema and bradycardic afib.
Clinical case: 82 y.o. female admitted to an outside hospital with weakness and confusion. She had a history of hypothyroidism and had not been taking her medications for three years. She was found to be delirious, with rectal temperature (T) of 30[deg]C, BP 100/60, HR 50bpm, and weight 123kg. EKG showed bradycardic afib. TSH 74.8 (0.2- 5 [mu]IU/mL), total T4 2.2 (5-14 [mu]g/dL), cortisol 22 (2-9 [mu]g/dL), and glucose 56 (70-99 mg/dL). ABG was consistent with chronic respiratory acidosis. She was given T4 25[mu]g IV bolus, 50[mu]g orally, antibiotics, and warm IV fluids and was transferred to our institution. Because of concerns of precipitating rapid afib or MI, we administered a total of 100[mu]g IV T4 infused as a drip over a period of two 4 hour periods. During the infusion her T increased from 35.5 to 36.1[deg]C, BP from 107/85 to 122/70, and more importantly the patient did not become tachycardic with HR increasing from 63 to 82 bpm. 2 hours after infusion was stopped HR was 67bpm. Given her improving mental status and vital signs, the decision was made to only treat further with T4 100[mu]g PO daily. One week later, TSH was 29 [mu]IU/mL. The patient has continued to show clinical improvements 1 month later.
Discussion: Myxedema coma is a rare endocrine emergency which carries a high mortality. The use of a T4 IV drip for purposes of initial myxedema treatment has not been previously reported in the literature. A recent study showed that levothyroxine sodium 0.4[mu]g/mL in 500mL 0.9% sodium chloride is stable for 24 hours at room temperature when protected from light (1). We propose that the initial treatment of myxedema with IV levothyroxine drip as opposed to bolus, be considered in patients with highest risk of cardiovascular complications. This has the benefit of being able to monitor HR and clinical response and being able to stop the infusion if a complication is noted.

(1) Stadalman KA et al., Prog Transplant 2009; 19:354

Nothing to Disclose: HZ, HM, HB

sort_order 2694
Pub # P3-625
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)
Title Comparison of the Intestinal Absorption of Levothyroxine (LT4): Tablet vs. Soft Gel Capsule Formulation
Author String S Benvenga, MP Ducharme
University of Messina, Messina, Italy; University of Montreal, Montreal, Canada
Body Malabsorption of LT4 tablets swallowed with coffee has been previously evidenced in patients by inappropriately high TSH levels(1). We then observed that some patients taking LT4 in the form of a soft gel capsule with coffee maintained normalized TSH.
In search for a possible explanation, we evaluated a number of indices of LT4 intestinal absorption (T4-IA) in a post-hoc analysis of data deriving from two studies. A first randomised, cross-over study was performed by administering 600 mcg of LT4 (Synthroid[®] tablet, Abbott Laboratories, USA or Tirosint[®] soft gel capsule, IBSA, Switzerland) to 24 adult healthy volunteers after a 10-hour overnight fast and 35-day wash-out between doses. Either formulation was swallowed with 240 mL water. Blood samples were obtained prior to and at several times up to 48 h after L-T4 administration to assay serum total T4. In a second pilot study the two formulations were administered in other 16 healthy volunteers (parallel groups) with 240 mL American coffee. After subtraction of endogenous T4 to obtain delta T4 ([Delta]T4) values, differences were analyzed by ANOVA (means±SD) and Fisher's exact test (proportions). Results are presented as tablet vs. capsule. Upon intake with water, the two formulations are bioequivalent based on the FDA criteria. AUC₀₋₄₈ and AUC₂₄ were equal to 1730±449 ng[middot]h/mL vs. 1820±635 (+5.2%) and 953±264 vs. 1032±379 (+8.3%) (P>0.4). A closer scrutiny of data disclosed some trends on calculated indices, especially at the earliest times: AUC_{0.5} 3.4±3.0 vs. 0.2±0.9, -94.6%, P<0.0001; AUC₁ 17.8±9.9 vs. 11.6±7.4, -34.9%, P<0.05; AUC_{1.5} 45.6±22.2 vs. 38.9±20.9, -14.8%, P>0.05. Moreover, [Delta]T4 at 30 min was 13.0±11.7 vs. 0.9±3.6 (P<0.0001). Also, the no. of volunteers with [Delta]T4<50 ng/mL at all time points between 12 and 48 h was greater with tablet vs. capsule (21 vs. 15, P<0.05). Upon intake with coffee, AUC_{0.5} was 1.9±1.0 vs. 0.6±0.8, -66.2% (P<0.05). The situation was reversed immediately after, with Tirosint displaying superior AUC up to 12 h (P>0.1). [Delta]T4 at 30 min was 7.6±3.9 vs. 2.6±3.3 (P<0.05).
Conclusion- Based on classical indices, the performance of two formulations on the T4-IA can be judged superimposable. However, the slower absorption at the earliest times may give Tirosint the relevant advantage of being less available for mixing/sequestration by pharmacological or non-pharmacological compounds that are ingested orally simultaneously with or shortly after LT4. Confirmatory tests are ongoing.

Benvenga S et al. Thyroid 2008;18(3):293-301

Nothing to Disclose: SB, MPD

sort_order 2695
Pub # P3-626
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)
Title Differential Diagnosis among Patients with Total Thyroidectomy, Thyroid Dysgenesis and Mutations in the Thyroglobulin Gene by a Novel Ultrasensitive EIA for Human Thyroglobulin
Author String H Katakami, S Hashida, H Iwasaki, A Hishinuma, S Fukata, A Matsuno, T Ieiri
Teikyo University Chiba Medical Center, Ichihara, Japan; Tokushima Bunri Univ, Tokushima, Japan; International University Health Welfare Atami Hospital, Atami, Japan; Dokkyo, Mibu, Japan; Tajiri Clin, Kumamoto, Japan; Teikyo University Chiba Medical Center, Ichihara, Japan; International University Health Welfare Shioya Hospital, Yasaka, Japan
Body Serum thyroglobulin (Tg) is a useful tumor marker to quantitatively measure residual thyroid cancer cell functions in patients (Px) with differentiated thyroid cancer (DTC) after total thyroidectomy (THX). It is also useful to assess functions of normal thyroid follicular cells in patients with thyroid hypogenesis (Thp) or mutations in the Tg gene (TgM). Current measurements of serum Tg (least detectable value, LDV: IRMA 5,000pg/ml, or ECLIA 200pg/ml) are sometimes not sensitive enough to detect recurrence of DTC, or to assess inborn hypogenesis of the thyroid gland. In order to establish differential diagnosis among THX, Thp and TgM, we developed an ultrasensitive EIA for Tg, and measured serum Tg in patients with various thyroid diseases. All subjects examined were free of autoantibodies to Tg. CNT: n=80. THX: THX alone for Basedow's ophthalmopathy, adenomatous goiter, or DTC (clinical stage 1), n=10. THX+I31-I: for DTC (clinical stage 2-4), n=16. Thp of unvisualized scintigraphy and of undermined etiology, n=3. TgM, n=7, Cys282Arg (n=1), Cys1245Arg (n=6). All patients with THX, Thp or TgM were treated with physiological doses of levothyroxine and showed euthyroidism (TSH: 0.4-4.0uIU/mL). We developed a novel and ultrasensitive immune complex transfer-enzyme immunoassay [ICT-EIA] for Tg by utilizing mouse monoclonal antibodies conjugated with β -galactosidase or biotinylated- and DNP-BSA. Ag-Ab complexes were then transferred to streptavidin-coated polystyrene beads. Specific immunofluorescence was measured. Serum Tg levels in all of the subjects examined were well measurable (LDV 5.0pg/ml, 75.8zmole/tube), including CNT: 4,520 - 28,610pg/ml, THX alone; 853 - 6,508pg/ml, THX+I: 93 - 1,477pg/ml, Thp; 550 - 2,700pg/ml, TgM: Cys282Arg; 24pg/ml, Cys1245Arg; 209 - 5,344pg/ml. Subsequent measurements of serum Tg after treatments with I31-I in euthyroid THX resulted in gradual decreases in serum Tg levels by months, but remained still far above the LDV. The present results show that without stimulation by human recombinant TSH, serum Tg levels in Px with THX+I were well above the LDV, and indicate that current follow-up protocols for the diagnosis of Px with recurrent DTC utilizing the human recombinant TSH may not be needed. The results obtained by the ultrasensitive Tg EIA also suggest the possibilities that degree of thyroid genesis and types of mutated Tg genes will well be defined.
Nothing to Disclose: HK, SH, HI, AH, SF, AM, TI

sort_order 2696
Pub # P3-627
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Causes & Treatment of Hypothyroidism (1:30 PM-3:30 PM)
Title The Role of Thyroid Dysfunction in Acutely Decompensated Heart Failure Subjects
Author String J Prague, G Schulze, P Rudd, A Khwanda, SP Karwatowski, A Banerjee
South London Healthcare Trust, Farnborough Common, Orpington, UK; South London Healthcare Trust, Farnborough Common, Orpington, UK
Body **Background:** Brain natriuretic peptide (BNP) is a prognostic indicator in heart failure; a rise in BNP is associated with excess cardiovascular risk. Thyroid dysfunction is associated with heart failure. Association of subclinical hypothyroidism with heart failure is not well established.
Aim: To determine the relationship of TSH values with acute decompensated heart failure in a large inner-city hospital in London.
Methods: A retrospective analysis of a cohort of 102 cases with a primary diagnosis of confirmed decompensated heart failure was analysed (July 2009-December 2010). Patients with creatinine > 250mmol/L (chronic kidney disease stage 4) were excluded.
Results: Sixty-seven cases were identified with complete data and a mean age of 77.8±11.4 years (Mean±SD). The clinical characteristics were as follows male gender (53%), haemoglobin 12.7±2.3 gm/dL and creatinine 123.9±37.2 mmol/L.
The mean BNP was 177.8±242 pmol/L, which increased with symptomatic heart failure assessed by NYHA class. Subjects with a TSH >9 [micro]IU/mL had a significantly increased BNP compared to subjects with TSH <9 [micro]IU/mL (419.4 pmol/L ± 358.3 vs. 158.3 pmol/L ± 223.2; p<0.02).
Subjects with a TSH >9 [micro]IU/mL had a similar characteristics compared to subjects with TSH <9 [micro]IU/mL including age (74.3±13.6 vs 78.1±11.3 years; p=0.49); thyroxine 13.6±3.8 vs. 15.6±3.5 mcg/dL; p=0.24); haemoglobin 13.5±3.3 vs. 12.8±2.2 gm/dL; p=0.49); creatinine (126.4±40.5 vs. 123.6±37.3 mmol/L; p=0.88).
Conclusion: Thyroid dysfunction with TSH >9 [micro]IU/mL is associated with a raised BNP with no changes in of age, creatinine and haemoglobin. This study does not prove that treatment of such cases with raised TSH in heart failure is useful. We propose that a randomized study of treatment of patients with TSH >9 [micro]IU/mL in acutely decompensated heart failure individuals is needed.
Nothing to Disclose: JP, GS, PR, AK, SPK, AB

sort_order 2697
Pub # P3-628
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Thyroid Nodules & Cancer (1:30 PM-3:30 PM)
Title Absence of Correlation of Size of Toxic Thyroid Adenoma and Suppression of TSH Levels
Author String SL Lee, AR Jackson
Boston Medical Center, Boston, MA
Body **Objective:** Toxic adenomas may present with suppressed TSH levels. In patients with larger toxic adenomas, greater TSH suppression and hyperthyroidism is observed. It is controversial what the minimum size of a toxic adenoma is associated with a suppressed TSH. The objective of this study is to determine if the volume of an autonomous nodule is associated the TSH level.
Methods: Patients were selected from Endocrine clinic visits between October 2003 and March 2010 coded with the ICD-9 for toxic thyroid adenomas(242.10). Diagnosis of a single autonomous nodule was confirmed by individual examination by both authors of nuclear scans. Nodule volume was calculated using the American Thyroid Association calculator (www.thyroid.org/professionals/calculators/CINV.php). TSH levels were collected from the medical records. The toxic adenoma volumes and corresponding TSH levels were graphed and analyzed.
Results: The original population size contained 231 unique patients. 106 patients(45.9%) of this initial cohort were correctly coded as toxic adenomas. Only patients with a nuclear thyroid scan confirming the diagnosis of a single toxic adenoma without cystic degeneration were evaluated. Results showed that TSH suppression did not directly correlate with autonomous nodule volume. Nodules of varying sizes showed comparable TSH suppression. Nodules larger than 1.74 cm³ were never associated with a TSH within the reference range or higher. The smallest nodule measuring 0.79 cm³ had a TSH of less than 0.23 mU/L without suppression of the normal thyroid uptake on nuclear thyroid scan
Discussion: Toxic adenomas are autonomously functioning nodules that secrete thyroid hormone independent of the TSH level. Many toxic adenomas result from somatic activating mutations of the TSH receptor gene. Variation of these mutations may lead to different levels of TSH receptor activation resulting in a lack of correlation between toxic adenoma volume and TSH level.
Conclusion: Although patients with larger toxic adenomas may often have lower TSH levels, TSH suppression may depend on the specific somatic mutation of the TSH receptor gene and level of activation in addition to the volume of the autonomously functioning nodule. There is no discrete cut-off for size that excludes thyroid nodule autonomy but in this cohort of patients there were no autonomous nodules larger than 1.74 cm³ with a non-suppressed TSH level.
Nothing to Disclose: SLL, ARJ

sort_order 2698
Pub # P3-629
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Thyroid Nodules & Cancer (1:30 PM-3:30 PM)
Title Long-Term Observation of Benign Thyroid Nodules in an Iodine-Deficient Area
Author String R Gaertner, J Pronath
University of Munich, Munich, Germany
Body
OBJEKTIVE: Benign thyroid nodules are common in iodine deficient areas. Long-term growth rate of these nodules in adults with and without treatment is scarcely evaluated.
METHODS: A total of 279 benign thyroid non-functioning nodules with one diameter > 1 cm in 205 patients (158 females 47 males), mean age 53 ± 12 years were observed by ultrasound with Duplex-sonography over a mean time of 6.65 years (3.5-5y n=86, 5-9.9y n=163 and > 10 y n=30). The size (max thickness and width), the echoic pattern as well as grade of perfusion were documented about once a year during follow-up by the same physician and evaluated retrospectively. The intra-observer variation of volume measurement was 10%. One hundred patients (142 nodules) were treated with 200 [micro]g iodide per day, 41 patients were suffering from autoimmune thyroiditis in addition to thyroid nodules and treated with L-Thyroxine to keep TSH in the low normal range, no TSH-suppressive therapy was performed. Statistical calculation was done using paired T-test after logarithmic transformation.
RESULTS: The mean nodular size did not significantly change during the observation period. It was 1.70 cm² (range 1-13.64) at study entry and 1.76 cm² (range 0.12-16.83) after the mean follow-up of 6.65 years. From all nodules 6.9 % decreased in size more 10%, 6.5% increased, the remaining were unchanged and there was no correlation with the length of the observation period gender, age or whether the patients were substituted with iodine or not. Only in the subgroup of patients with autoimmune thyroiditis 20 out of 41 nodules increased in size but 10 decreased and 11 were unchanged. There was no difference in the growth rate whether the ultrasound pattern was normal, hypo- or hyperechoic or whether the perfusion was increased compared to normal tissue or not. None of the nodules turned out to become malignant determined by fine needle aspiration in cases of significant growth or change of ultrasound pattern.
CONCLUSION: In adults benign thyroid nodules exhibit no significant growth anymore. The nodules obviously develop during the youth and stop growing or even decrease in size independently on iodine supplementation. Significantly more nodules in patients with autoimmune thyroiditis increased in size, which might be due to a paracrine growth stimulation or lymphocytic infiltration of the rim.

Nothing to Disclose: RG, JP

sort_order 2699
Pub # P3-630
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Thyroid Nodules & Cancer (1:30 PM-3:30 PM)
Title Coccidioidomycosis Diagnosed during Evaluation of an Asymptomatic Thyroid Nodule
Author String NE Speil, L Bilodeau, D Mazzu, A Greenberg, M Jakoby
Body Southern Illinois University School of Medicine, Springfield, IL; University Medical Center, Las Vegas, NV; University Medical Center, Las Vegas, NV; University Medical Center, Las Vegas, NV
Coccidioidomycosis is an invasive infection caused by *Coccidioides immitis*, a dimorphic fungus endemic in the southwestern United States and northern Mexico. *Coccidioides* typically infects the respiratory tract. Fungal thyroiditis is rare, and to date only five cases of coccidioidal thyroiditis have been reported in the English language peer-reviewed literature. We report a case of coccidioidomycosis diagnosed during evaluation of a thyroid nodule.
A 48 year old African-American female was referred for a second opinion regarding a right lower pole thyroid nodule. She was a 20 year resident of Las Vegas, NV with a medical history notable for obesity, gastric banding, Stage II chronic kidney disease, and diet managed Type 2 diabetes mellitus (HbA1c 6.7%). A modest, non-tender goiter without palpable focal nodules was appreciated on examination. The patient denied noticing anterior neck enlargement, focal masses, or discomfort and generally felt well. Initial sonographic evaluation was notable for a 1.8 cm solid right lobe nodule. Since the patient was biochemically euthyroid (TSH 1.27 mU/L, 0.40-4.20), fine needle aspiration of the nodule was performed.
The pathology report indicated abundant multinucleated giant (MNG) cells on a background of bland follicular groups and colloid. Slides were obtained for direct review, and MNG cells were noted to engulf spherules characteristic of *Coccidioides* species. *Coccidioides* complement fixation titer was significantly elevated (1:32, reference < 1:2). HIV ELISA was nonreactive, and chest imaging was unremarkable. A diagnosis of coccidioidomycosis was made, and the patient was treated with a five month course of fluconazole. After treatment *Coccidioides* complement fixation titer was undetectable (< 1:2). A modest, non-tender goiter persisted.
Extrapulmonary infection accounts for only 1% of coccidioidomycosis cases. Disseminated infection without antecedent respiratory infection is documented but very uncommon. This patient's case was also unusual because there were no signs or symptoms of subacute thyroiditis, abscess, or thyrotoxicosis as documented in previous cases of coccidioidal thyroiditis. African-American ethnicity and diabetes mellitus were the patient's primary risk factors for disseminated *Coccidioides*. It is possible that thyroid involvement in disseminated coccidioidomycosis is under recognized due to lack of thyroid related symptoms as observed in this patient.

Nothing to Disclose: NES, LB, DM, AG, MJ

sort_order 2700
Pub # P3-631
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Thyroid Nodules & Cancer (1:30 PM-3:30 PM)
Title Intrathyroidal Hemorrhage after Fine Needle Aspiration (FNA) of Thyroid Nodules
Author String J Yoon, H Chung, E Jung, H Chang, K Won, H Lee
Yeungnam University Hospital, Daegu, Republic of Korea; DaeguCatholic University Hospital, Daegu, Republic of Korea; Yeungnam University Hospital, Daegu, Republic of Korea
Body Thyroid nodule is common disease and the incidence increasing as development of radiologic technique. It was reported that about 275,000 were discovered annually in United States. Fine-needle aspiration (FNA) is a technique widely used in the workup of thyroid nodules. FNA of the thyroid gland has a low morbidity rate with hematoma which is self-limited and causes only minimal pain and discomfort. Thereby we present a case of intra-thyroidal hemorrhage not hematoma after fine needle aspiration of thyroid nodule. The patient who was 54-year-old men receiving hemodialysis for end-stage renal disease in local clinic was revealed having secondary hyperparathyroidism showing intact PTH 1,111 pg/ml, Ca 9.4 mg/dl, P 7.4mg/dl and two thyroid nodules on ultrasonography. So he was referred to Yeungnam university medical center for FNA of thyroid nodules. The patient had been receiving regular hemodialysis and no recent history of taking medicines causing bleeding tendency like aspirin. Laboratory test showed free-T4 13.04 pmol/L, TSH 1.71 mu/l, anti-thyroglobulin antibody (-) and anti-TPO antibody (-). Thyroid ultrasonography showed 0.6cm, 1cm hypoechoic nodules in right lobe, 0.6cm hypoechoic nodule in left lobe and parathyroid gland hyperplasia. He received FNA by an experienced radiologist for diagnosis of asymptomatic bilateral hypoechoic thyroid nodules. Immediately after aspiration, the patient complained progressive pain and swelling in the low anterior neck and at the same time diffuse swelling and findings of hemorrhage in bilateral thyroid lobes were showed on thyroid ultrasonography. We instantly compressed lower anterior neck and injected steroid intramuscularly. After one hour observation, the patient didn't complain any more pain and swelling and was discharged. One week later, microscopic results showed a few follicular cell without atypical cell and follow-up thyroid ultrasonography didn't show intrathyroid hemorrhage. He was continuously observed out of the hospital.
Nothing to Disclose: JY, HC, EJ, HC, KW, HL

sort_order 2701
Pub # P3-632
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Thyroid Nodules & Cancer (1:30 PM-3:30 PM)
Title The Prevalence of Hypothyroidism and Its Correlation with Diffuse FDG Uptake in Thyroid Gland on PET-CT in Korean Patients
Author String DK Kim, SK Park, J-Y Mok, IJ Kim, H-J Lee, M-K Park
Dong-A Medical Center, Busan, Republic of Korea; Pusan National University Hospital, Busan, Republic of Korea; School of Medicine, Dong-A University, Busan, Republic of Korea
Body The aim of this study was to investigate the prevalence of hypothyroidism in the patients with diffuse FDG uptake on PET-CT and also the correlation between thyroid function and autoimmunity and diffuse FDG uptake on PET-CT. We analyzed 4569 PET-CT cases performed during previous 2 years retrospectively. Correlation of maximum standardized uptake value (SUVmax) on PET-CT and serum TSH, thyroid autoantibody were analyzed. One hundred twenty-nine (2.8%) and one hundred forty-nine (3.3%) were found to have focal and diffuse FDG uptakes in the thyroid gland on PET-CT, respectively. Among 149 patients those have diffuse FDG uptake in the thyroid gland, 90% of them were female and 83 patients were evaluated for thyroid function. Among them, thirty-five patients (42%) had elevated serum TSH level above reference range. Thyroid autoantibody (anti-TPO antibody) were positive in 31/52 (60%) patients. However, we couldn't find significant correlation between SUVmax and TSH (with or without thyroid autoantibody). Conclusively, the prevalence of hypothyroidism is 42% in diffuse thyroid uptake on PET-CT. It is associated with chronic thyroiditis. So the incidentally identified diffuse thyroid uptake on PET-CT should be followed carefully for future development of hypothyroidism.
Nothing to Disclose: DKK, SKP, J-YM, IJK, H-JL, M-KP

sort_order 2702
Pub # P3-633
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Thyroid Nodules & Cancer (1:30 PM-3:30 PM)
Title Multiple Positive Areas of Uptake on PET-CT Scan in a Thyroid Cancer Patient: Is It All Bad News?
Author String E Safar Zadeh, PW Butler, C Cochran, J Reynolds, FS Celi
NIH, Bethesda, MD; NIH, Bethesda, MD
Body
A 22-year-old man was evaluated for recurrent papillary thyroid cancer (PTC). The previous year he underwent total thyroidectomy with neck dissection for a 5 cm PTC, tall cell variant which extended into the adjacent soft tissues with vascular invasion and level IV and VI lymph node metastasis. He was initially treated with 150 mCi ¹³¹I, and post-therapy scan showed residual uptake in the thyroid bed. He was then treated for one year with L-T4 suppressive therapy.
At follow-up the neck ultrasound showed small nodes bilaterally and an 8 mm mass in the left thyroid bed. rTSH-¹²³I whole body scan was negative, but thyroglobulin (Tg) was marginally elevated at 2.5 ng/mL. In view of the Tg level, the advanced TNM stage, and the histopathology, a ¹⁸F-FDG PET-CT scan was performed. The study demonstrated diffuse pathologic uptake in the cervical area and supraclavicular spaces bilaterally, left superior mediastinal pleura, and axillary regions. Areas of increased uptake were also present bilaterally in the oropharynx. Finally, pathologic uptake was evident in the inguinal area, bilaterally, with possible uptake in the skeleton, particularly within the mid thoracic vertebral body and in the sacrum. The scan was considered consistent with widely-diffuse metastatic dissemination of PTC.
A thorough assessment of the patient revealed the presence of chronic tonsillitis with adenoid tissue hyperplasia, poor dentition with multiple cavities, and severe, bilateral tinea pedis with inguinal lymphadenopathy. The uptake in the cervical and supraclavicular regions was reconsidered as brown adipose tissue (BAT).
The patient received antibiotics and underwent total tonsillectomy with adenoidectomy, first left inferior molar extraction, and was treated with topical Terbinafine.
At 3 months, a repeat ¹⁸F FDG PET-CT scan was performed after pre-treating the patient with diazepam with the room temperature kept at 27 C^[deg] before the tracer injection and throughout the equilibration period to prevent BAT activation. Under these conditions the scan showed no areas of pathologic uptake. This unusual case illustrates the potential multiple pitfalls of the ¹⁸F FDG PET-CT, namely inflammation and BAT activation. The latter is particularly relevant in the evaluation of thyroid cancer since the uptake collimates with the area of loco-regional spread of the disease.

Nothing to Disclose: ESZ, PWB, CC, JR, FSC

sort_order 2703
Pub # P3-634
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Thyroid Nodules & Cancer (1:30 PM-3:30 PM)
Title A Case of Sclerosing Mucoepidermoid Carcinoma (SMECE) of the Thyroid Gland with a BRAF Mutation
Author String D Purohit, BJ Welch, S Sukumar
UT Southwestern Medical Center, Dallas, TX; Private Practice, Dallas, TX

Body

SMECE is a rare form of thyroid carcinoma. We report a case of a 70 year old female with concomitant papillary thyroid cancer and SMECE of the thyroid that later had biopsy-proven distant metastasis to the kidney. She was status post total thyroidectomy, total larygectomy, and bilateral neck dissection. She received 150 mCi of radioactive iodine ablation (RAIA). PET scan revealed a new 1.5cm pulmonary nodule adjacent to left hila of the left upper lobe and right kidney hydronephrosis 4 months after surgery. She received a course of external beam radiation (EBR). She had a CT guided biopsy of the kidney mass, which tested positive for SMECE and had the V600E BRAF mutation by PCR. This will be the first case reported in the literature of a patient with SMECE with a positive BRAF mutation and kidney metastasis. There have been 24 cases of SMECE reported in the literature (1). It occurs more common in females (2). Initial descriptions of the tumor were indolent in nature but rare cases have shown more aggressive behavior (3). Immunohistochemistry is positive for cytokeratin, mucin or carcinoembryonic antigen and negative for thyroglobulin and calcitonin (2,7). Histologically, it can be difficult to differentiate SMECE from squamous metaplasia associated with Hashimoto's thyroiditis (4). These tumors can be locally invasive to the surrounding tissues, trachea, esophagus, lymph nodes. Distant metastasis to lungs, liver, mediastinum, and bone has been described (1,5). Total thyroidectomy and neck dissection is the therapy of choice (5). SMECE is not usually responsive to RAI. Other treatment modalities include EBR, carboplatin, and doxorubicin, but none are very successful (6,7). BRAF mutation is the most common genetic alteration in thyroid cancer, occurring in 45% of sporadic papillary thyroid cancers in cytological and histological specimens. It is associated with a poor clinicopathological outcome and is a novel independent molecular prognostic marker in the risk evaluation of thyroid cancer (8). Tyrosine kinase inhibitors (TKI) are being used to target RAF kinase. Given the aggressive nature of our patient's tumor, she did not survive long enough to receive TKI (9). This case demonstrates that these tumors should be tested early for BRAF mutation and provides insight into potential mechanisms for the development of SMECE. BRAF inhibitors are currently in investigation and may prove to be a useful targeted medical therapy in the treatment of SMECE.

- (1) Kanat et al Turkish Journal of Cancer; 2004 34 (3)
- (2) Zubair et al., Mod Pathol 2000;13(7):802- 807
- (3) Sim et al., Human Pathology; 28:1091-1096
- (4) Musso-Laselle et al., Pathology - Research and Practice; 202 (2006) 379-383
- (5) Shehadeh et al., Thyroid 2004;25:48-53
- (6) Geisinger KR et al., Am J Clin Path 1998;109:294-301
- (7) Chan JK et al., Am Surg Pathol 1991; 15:438-448
- (8) M Xing., Endocrine-Related Cancer 2005; 12 245-262
- (9) Cabanillas et al., JCEM 2010; 95 (6) 2588-259

Nothing to Disclose: DP, BJW, SS

sort_order 2704
Pub # P3-635
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Thyroid Nodules & Cancer (1:30 PM-3:30 PM)
Title Papillary Thyroid Carcinoma and Hemoptysis: A Misleading Presentation
Author String VG Budharaju, N Pagedar, G Doelle
University of Iowa, Iowa City, IA; University of Iowa, Iowa City, IA

Body

Background: Hemoptysis and Dyspnea may be misleading in patients with thyroid carcinoma.

Clinical case: A 24-year female presented to student health service on several occasions complaining of shortness of breath and intermittent hemoptysis. She was considered to have asthma and/or bronchitis and was treated as such. Her symptoms, however, did not improve on any kind of consistent basis and she eventually presented to our Emergency Room with hemoptysis. Neck exam revealed a 3 cm right thyroid mass. Chest CT showed enlargement and inhomogeneity of the right lobe of the thyroid with endobronchial extension of the thyroid tissue into the lumen of the trachea resulting in a 50% luminal narrowing. Flexible fiber-optic laryngoscopy confirmed the presence of a right tracheal mass in the cervical trachea which was beefy red in appearance though not actively bleeding. Ultrasound examination showed a 2.5 x 2.6 x 1.9 cm nodule in the right mid lobe of the thyroid. Cytology revealed papillary thyroid carcinoma. She underwent total thyroidectomy as well as tracheal resection and the primary tumor measured 2.6 cm in greatest dimension extending into the posterior soft tissue as well as the trachea, both wall and mucosa. All margins were involved with tumor and there was vascular space invasion. 5 of 9 level VI nodes were positive for tumor. Post-operative TNM staging was T4aN1aMX. She then underwent radio iodine ablation 3 months later with 144.2 mCi of I-131. Post-therapy WBS showed foci of residual thyroid tissue in the thyroid bed with uptake in the lung concerning for microscopic disease. She is currently doing well on levothyroxin suppression without any evidence of tumor recurrence based on thyroglobulin measurements (Thyrogen-stimulated thyroglobulin < 0.4 ng/mL) and a negative neck ultrasound as well as PET-CT of the chest.

Conclusion: Hemoptysis is a rare but important symptom of differentiated thyroid carcinoma. In a previously reported 10 yr case series from UCLA, hemoptysis occurred in only 2 (0.4%) of 269 patients with papillary thyroid carcinoma both of whom had tracheal invasion. Our case highlights two points 1) Hemoptysis and other respiratory symptoms may be misleading in thyroid cancer 2) Fiberoptic Laryngoscopy is an effective means of establishing the diagnosis in this unusual subset of patients with thyroid carcinoma invading the trachea, and should be considered as an early diagnostic procedure in a patient with a thyroid mass and hemoptysis.

Nothing to Disclose: VGB, NP, GD

sort_order 2705
Pub # P3-636
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Thyroid Nodules & Cancer (1:30 PM-3:30 PM)
Title Severe Hyponatremia with Low Iodine Diet Prior to Radioactive Iodine-131 Ablation Therapy
Author String N Roopnarinesingh, A Thomas
Sinai Hospital of Baltimore, Baltimore, MD; Sinai Hospital of Baltimore, Baltimore, MD; Johns Hopkins University School of Medicine, Baltimore, MD
Body **Background:** Severe Hyponatremia (Serum Sodium [Ie] 125 mEq/L) in thyroid cancer patients on low iodine diets prior to radioactive iodine therapy occurs rarely, but is a clinically important issue particularly in elderly patients with polypharmacy.
Clinical Case: An 81 year old woman with newly diagnosed papillary thyroid cancer status post total thyroidectomy, hypertension, and hyperlipidemia was initiated on a low iodine diet 2 weeks prior to anticipated radioactive iodine therapy. She continued on her usual home medications including levothyroxine and hydrochlorothiazide (hctz) therapy with anticipated thyrotropin alfa use for ablation.
During the week of her scheduled radioactive iodine dose, she presented with symptoms of nausea, gait instability and an overall sense of feeling unwell prior to therapy. Laboratory data revealed a sodium of 108 mEq/L (135-145 mEq/L range), urine sodium 34 mmol/L, and the patient was admitted to the inpatient medicine service. 48 hours of intravenous normal saline 0.9% was infused which corrected the sodium to 132 mEq/L and resulted in resolution of her symptoms. The hctz therapy was discontinued permanently. The patient had normal adrenal function. The hyponatremia was attributed to hctz use and a low iodine diet in which the patient had severely restricted salt and solute intake. On followup, the patient was at baseline with serum sodium of 142 mEq/L.
Discussion: Hyponatremia in thyroid cancer patients on low iodine diets requiring hospitalization has previously been described in seven patients (five developed SIADH, one was on hctz and one eliminated all salt from the diet), the youngest of whom was 66 years of age. None of those reported patients had a serum sodium as low as 108 mEq/L. This patient's advanced age, hctz use, strict adherence to the low iodine diet as well as small body habitus all contributed to her severe, lifethreatening presentation.
Conclusion: Low iodine diets need to be monitored, particularly in elderly patients who may be on multiple medications which put them at risk for hyponatremia. Morris et al challenged the need for a strict low iodine diet in terms of outcomes in radioiodine treatment of thyroid carcinoma in comparison to those patients who followed a [ldquo]regular diet[rldquo] and avoided seafood, iodized salt and vitamins with iodine. This is an area of consideration, particularly in an elderly population. Patients embarking on a low iodine diet need careful education and appropriate supervision.

Morris LF, Wilder MS, Waxman AD, Braunstein GD; 2001; Reevaluation of the Impact of a Stringent Low-Iodine Diet on Ablation Rates in Radioiodine Treatment of Thyroid Carcinoma. Thyroid 11 (8): 749-755
Krishnamurthy VR, McDougall IR; 2007; Severe Hyponatremia: A Danger of Low-Iodine Diet. Thyroid 17(9): 889-892
Mohamed K.M. Shakir, inda S. Krook, Frank V. Schraml, James H. Hays, Patrick W. Clyde; 2008; Symptomatic Hyponatremia in Association with a Low-Iodine Diet and Levothyroxine Withdrawal Prior to I-131 in Patients with Metastatic Thyroid Carcinoma. Thyroid 18(7): 787-792

Nothing to Disclose: NR, AT

sort_order 2706
Pub # P3-637
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Thyroid Nodules & Cancer (1:30 PM-3:30 PM)
Title Thyroglobulin Antibodies and Aberrant Uptake on Whole Body Scan in a Patient with Papillary Thyroid Cancer and Cystic Fibrosis
Author String L Horine, M Agarwal
University of Arkansas for Medical Sciences, Little Rock, AR; Central Arkansas Veterans Healthcare System, Little Rock, AR
Body
Background: In papillary thyroid cancer (PTC) patients, serum thyroglobulin (TG) levels in conjunction with imaging studies including thyroid ultrasound and diagnostic whole-body radioactive iodine (RAI) scan are used to evaluate for recurrence or persistent disease. The postoperative surveillance is challenging in patients with cystic fibrosis (CF) and papillary thyroid cancer in the presence of thyroglobulin antibodies (TGAb) and abnormal radioiodine uptake in the lungs on whole-body RAI scan.
Case: A 26-year-old Caucasian female with CF, complained of tender nodule in her neck associated with hoarseness and difficulty swallowing. On examination, she had a mildly tender, mobile, solitary, two cm nodule in the left lobe of the thyroid. There was no cervical lymphadenopathy. The thyroid function tests were normal. The thyroid ultrasound showed an ill defined hypoechoic lesion measuring 2.6 cm in the maximum dimension. Fine needle aspiration biopsy was positive for malignant cells. She underwent total thyroidectomy with central neck dissection. The pathology revealed a 1.8 cm papillary carcinoma and 10 out of 31 lymph nodes were positive for malignant cells. Post surgery, she was treated with 149 mCi RAI. The post treatment whole-body RAI scan showed increased uptake in the neck consistent with residual thyroid tissue and abnormal increased tracer in the lung apices. The chest x-ray revealed interstitial markings in the upper lobes and apical pleural thickening on the left. A prior CT scan showed airspace opacities with air bronchograms and cystic bronchiectasis almost replacing the lung apices. She was started on TSH suppressive therapy. The presence of TGAb interfered with measurement of TG levels. Both TG and TGAb were measured by radioimmunoassay (RIA) and immunometric assay (IMA) methods. TGAb levels decreased with both methods on serial testing. The patient ultimately died of CF related complications.
Conclusion: Careful interpretation of the whole-body RAI scan in cystic fibrosis is important as false positive pulmonary uptake with low to undetectable TG in the absence of TGAb has been reported in patients with PTC (1, 2). It is not clear why radioiodine is concentrated in the pulmonary inflammation induced by CF. Likewise, abnormal lung uptake has been reported in bronchiectasis. In CF patients with TGAb, the trend in TGAb concentration on sequential measurements may be useful for long term surveillance (3).

1. Modoni S, et al., *Thyroid* 2005; 15:88-89.
2. Zanardelli M, et al., *J Cyst Fibros* 2008; 7:S24-25.
3. Kim WG, et al., *J Clin Endocrinol Metab* 2008; 93:4683-4689.

Nothing to Disclose: LH, MA

sort_order

2707

Pub #

P3-638

Session Information

POSTER SESSION: CLINICAL/TRANSLATIONAL - Thyroid Nodules & Cancer (1:30 PM-3:30 PM)

Title

Adult-Onset Still Disease as a Paraneoplastic Syndrome of Papillary Thyroid Carcinoma: A Case Report

Author String

A Gedik, V Gerdan, M Yilmaz, F Onen, A Comlekci
Dokuz Eylul University Medical Faculty, Izmir, Turkey; Dokuz Eylul University Medical Faculty, Izmir, Turkey

Body

INTRODUCTION: Thyroid papillary cancer is the most common thyroid malignancy. There have been a few case reports about paraneoplastic syndromes of papillary cancer. We here present a case of papillary thyroid cancer detected via its paraneoplastic syndrome, adult onset Still's disease (AOSD). CASE: A 57 year old woman presented to rheumatology outpatient clinic in our hospital complaining of high spiking fever, pruritic maculopapular rash and polyarthralgia. She was hospitalized with a presumptive diagnosis of AOSD and was consulted by our clinic about her thyroid nodule. Her past medical history was unremarkable except for controlled hypertension and hysterectomy. On physical examination, a body temperature of 39.4°C, blood pressure of 150/90 mmHg, excoriated maculopapular rash on trunk, upper extremities and gluteal region, a fixed nodule in right lobe on thyroid palpation and a right cervical lymph node were detected. Laboratory evaluation revealed, WBC:20.8x10³ U/L (4-10.3 x10³) AST:187 U/L (5-34), ALT:151 U/L(0-55), CRP:240 mg/L (0.1-8.2), ESR:48 mm/hr (0-20), ferritin:13347 ng/ml (5-148), TSH:1.07 uIU/ml (0.4-5), FT4:1.16 ng/dl (0.8-1.9), anti-TPO:197 IU/ml (0-50). A dominant nodule with a diameter of 20x16x16 mm in right thyroid lobe and right cervical reactive lymph nodes were established on neck sonography. Thorax and abdominal tomography were negative for a possible underlying malignancy. Fine needle aspiration biopsy of the thyroid nodule was suspicious for malignancy. She underwent total thyroidectomy which revealed a pathological diagnosis of papillary thyroid cancer (17 mm in diameter with positive lymphatic vessel invasion without capsular, vascular, intrathyroidal invasion). Interestingly, her pruritic skin rash, fever and acute phase reactants including serum ferritin levels (78.1 ng/ml) dramatically resolved immediately after thyroid surgery. After receiving radioiodine ablation therapy, TSH suppression therapy has been started recently. The AOSD in this patient is accepted as a paraneoplastic syndrome since the disease resolved after removal of the cancer tissue from the body. CONCLUSION: Adult onset Still's disease is a diagnosis of exclusion. The resolution of the symptoms and signs of AOSD in our patient after thyroidectomy suggests that AOSD had developed as a paraneoplastic syndrome. This report is the first case in which the relationship between thyroid papillary cancer and AOSD as a paraneoplastic syndrome could be defined.

Nothing to Disclose: AG, VG, MY, FO, AC

sort_order 2708
Pub # P3-639
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Thyroid Nodules & Cancer (1:30 PM-3:30 PM)
Title Pitfalls of a Pituitary Mass Presentation -- A Rare Form of Metastatic Thyroid Carcinoma
Author String CS Liboni, ML Sulzbach, JR de Sa, AM Lengyel, RMdB Maciel, JRM Martins
Universidade Federal de São Paulo - UNIFESP/EPM, São Paulo, Brazil

Body Background: Thyroid cancer is the most common endocrine neoplasia and the vast majority of patient has a good outcome. On the other hand, less than 10% of patients have systemic metastases on first presentation and, in these cases, lung and bone are the preferential sites involved. Intracranial metastases associated with these tumors are rare and sellar metastases are only scarcely described in the medical literature. Clinical case: A 55-year-old woman presented in our service with a complaint of 3-month diplopia. She had hypertension and a history of a follicular thyroid carcinoma 7 years before. She had been submitted to a total thyroidectomy and ¹³¹I ablation twice (200 mCi and 350 mCi, seven and four years ago, respectively) on another service and she told us to believe that was cured. On physical exam she had a VI cranial-nerve palsy. Computed tomography revealed a large mass (4.5 x 2.4 cm) contiguous to the pituitary and invading the base of her skull. The hypotheses made were invasive pituitary macroadenoma or cordoma. Anterior and posterior hypopituitarism was excluded. Then, she underwent transsphenoidal removal of the mass. Pathological examination revealed an epithelial neoplasm with immunohistochemical analyses suggestive of neuroendocrine neoplasia. Recording her previous exams we noticed that the last ¹³¹I whole body scan was negative but her thyroglobulin (Tg) was 10,631ng/dL at that time. In addition, serum Tg after surgery was higher than 1,000 ng/dL and immunohistochemical for Tg on pituitary mass was positive. Further investigation found bone metastasis in skull, ribs, scapula and various vertebrae and the sellar metastasis kept growing. Radiotherapy was used to treat some lesions. She also took chemotherapy for 4 months with no response on metastasis and with a lot of side effects. The chemotherapy was suspended and she is taking intravenous pamidronate to treat hypercalcemia and levothyroxine to suppress TSH. Conclusion: Sellar metastases from differentiated thyroid cancer are an exceedingly rare condition. Only 14 cases have been described at that time. Autopsy studies have been shown that in about two-thirds of these cases the pituitary glands are macroscopically normal and, sometimes, there are not association with previous clinical symptoms. However, in patients with known primary cancer, a pituitary lesion should be considered as a pituitary metastasis of that tumor.

(1)Haugen BR, Kane MA. J Clin Endocrinol Metab 2010; 95:987

(2)Prodan F, Pagano L, Belcastro S, Golisano G, Busti A, Sama M, Caputo M, Bellone S, Voci A, Valente G, Aimaretti G. Thyroid 2010; 20:823

Nothing to Disclose: CSL, MLS, JRdS, AML, RMdBMM, JMM

sort_order 2709
Pub # P3-640
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Thyroid Nodules & Cancer (1:30 PM-3:30 PM)
Title Prediction of Diffuse Thyroid ¹⁸F-FDG Uptake after Treatment of Breast Cancer
Author String JH Kang, YB Lim, BG Choi, MR Kim, YK Jeon, SS Kim, BH Kim, YK Kim, IJ Kim
Pusan National University Hospital, Pusan, Korea; Kim Yong Ki Internal Medicine Clinic, Pusan, Korea
Body **Purpose:** The aim of the present study was to define predictive factors for the development of diffuse thyroid uptake in F-18 FDG after treatment of breast cancer without prior thyroid disorders.
Methods: A retrospective review of the PET-CT database revealed that 290 female patients underwent PET-CTs both before and after breast surgery. Of these 290 patients, 246 were enrolled in this study, and 44 were excluded due to previous thyroid disorders and other concurrent malignant disorders.
Results: Of the 246 patients, 23 (9.3 %) showed new diffuse thyroidal uptake on PET-CT during the follow-up period. The median follow-up period was 21.1 months (range, 3.1-47.3 months). Patient with new thyroid FDG uptake were younger than those without ($P = 0.011$). Patients with new thyroid FDG uptake underwent radiotherapy more frequently (82.6 % vs. 49.8 %, $P = 0.003$). Age (age ≥ 55 years; HR = 0.15, 95% CI 0.03-0.65; $P = 0.012$), bilaterality of breast cancer (HR = 3.87, 95% CI 1.02-14.62; $P = 0.046$) and radiotherapy (HR = 3.06, 95% CI 1.03-9.16; $P = 0.045$) showed independent association with new thyroid FDG uptake in multivariate analysis. Patients with new thyroid FDG uptake received larger radiation doses than those without (56.3 vs. 32.4 Gy; $P = 0.003$). There was a significant correlation between radiation dosage and TSH level during the follow-up period ($r = 0.182$, $P = 0.006$).
Conclusions: The results of this study suggest that radiotherapy in breast cancer may be an independent predictive factor for the development of new diffuse thyroidal uptake in PET-CT during follow-up. More careful observation of thyroid disorder is needed in younger women with radiotherapy during follow-up.
Nothing to Disclose: JHK, YBL, BGC, MRK, YKJ, SSK, BHK, YKK, IJK

sort_order 2710
Pub # P3-641
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Thyroid Nodules & Cancer (1:30 PM-3:30 PM)
Title Two Cases of Metastatic Struma Ovarii: Clinical Presentation and Management
Author String RA Steinman, I De Castro, VU Chengazi, EJ Giampoli, SR Hammes, R Hou
University of Rochester School of Medicine, Rochester, NY
Body
Background: Struma ovarii is a rare form of ovarian teratoma in which thyroid tissue is the predominant histological component. The presence of thyroid malignancy in struma ovarii occurs in less than 5% of all cases of struma ovarii with metastatic disease reported in 5-6% of malignant struma ovarii cases. We describe two patients with metastatic malignant struma ovarii and their management.
Clinical Cases: Patient GG is a 22-year-old female with malignant struma ovarii of the papillary thyroid carcinoma subtype confined to the left ovary. She was treated with a left laparoscopic salpingo-oophorectomy. Total thyroidectomy excluded primary thyroid cancer metastasis to the ovary. A post-operative radioactive iodine scan revealed foci of iodine uptake in the thyroid and left anterior pelvis. Subsequently, she was treated with I-131 ablation. Six months after the radioactive iodine ablation, an abdominal and pelvic CT scan did not reveal an anterior pelvic abnormality and her TSH-stimulated thyroglobulin has been negative.
Patient MB is a 49-year-old female with a right malignant struma ovarii of the follicular variant of papillary thyroid carcinoma identified on surgical pathology after having presented with ovarian torsion in 1996. An evaluation of progressive left hip pain in 2007-2008 identified metastases to the left hip and abdomen. She was treated with resection of the pelvic tumor, total thyroidectomy and I-131 ablation with eventual resolution of the abdominal and left hip foci. Thyrogen-stimulated I-131 total body scans on two consecutive years showed no evidence of recurrent or residual iodine avid disease. Her thyroglobulin levels continue to be followed.
Conclusion: Metastatic struma ovarii is rare. We present two cases of metastatic malignant struma ovarii, one with metastasis to the left anterior pelvis (as determined by clinical assessment) and another with histologically-confirmed metastasis to the left hip as well as abdominal metastasis. In both cases, total thyroidectomy was needed to facilitate treatment and post-operative management. This illustrates the complexity of managing malignant struma ovarii. A multidisciplinary approach that includes primary surgical resection with salpingo-oophorectomy, prophylactic total thyroidectomy, radioactive iodine ablation, and long-term thyroid hormone suppression may be recommended.
Nothing to Disclose: RAS, IDC, VUC, EJG, SRH, RH

sort_order 2711
Pub # P3-642
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Thyroid Nodules & Cancer (1:30 PM-3:30 PM)
Title Detection of Metastatic Thyroid Carcinoma by ¹⁸F-Fluorodeoxyglucose (FDG) Positron Emission Tomography Scan (PET) in Patients with Modestly Elevated Serum Thyroglobulin Levels and Negative Iodine-123 Whole Body Scan
Author String TD Hoang, VQ Mai, PW Clyde, MKM Shakir
National Naval Medical Center, Bethesda, MD
Body Background: Patients (pts) with recurrent thyroid papillary carcinoma (Ca), negative whole body scan and modestly elevated serum thyroglobulin levels (Tg) (<50 ng/mL) present a therapeutic dilemma. It is preferable to surgically remove metastatic thyroid Ca prior to ¹³¹I treatment. We report 3 pts with PET done while in iodine-depleted state (urine iodine <50 mcg/24H) in order to localize residual Ca so that excision could be performed prior to ¹³¹I ablation.
Clinical cases:
Case 1: A 70 y/o male, s/p thyroidectomy and ¹³¹I treatment (191 mCi) for a 3cm tumor with central cervical lymph node metastasis in 2002, underwent retreatment with 145 mCi ¹³¹I in 2003. In 2010 a rhTSH stimulated Tg of 29 ng/mL (with negative Ab) was detected. At this time a T4 withdrawal ¹²³I scan (TSH 144 uIU/mL, Tg 47 ng/mL) was negative for metastatic Ca. However, a PET suggested metastasis to a right submandibular lymph node. Pt underwent resection and pathology confirmed metastatic Ca. Following dosimetry he was treated with 180 mCi ¹³¹I. Post-treatment scan also did not reveal any metastatic Ca.
Case 2: A 38 y/o male underwent thyroidectomy (right 3.7cm papillary Ca with 4 positive lymph nodes) and post-rhTSH ¹³¹I ablation with 150 mCi in 7/2009. T4 withdrawal in 6/2010 revealed a serum Tg of 37 ng/mL and TSH of 132 uIU/mL. At this time an ¹²³I scan was negative for metastatic Ca but PET revealed 2 foci at level VI lymph nodes in the neck. During surgery 3 metastatic lymph nodes were removed. Following dosimetry, pt was treated with 385 mCi ¹³¹I in 11/2010. Post-treatment survey revealed only physiologic uptake.
Case 3: A 78 y/o female, s/p thyroidectomy and ¹³¹I treatment in 1978, has undergone 4 subsequent surgeries to remove recurrent tumor followed by ¹³¹I treatments. In 5/2010 she underwent T4 withdrawal and laboratory values were Tg 25 ng/mL, TSH 220 uIU/mL. ¹²³I scan did not show iodine-avid thyroid tissue. However, PET revealed a 2 cm focus in the left neck. Pt underwent left cervical lymph node dissection and pathology confirmed metastatic Ca. Pt was subsequently treated with 190 mCi ¹³¹I. Post-treatment scan did not show any residual foci.
Conclusions: Previous studies have shown that there is a high incidence of true-positive PET scans in pts with high serum Tg levels (>100 ng/mL). Our 3 cases show that even with modestly elevated Tg levels (<50 ng/mL), PET done while in iodine-depleted state can localize metastatic thyroid Ca in pts with negative scan.
Schluter B et al. J Nuc Med 2001: 42: 71-76.
Nothing to Disclose: TDH, VQM, PWC, MKMS

sort_order 2712
Pub # P3-643
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Thyroid Nodules & Cancer (1:30 PM-3:30 PM)
Title Development of Hashimoto Thyroiditis with Hypothyroidism in a Patient with a TSH-Producing Pituitary Adenoma: An Extremely Rare Association
Author String CK Chew, R Dalan
Tan Tock Seng Hospital, Singapore
Body
Introduction : TSH producing pituitary adenomas are extremely rare and is present in only 1-2% of pituitary adenoma patients (1). The association of this condition with autoimmune thyroiditis and hypothyroidism has been rarely reported in the literature but its development can effectively treat the patient of the hyperthyroid state.
Case Presentation : A 31 years old lady first presented to obstetrician with fatigue, exertional dyspnoea and palpitations at 12 weeks of pregnancy. Thyroid function test showed fT4 of 34 pM (RI: 8-21) and TSH of 5.99mIU/L (RI: 0.34-4.5). She was started on 50 mg of Propylthiouracil which was discontinued on delivery. However her symptoms did not improve and her thyroid function test constantly showed high fT4 with non-suppressed TSH concentrations. Two weeks after delivery her fT4 was 34pM and TSH was 5.99 mIU/L. She was tachycardic with a pulse rate of 100/min and blood pressure 110/66 mm hg. She did not have a goitre or any signs of thyroid eye disease. A repeat thyroid profile revealed : fT4: 24.9 pM, TSH: 8.52 mIU/L, fT3 :16.9 pM (RI: 4.3-8.3), TRAb : 0.4 IU/L (RI: 0-1.5), TPO Ab : 2253 IU/ml (RI < 50). The differential diagnosis at this point was TSH resistance syndrome versus TSH producing pituitary adenoma. A MRI of the pituitary showed a 2.5 x 2.3 mm microadenoma in the left anterolateral aspect of the pituitary gland. Unfortunately before any further dynamic tests could be done, 2 months later, she presented with weight gain of 3 kg and with pulse rate of 67/minute and blood pressure of 119/81 mmHg. Her thyroid function test showed fT4 of 3.0 pM and TSH of 18.24 mIU/L and a subsequent test 2 weeks later showed fT4 2.0 pM and TSH of 48.41mIU/L suggestive of hypothyroidism likely secondary to autoimmune thyroiditis. At this time thyroxine was started and titrated upto 100 mcg daily. Approximately 2 months after institution of thyroxine 100 mcg daily her fT4 was 4.0 pM and TSH 48.26mIU/L.
Discussion and Conclusion : TSH secreting pituitary adenomas tend to present much later in women and tumors tend to be very small with few symptoms (1). The association of Hashimoto's thyroiditis developing after presentation of a TSH producing pituitary adenoma resulted in the biochemical remission of hyperthyroidism but the negative feedback from hypothyroidism may result in increase in the size of the pituitary adenoma over years (1). Hence this patient will need to be followed up closely.

1. Mindermann T, Wilson CB. Thyrotropin-producing pituitary adenomas. J Neurosurg 1993;79:521-7.

Nothing to Disclose: CKC, RD

sort_order 2713
Pub # P3-644
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Thyroid Nodules & Cancer (1:30 PM-3:30 PM)
Title Papillary Carcinoma Mimicking Subacute Thyroiditis in a Postpartum Female
Author String C Gordner, P Butler, K Shoukri, I Osakwe
Baystate Medical Center, Springfield, MA

Body
Introduction: Thyroid cancer is increasing in incidence with papillary carcinoma being the most common subtype. There is a female preponderance with most cases occurring in the fourth and fifth decade. About 10% of thyroid cancers occurring during the reproductive years are diagnosed during pregnancy or in the first year after birth. Some authors have suggested an increased incidence of thyroid cancer during pregnancy, perhaps as a result of a pregnancy-associated trophic effect on the thyroid gland. We are unaware of any case reports of papillary carcinoma mimicking subacute thyroiditis in the postpartum period. We now present a postpartum female who presented with a painful thyroid mass which was subsequently diagnosed as papillary carcinoma.
Clinical Case: A 20 year old previously healthy female presented at 9 weeks postpartum with a painful left sided thyroid mass. The patient reported an exquisitely tender mass which had increased in size over the past 2 months. She denied any fevers, heat-intolerance, palpitations or tremulousness and there was no preceding illness. Physical exam identified an enlarged left thyroid lobe without focal nodule with extreme tenderness which limited exam. There was no overlying erythema or cervical lymphadenopathy. She had no family history of thyroid carcinoma or history of radiation exposure. Thyroid function tests were obtained and were normal with TSH 2.03 mIU/mL (0.4-4.0), FT4 0.97 ng/dL (0.7-1.8) and inflammatory markers were low with CRP < 0.1 mg/dL (0-0.5) and ESR 7 mm/hr (0-20). She was subsequently referred for thyroid ultrasound which identified a hypoechoic nodule measuring 3.03 cm in the largest dimension with indistinct margins and no internal vascularity. An FNA was performed and histology was consistent with papillary carcinoma. The patient was subsequently referred for total thyroidectomy.
Clinical Lessons: This case reminds clinicians that rapidly growing thyroid cancer may be tender and mimic subacute thyroiditis. Hormonal factors and the immune dysregulation of pregnancy may play a role in the presentation of thyroid cancer in the postpartum period.

Nothing to Disclose: CG, PB, KS, IO

sort_order 2714
Pub # P3-645
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Thyroid Nodules & Cancer (1:30 PM-3:30 PM)
Title Poorly Differentiated Thyroid Tumor: A Rare Case Report
Author String MF Ronsoni, CG Pereira, JB Daltrazo, MHB Canalli, ME Kowalski, DS Vieira, JC Nunes, MH Coral, A Hohl
University Hospital - Federal University of Santa Catarina, Florianopolis, Brazil; University Hospital - Federal University of Santa Catarina, Florianopolis, Brazil
Body **Background:** Poorly differentiated thyroid carcinoma occurs rarely and, is described with more aggressive behaviour, poorer prognosis, and higher mortality than well differentiated thyroid carcinoma. This type of carcinoma is a still a challenge both for pathologists and clinicians (1).
Case presentation: A 35 y.o. white, female, with a nodule arising anterior cervical region, an increase of 6 months. Ultrasound thyroid nodule shows hypoechoic, homogenous, well-contoured, situated on the isthmus, extending to the thyroid lobes, especially the left, measuring 3.6 x 2.6 x 1.9 cm (V: 9.7 cm³). Power Doppler vascularity preferring that more central (Chammas type 3). According nodule inferiorly (or lobulation of the former) with 1.8 x 1.2 x 1.1 (V: 1.1 cm³), both suggestive of colloid goiter. Fine needle aspiration biopsy compatible with follicular lesion, favored for follicular neoplasm. Underwent total thyroidectomy in May 2010. Histopathological: Poorly differentiated carcinoma with oxyphilic cells and mucoid matrix, located in the isthmus and left lobe (5.6 x 4.4 x 2.5 cm). Multiple microscopic foci lobe, presence of vascular infiltration, this extension extrathyroid, circumferential margin committed in the isthmus, metastasis in seven of nine lymph nodes examined (pT4a N1b). Serum thyroglobulin 0.91 ng/mL (nl <55 ng/mL), anti-thyroglobulin antibodies <20 (nl <40), TSH 0.24 [mu]IU/ml (nl 0.4 to 4.0 [mu]IU/ml), calcitonin <2.0 pg/mL (nl <5.0 pg/mL). Immunohistochemistry: positive TTF1, thyroglobulin and calcitonin negative, focally positive p53, CEA and p63 negative. Less than 5% of neoplastic cells in cycle (MIB1/Ki63). Emergence of bilateral cervical lymphadenopathy, painful, at 30 days postoperatively. Underwent bilateral cervical lymph node dissection with metastases present in several lymph nodes examined.
Clinical lessons/Conclusion: Together with clinical and histological results of immunohistochemical study point to the diagnosis of poorly differentiated carcinoma / undifferentiated spindle-cell and mucus-secreting, highly aggressive clinical point of view. Unfortunately it's a case of very poor prognosis for this tumor does not express thyroglobulin, not responding to radioactive iodine and also, are generally resistant to radiotherapy and chemotherapy. Due to poor prognosis, medical follow-up remains uncertain.

(1) Walczyk A, Kowalska A, Sygryt J. The clinical course of poorly differentiated thyroid carcinoma (insular carcinoma) - own observations. Endokrynol Pol. 2010 Sep-Oct;61(5):467-73.

Nothing to Disclose: MFR, CGP, JBD, MHBC, MEK, DSV, JCN, MHC, AH

sort_order 2715
Pub # P3-646
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Thyroid Nodules & Cancer (1:30 PM-3:30 PM)
Title Nine Years of Follow-Up of a Patient with Thyroid Metastasis from Clear Cell Carcinoma: A Case Report
Author String JB Daltozo, CG Pereira, MF Ronsoni, MH Coral, A Hohl
University Hospital - Federal University of Santa Catarina, Florianopolis, Brazil

Body

Background: Nodularity of thyroid tissue is extremely common in females. In a large population study (Framingham, MA), as an example, clinically apparent thyroid nodules were present in 6.4 percent of women (1). Kidney cancer, and especially clear cell carcinoma, has an unpredictable clinical course, with metastatic potential that is variable over time and in location. Metastasis to the thyroid is rare (2). The median survival for patients with stage IV disease is only 16 to 20 months in contemporary reports, and the five-year survival rate is less than 10 percent for patients with distant metastases (3,4).

Case presentation: A 68 y.o. white, female, with the appearance of asymptomatic increased volume cervical, in May 2001. History of left nephrectomy for renal cell carcinoma, in May 1995, keeping oncology follow. Physical examination: thyroid asymmetric, bulky, more marked on the left, painless, irregular surface. TSH 1.68 [mu]IU/mL (nl 0.35 to 5.5 [mu]IU/mL), free T4 1.2 ng/dL (nl 0.89 to 1.76 ng/dL). Anti-TPO antibodies negative. Chest x-ray with tracheal deviation to the right. Cervical ultrasonography showed substernal goiter. Performed 2 fine needle aspiration biopsy: first diagnosed colloid goiter and second with follicular lesion. Underwent total thyroidectomy in August 2002. Histology revealed a clear cell carcinoma in two nodules in left lobe (the larger 4.0 x 4.0 x 3.5 cm and the smallest 3.5 x 2.5 x 2.0 cm) and adjacent lymphocytic thyroiditis. Immunohistochemical CD10 positive and tireoglobulin negative. Restaging at the time showed no other metastatic lesions. Oncological follow-up without new evidence of neoplastic foci. Currently, outpatient follow, treated with levothyroxine 100 meg daily, statins and calcium, normal bone densitometry and TSH 0.58 [mu]IU/mL (nl 0.35 to 5.5 [mu]IU/mL), free T4 1.36 ng/dL (nl 0.89 to 1.76 ng/dL).

Clinical lessons/Conclusion: Metastatic thyroid cancer is a rare condition, however, must be included in the differential diagnosis of nodules of this gland, particularly with the report of a previous malignancy. The advances allowed by immunohistochemistry facilitated the diagnosis, and although the etiology and prognosis of advanced renal tumors, the patients had good clinical outcome with disease-free survival of 9 years.

- (1) Vander JB, Gaston EA, Dawber TR: The significance of nontoxic thyroid nodules. Final report of a 15-year study of the incidence of thyroid malignancy. *Ann Intern Med.* 1968;69(3):537-40.
- (2) Morvan JB, Veyri[egrave]res JB, Mimouni O, Chathelinaud O, Allali L, Verdalle P. Clear-cell renal carcinoma metastasis to the base of the tongue and sphenoid sinus: Two very rare atypical ENT locations. *Eur Ann Otorhinolaryngol Head Neck Dis.* 2010 Dec 30.
- (3) Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol.* 1999;17(8):2530-40.
- (4) Mekhail TM, Abou-Jawde RM, Boumerhi G, Malhi S, Wood L, Elson P, Bukowski R. Validation and extension of the Memorial Sloan-Kettering prognostic factors model for survival in patients with previously untreated metastatic renal cell carcinoma. *J Clin Oncol.* 2005;23(4):832-41.

Nothing to Disclose: JBD, CGP, MFR, MHC, AH

sort_order 2716
Pub # P3-647
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Thyroid Nodules & Cancer (1:30 PM-3:30 PM)
Title Oncocytic Variant of Papillary Thyroid Cancer with Thyroid Hemiogenesis
Author String AM Ayyagari, DJ Rubin
Temple University Hospital, Philadelphia, PA

Body

Objective: To report a rare case of oncocytic variant of papillary thyroid cancer (OVPTC) with coexistent thyroid hemiogenesis.

Case Report: A 60 year-old female with a history of hypothyroidism presented with papillary thyroid cancer diagnosed by fine-needle aspiration biopsy. Two thyroid ultrasounds done at 8-year intervals for goiter revealed a right lobe measuring 1.9 x 1.2 cm with multiple calcified nodules, the largest of which measured 1.2 cm. The left lobe was not visible. There were multiple enlarged right jugular lymph nodes. CT scan of the neck revealed a 1.3 x 0.8 cm calcified right thyroid nodule and multiple cervical lymph nodes. Intraoperatively, the left thyroid lobe could not be located. Pathology revealed a 3 cm tumor in the right lobe, partially surrounded by a fibrous capsule with psammoma bodies, and OVPTC with capsular and perithyroidal soft tissue extension was diagnosed. None of the eleven lymph nodes resected contained cancer. The post-I131 treatment scan showed uptake in a right supraclavicular lymph node.

Discussion: OVPTC is a rare variant of PTC with distinctive clinical and histopathological features. Although OVPTC is reported to comprise 1-11% of all PTC cases, it may be under recognized in clinical practice. OVPTC is most common in women 60-70 years old. It has a distinct morphology characterized by complex branching papillae with predominant oncocytes, large polygonal cells with eosinophilic, granular cytoplasm, surrounding a thin fibrovascular core. The malignant potential and clinical behavior is variable, which may be due to the lack of precise histological diagnostic criteria. Although the prognosis of OVPTC appears similar to that of classic PTC, certain features are of concern. The oncocytic variant is less iodine avid than classic PTC, rendering it less responsive to radioactive iodine. Furthermore, OVPTC may be more locally invasive than typical PTC. Post-surgical ablation therapy and monitoring may need to be more aggressive than for classic PTC. Thyroid hemiogenesis is rare, with prevalence estimated at 0.05-0.2% of the general population. There are very few reported cases of thyroid cancer in the setting of thyroid hemiogenesis. To our knowledge, there are no reported cases of OVPTC with hemiogenesis. Greater awareness of OVPTC may lead to improved outcomes for affected patients.

Nothing to Disclose: AMA, DJR

sort_order 2717
Pub # P3-648
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Thyroid Nodules & Cancer (1:30 PM-3:30 PM)
Title Cardiac Metastasis of Papillary Carcinoma
Author String LG Rodriguez, JA Gamboa, A Rolon
Hospital Miguel Hidalgo, Aguascalientes, Mexico
Body
INTRODUCTION.
The thyroid cancer represents the 1.3 % of cancer in adult. Differentiated thyroid cancer that arises from the thyroid follicular cells accounts for more than 90 % of thyroid cancer cases diagnosed. The 5-year survival rate in patients presenting with distant metastatic disease can be as low as 56 %(1).
CLINICAL CASE
52 year old man, with a history of smoking, 3 months before admissions he noticed nodule of 2.5 cm in right thyroid lobe. In a sudden had vomiting and syncope, which was transferred to an emergency of this hospital, supraventricular tachycardia was detected with heart rate of 190 per minute and cardioversion was performed. The thyroid profile showed TSH 1.2 mUI/ml (range 0.5 to 4 mUI/ml), Free T4 ng/dl (range 0.8 to 1.9 ng/dl), and total T4 8 [mu]g/dl (range 4 to 12 [mu]g/dl).
Ultrasound confirmed a 2.5 cm nodular lesion in right lobe of the thyroid and 3 ipsilateral cervical lymphadenopathy, where as echocardiography and MRI showed a 5 cm mass in right ventricle.
FNAB of thyroid nodule and heart lesion biopsy were performed, which reported as papillary cancer with immunohistochemistry positively for thyroglobulin.
Total thyroidectomy and anterior neck dissection was operated. But at the time of preparation for administration of radioactive iodine 131 ablation and radiation therapy to cardiac injury, the patient had sudden death associated with supraventricular tachycardia.
CONCLUSION.
Most patients with thyroid cancer present with an asymptomatic painless mass in the thyroid that is detected by the patient or family physician, should be educating the health personnel to refer promptly for treatment in these patients to specialized care centers, and to avoid the appearance of distant metastases. Since the 5-year survival of patients with thyroid cancer and distant metastases, is reduced by 98% to less than 56%.

(1) R.Michael Tuttle et al. Papillary thyroid cancer: Monitoring and therapy. Endocrinol Metab Clin N Am 36(2007) 753-778.

Nothing to Disclose: LGR, JAG, AR

sort_order 2718
Pub # P3-649
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Thyroid Nodules & Cancer (1:30 PM-3:30 PM)
Title How Benign Is Iodine? Clinical Complication in the Setting of RAI (Radioactive Iodine) Therapy for Metastatic Thyroid Carcinoma, Follicular Variant
Author String SB Mayer
Duke University Medical Center, Durham, NC
Body Background: In the US, based on the Rev. Am. Thyroid Assoc. Mgt. Guidelines, RAI is a mainstay of therapy for stage IV-V differentiated thyroid CA. Given its frequency of use, keeping abreast of untoward effects of RAI therapy is critical.
Clinical Case: 52 y.o. lady with a Hx of infiltrating ductal breast CA s/p wide excision, adjuvant chemotherapy and radiation therapy had an incidental finding of a calcified LN in the paratracheal region seen on CXR, 7 years later, leading to PET scan evaluation. Focal intense FDG activity, localizing to two borderline enlarged right cervical LNs as well as an enlarged enhancing right paraesophageal LN led to core biopsy, path read as metastatic thyroid CA, follicular variant. Classified as stage 4A T1 N1b M0 at time of total thyroidectomy and right modified radical neck dissection with 11/11 + lymph nodes, she was recommended for RAI therapy. Post-op total body iodine scan showed focal increased activity in the thyroid bed and neck with uptake in the thyroid bed of 17.14%. Pre-op thyroglobulin level 98.3 ng/ml, pre-RAI fell to 15.3 [<33.0]. Pre-RAI TSH 50.10 uIU/mL [0.34-5.66], FT4 0.33 ng/dL [0.52-1.21]. After two wks of a low iodine diet she proceeded to I-131 radioablation with 186 mCi. A post RAI total body iodine scan showed a focus of intense uptake in the left posterior paratracheal region, and diffuse uptake in the neck extending into the parasternal region of the upper chest in a very unusual pattern. No clear anatomic correlate was seen on CT. Subsequent to the procedure, the next day at home, she noted a hoarse voice, SOB, chest heaviness, wheezing, and neck swelling. In the ED, she received Benadryl, Famotidine, NS, and decadron IV and was readmitted. On PE her throat had no tonsillar inflammation, no airway obstruction, her neck was mildly tender with soft tissue swelling, no crepitus, no cervical LAD. Trachea was midline. No stridor. Laryngoscopic evaluation demonstrated evidence of angioedema but no airway collapse. With ongoing therapy for RAI induced thyroiditis with IV steroid and anti-histamine therapy tumescence improved, neck diameter decreased by 1 cm prior to discharge on a rapid steroid taper.
Conclusion: It behooves physicians, who refer or administer RAI therapy, to remain vigilant for complications such as RAI induced thyroiditis. Furthermore, elevated uptake on iodine scan, despite falling thyroglobulin levels, requires discussion regarding timing of therapy and need for neck re-exploration.

Nothing to Disclose: SBM

sort_order

2719

Pub #

P3-650

Session Information

POSTER SESSION: CLINICAL/TRANSLATIONAL - Thyroid Nodules & Cancer (1:30 PM-3:30 PM)

Title

Extensive Metastatic Thyroid Papillary Carcinoma as an Initial Presentation of a Well-Differentiated Thyroid Carcinoma

Author String

JJ Shin, E Nunez

Veterans Affairs New Jersey Healthcare System, East Orange, NJ; UMDNJ-New Jersey Medical School, Newark, NJ

Body

We present an unusual case of a 66 year old man with a large well-defined heterogeneous mass in the right neck measuring approximately 14 cm x 8.5 cm x 11 cm in greatest dimensions. The patient presented to the Endocrine service after having a radical neck dissection for the mass which had been growing slowly over the past 5 years. There was no radiographic or clinical evidence of a thyroid mass. Gross examination revealed a complex, solid and cystic hemorrhagic and necrotic mass. Microscopic examination revealed metastatic papillary thyroid carcinoma. The patient had a total thyroidectomy two weeks after the radical neck dissection. No significant thyroid lesions were noted on gross examination. Microscopic examination revealed a microscopic (1.4 mm) focus of papillary thyroid carcinoma in a section of the mass. On subsequent whole body scanning with I-131 sodium iodide the patient was found to have right parotid gland and right lower neck lymph node involvement. Considering the extrathyroidal involvement, the patient was given therapy with 123mCi of I-131. The post-therapy scan again showed the same involvement of the parotid gland and lymph node noted in the pre-therapy scan. This is an unusual presentation of thyroid micropapillary carcinoma, initially presenting as metastatic thyroid carcinoma in a radical neck dissection.

Nothing to Disclose: JJS, EAN

sort_order 2720
Pub # P3-651
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Thyroid Nodules & Cancer (1:30 PM-3:30 PM)
Title Cerebral Edema: An Unusual Complication of Radioactive Iodine Therapy for Papillary Thyroid Carcinoma
Author String MT Cating-Cabral, IT Isip-Tan
University of the Philippines - Philippine General Hospital, Manila, Philippines
Body
Background
Among the complications of radioactive iodine (¹³¹I) therapy for thyroid remnant ablation, cerebral edema is the most important acute complication, usually due to swelling of brain metastases. This is a report of a case where cerebral edema developed after ¹³¹I therapy in the absence of such metastases.
Clinical Case
A 30-year-old female with papillary thyroid carcinoma Stage I (T₃N₀M₀) received ¹³¹I 100 mCi and 6 hours later she complained of lightheadedness, nausea and vomiting. This persisted for 24 hours, but adequate oral fluid intake was maintained and some relief obtained with metoclopramide. 2 hours after being seen on the second hospital day she was found unconscious and could not be roused. Physical examination was unrevealing. Significant laboratory results showed hyponatremia (serum sodium: 118, reference values 140-148 mmol/L), and normoglycemia. Differential diagnoses included encephalopathy due to the hyponatremia and sodium correction was started. Another was possible cerebral edema from undetected brain metastases and dexamethasone was given. Plain cranial computed tomographic (CT) scan then showed acute bilateral frontal infarcts with mild pontine and cerebral edema which was treated with mannitol and furosemide. The patient regained consciousness the next day, 16 hours after the syncopal episode. Physical examination did not reveal any signs of an acute cerebral event. Repeat serum sodium was 128. A follow up cranial CT scan with contrast showed no evidence of the previously seen frontal infarcts with resolution of the cerebral edema. A post-ablative whole body scan 7 days after ¹³¹I showed only functioning residual thyroid tissue in the anterior neck.
The etiology of syncope in this case is likely multifactorial. Cerebral edema after ¹³¹I is rare and has been reported to occur due to edema or hemorrhage of brain metastases (1), which were not found in this case. The patient presented with symptomatic hyponatremia which is also uncommon in the setting of ablative ¹³¹I. This has been seen in elderly patients placed on low iodine diets prior to ¹³¹I who equate this with a low sodium diet(2). Patients who receive ¹³¹I are also advised liberal fluid intake during their hospital stay, and this along with vomiting may have been contributory.
Conclusion
The development of cerebral edema after ¹³¹I is uncommon and may occur in the setting of hyponatremia exacerbated by a low iodine diet and excessive fluid intake.

(1) Datz FL, J Nucl Med 1986; 27: 637-640
(2) Shakir MK et al., Thyroid 2008; 18: 787-792

Nothing to Disclose: MTC-C, ITI-T

sort_order 2721
Pub # P3-652
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Thyroid Nodules & Cancer (1:30 PM-3:30 PM)
Title Papillary Carcinoma Presenting as Massive Retrosternal Goiter with Atypical Symptoms and Successful Surgical Management
Author String H Wang, MI Goodchild, PC Siwawa, S Nazir, AP Singh, AR Go, MY Jun, D Cai, AP Asarian, PJ Pappas
The Brooklyn Hospital Center, New York, NY; Albert Einstein College of Medicine, New York, NY
Body Retrosternal goiter is usually defined as a thyroid that is 50% or more below the thoracic inlet. The incidence in the general population varies from 0.02 to 0.4% with a malignancy rate of 0-5%. Common symptoms include neck mass, dysphasia, stridor, shortness of breath, and superior vena cava syndrome. We report a patient who presented with intermittent neck swelling for one year and was not diagnosed until superior vena cava syndrome developed. CXR identified a mass in the right upper thorax.
A 43 year-old female patient with history of intermittent lower neck swelling for one year with no conclusive diagnosis presented with neck pain and engorged veins of the neck and upper right chest for one week. The neck pain was severe in supine position but she denied any weight loss, dysphasia, stridor or shortness of breath and no any features of hypo or hyperthyroidism. On examination, no significant mass in neck was identified except engorged veins in the right lower neck and right upper chest. CT scan of neck and chest showed a large retrosternal goiter extending into right hemithorax, pushing the trachea to the left without any signs of obvious airway obstruction.
A Total thyroidectomy was successfully performed via a cervical approach. The infrathoracic thyroid was retracted into the neck utilizing a deep 2.0 silk ligature into the thyroid gland with the use of a retraction device. On the first post operative day, the patient was extubated, serum calcium was normal and she had an uneventful post operative recovery. Final pathology report shows encapsulated fragment of tan-pink soft tissue weighing 190 grams and measuring 9.0 x 8.5 x 3.0 cm papillary thyroid carcinoma. The patient is currently being followed every 3 months with no complication and no signs of tumor recurrence.
Goiter is more common in women than men. Many retrosternal goiters are asymptomatic making the early diagnosis difficult and management of these masses without absolute indications for surgery controversial. This patient presented with neck swelling as an initial sign which is uncommon and very easily to be ignored. Regular CXR may need to be imposed for middle aged woman with unexplained neck signs. Such large size retrosternal papillary carcinoma without symptoms of respiratory compromise has not been found to be reported by PubMed searching. Although cervical approach can still be applied by skilled surgeon, 4,5, sternotomy with wide excision of the mass may need to be considered.

1. Shah PJ, Bright T, Singh SS, Lang CM, Pyragius MD, Malycha P, Edwards JR. Large retrosternal goitre: a diagnostic and management dilemma. *Heart Lung Circ.* 2006 Apr;15(2):151-2. Epub 2006 Feb 21. PubMed PMID: 16490399.
2. Hardy RG, Bliss RD, Lennard TW, Balasubramanian SP, Harrison BJ. Management of retrosternal goitres. *Ann R Coll Surg Engl.* 2009 Jan;91(1):8-11. PubMed PMID:19126330; PubMed Central PMCID: PMC2752232.
3. Hardy RG, Bliss RD, Lennard TW, Balasubramanian SP, Harrison BJ. Management of retrosternal goitres. *Ann R Coll Surg Engl.* 2009 Jan;91(1):8-11. PubMed PMID: 19126330; PubMed Central PMCID: PMC2752232.
4. Raffaelli M, De Crea C, Ronti S, Bellantone R, Lombardi CP. Substernal goiters: Incidence, surgical approach, and complications in a tertiary care referral center. *Head Neck.* 2010 Nov 10. [Epub ahead of print] PubMed PMID:21069839.
5. Cannon CR, Lee R, Didlake R. Management of the substernal goiter: a team approach. *J Miss State Med Assoc.* 2010 Jul;51(7):179-82. PubMed PMID: 20830956.

Nothing to Disclose: HW, MIG, PCS, SN, APS, ARG, MJ, DC, APA, PJP

sort_order

2722

Pub #

P3-653

Session Information

POSTER SESSION: CLINICAL/TRANSLATIONAL - Thyroid Nodules & Cancer (1:30 PM-3:30 PM)

Title

67-Year-Old Woman with Rapid Increase in Cervical Volume

Author String

CDP Blankenburg, EDS Portes, RA Guerra, ER Barbosa, LB de Sa, AR Andrade, DL Belino, VC Machado
Hospital do Servidor P[uaacute]blico Estadual/SP, São Paulo, Brazil

Body

NMO, woman, 67-year-old, arrived at the emergency room of the Hospital do Servidor Publico Estadual/SP complaining of a significant increase in cervical volume for 1 month. The patient showed cervical ultrasound presenting normal thyroid lobes (with a volume of 8.28 ml) with heterogeneous echotexture and the presence of thick-walled cystic image regular 6.6 by 3.5 millimeters in the isthmus, without the presence of cervical lymphadenopathy. The patient underwent a new cervical ultrasound showing an enlarged thyroid very heterogeneous with 361 ml (increase about 4000% in 45 days) with extension below the sternum and a computed tomography (CT) of the cervicothoracic region which demonstrate lymph node at the levels IIa, IIb, III left and IV and V bilaterally, with tissue invading the trachea 3 centimeters below the sternal notch without involvement of the vocal cords. Other exams demonstrate substernal goiter, cervical lymph node and thyrotoxicosis. The diagnosis was revealed by lymph node biopsy: Non-Hodgkin's Diffuse Large Cell Lymphoma (NHL DGCB) with Immunophenotyping of B cells CD20 and CD79 positive. During the staging CT of the abdomen and pelvis revealed bilateral adrenal mass with no cleavage plane with the kidneys, liver and spleen, with density of 38 HU (Hounsfield Unit) in the right and 37 HU in the left, both measuring about 11x10 centimeters, displacing the kidney inferiorly. The stage was IVA (Ann Arbor), and treatment scheme started with Rituxmah, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone, with reduction of goiter in just 3 days after beginning of the first cycle. Primary Thyroid Lymphoma (PTL) is a very rare disease, and site of only 2% of all lymphomas and these 2% of all malignancies, a Danish study estimated the annual incidence of 2.1 per million. Hyperthyroidism with PTL to presentation is a rare condition: between 1 to 6%; thyrotropin may be suppressed by a prior Graves' disease or for thyrotoxicosis due to glandular destruction by tumor. The literature has described only four cases with adrenal involvement: 3 (75%) were men, disagreeing in this case, aged between 47 and 76 years old, in addition, 2 (50%) had adrenal insufficiency. Conclusion: The PTL is a rare and heterogeneous conditions, which should always be considered in patients with rapid increases in thyroid. It is important to search for adrenal involvement, since there may be at risk of adrenal insufficiency, worsening the prognosis.

Nothing to Disclose: CdPB, EdSP, RAG, ERB, LBdS, ARA, DLB, VCM

sort_order 2723
Pub # P3-654
Session Information POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)
Title The Outcomes of Adjuvant Radioactive Ablation Therapy after Reoperation for Locoregionally Recurrent/Persistent Papillary Thyroid Carcinoma in Patients Who Initially Underwent Total Thyroidectomy and Remnant Ablation
Author String EY Kim, YK Shong, JH Yim, TY Kim, JM Han, WB Kim, Wg Kim, G Gong, J-S Ryu, SJ Hong
Dongnam Institute of Radiological & Medical Sciences Cancer Center, Busan, Korea; Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; Asa Medical Center, University of Ulsan College of Medicine, Seoul, Korea; Asa Medical Center, University of Ulsan College of Medicine, Seoul, Korea
Body Context: Surgery is recommended for locoregionally recurrent papillary thyroid cancer (PTC) and adjuvant RAI therapy is also used following surgery if residual RAI avid disease is present or suspected. However, not much is known about appropriated therapy for patients with elevated stimulated thyroglobulin (stim Tg) after reoperation for locoregionally recurrent PTC.
Objective: This study is to evaluate the efficacy of adjuvant RAI therapy after reoperation in patients who have elevated stimulated (stim Tg) after reoperation for locally recurrent/persistent papillary thyroid cancer (PTC).
Design and Settings: This is a retrospective observational cohort study in a tertiary referral hospital.
Patients: A cohort of 55 consecutive patients who had stim Tg >2 ng/mL after reoperation for locoregionally recurrent PTC were included in this study. All patients had previously undergone initial total thyroidectomy followed by RAI remnant ablation. Seven patients with higher than 100 U/ml anti-Tg antibody and 3 patients who received initially low dose (30 mCi) remnant ablation therapy were subsequently excluded.
Main outcome measures: We measured changes of stim Tg after adjuvant RAI therapy and evaluated second clinical recurrence-free survival rate according to adjuvant RAI therapy.
Results: Twenty-three patients received adjuvant RAI therapy (Adjuvant RAI group) and the other 22 patients did not receive this additional treatment (No RAI group) after reoperation for locoregionally recurrent PTC. Stim Tg levels were changed from median 11.4 to 9.3 ng/mL in adjuvant RAI group (p=0.24) and from median 7.5 to 7.8 ng/mL in No RAI group (p=0.93). Only 16% patients in the adjuvant RAI group and 33% in No RAI group showed greater than 50% decrease in follow-up stim Tg. And stim Tg levels and percentage decreases of stim Tg were not different in both groups (p=0.62 and p=0.82). There was no significant difference in the clinical recurrence-free survival rate after reoperation between two groups (P=0.20).
Conclusion: This study revealed that the adjuvant RAI therapy has little benefit in patients who have remnant disease after reoperation for locally recurrent/persistent PTC. The adjuvant RAI therapy after reoperation should not be routinely recommended for such patients.

Nothing to Disclose: EYK, YKS, JHY, TYK, JMH, WBK, WGK, GG, J-SR, SJH

sort_order 2724
Pub # P3-655
Session Information POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)
Title Surgical Strategy's Impact on the Papillary Thyroid Carcinoma (PTC) Postoperative Staging
Author String MMS Sarquis, JB Brandao, AV Ramos, ML Weissheimer, EP Dias
Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; Hospital Felício Rocho, Belo Horizonte, Brazil
Body
In recently published guideline, the ATA recommended, in selected patients, the central lymph node compartment dissection (CLCD), for the primary surgical treatment of PTC and also for prophylaxis(1). This statement aroused our attention for the importance of surgical strategy in determining the staging and thus the post-surgical adjuvant treatment. We aim to determine the impact of two surgical procedures widely used in the treatment of PTC on the postoperative staging.
Material and Methods: All the patients had preoperative ultrasound (US) and anatomopathological results available for analysis and were divided in two groups: 30 underwent total thyroidectomy (TT) associated with prophylactic CLCD (group 1) and 30 underwent TT associated with clinically affected lymph node removal (group 2). Statistical analysis was done using Chi-square test.
Results: There was no difference in sex, age or tumors size between the groups. Regarding lymph node involvement in group 1 there were 27, out of 197 lymph nodes resected, with metastasis while in group 2 only 1 out of 10 lymph nodes identified was metastatic (p=0.02). These lymph nodes were not recognized by the pre operative US. Concerning the N staging, in group 1, 23 patients were classified as N0, 4 N1a, 3 N1b and no Nx. In group 2 there were 5 patients classified as N0, 1 N1a, no N1b and 24 Nx. Post operative risk stratification differed between the groups. In group 1 there were 15 patients classified as very low risk (T1, unifocal, N0, M0), 5 low risk (T1 multifocal, T2, N0, M0) and 10 high risk (T3 or T4, N1, M1) while in group 2 there were 24 patients unclassified (Nx), 5 very low risk, no Low risk and 1 high risk.
Discussion: The present study points out that the CLCD, as the initial surgical approach, significantly changes the postoperative staging and, consequently the adjuvant therapy to be adopted. In accordance with the literature, we showed that the preoperative neck US was not helpful identifying central lymph nodes involvement. Such information reinforces the fact that lymph nodes evaluation can only be reliably performed when such compartment is dissected.
The standardization of surgical techniques will better delineate follow-up and adjuvant therapy, avoiding the use of radioiodine-131 therapy in very low risk patients, improving patient's life quality and reducing treatment costs. Future longitudinal studies would be helpful identifying the risks and recurrence rate associated with each procedure.

(1) Cooper DS et al., Thyroid 2009; 19:1167

Nothing to Disclose: MMSS, JBB, AVR, MLW, EPD

sort_order 2725
Pub # P3-656
Session Information POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)
Title The Long-Term Clinical Outcome of Differentiated Thyroid Carcinoma Patients Who Initially Underwent Total Thyroidectomy and Remnant Ablation, and with Undetectable Stimulated Thyroglobulin Level One Year after Remnant Ablation
Author String JM Han, JH Yim, WB Kim, EY Kim, WG Kim, TY Kim, J-S Ryu, G Gong, SJ Hong, YK Shong
Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; Asan Medical Center, Seoul, Korea; Asan Medical Center, Seoul, Korea; Asan Medical Center, Seoul, Korea
Body Measurement of serum thyroglobulin level with TSH stimulation (stim Tg) is the cornerstone of monitoring for the recurrence or persistence of DTC in patients who have undergone surgery and remnant ablation. However, there have been several reports that an undetectable stim Tg could not warrant the absence of thyroid cancer during the follow-up.
Objective: This study were done to evaluate the long-term outcome of patients who achieved biochemical remission and to find clinical parameters to predict recurrence.
Design and Patients: This is a retrospective observational cohort study from 1995 to 2004 in a tertiary referral hospital. 1603 DTC patients received total thyroidectomy followed by remnant ablation without evidence of extracervical metastasis or positive anti-Tg autoantibodies at the time of 6-12 months after ablation. Among them, 1039 patients (112 male and 927 female) achieved biochemical remission (defined as stim Tg less than 1 ng/mL) at 6-12 months after ablation and were eligible for analysis. We evaluated clinical recurrence-free survival rate according to baseline characteristics.
Results: The median age was 46.3 years (range 13.0-76.4) and median size of tumor was 1.5 cm (range 0.1-8.5). The frequencies of extrathyroidal extension, tumor size larger than 4 cm, central neck lymph node metastasis, and lateral neck lymph node metastasis were 52%, 6%, 38%, and 7%, respectively. Sixteen patients (1.5%) showed clinical evidence of disease during median 80.8 months of follow-up. Male gender (log rank statistics = 7.95, df = 1, p = 0.005), tumor size larger than 4cm (log rank = 5.29, df = 1, p = 0.02), extrathyroidal extension (log rank = 6.51, df = 1, p = 0.01), and cervical lymph node metastasis (log rank = 13.5, df = 1, p < 0.001) were associated with recurrence by univariate analysis. In multivariate analysis, lateral neck lymph node metastasis (HR 7.44, CI 1.61-34.42, p = 0.01) was the only independent predictors of recurrence.
Conclusions: These data showed that a little portion of DTC patients who achieved biochemical remission 6-12 months after initial treatment still showed clinical recurrence during long-term follow-up. Male gender, large tumor size, extrathyroidal extension and advanced nodal involvement at the time of initial treatment could be predictive factors for the recurrent disease. Therefore, it is necessary to have a close follow-up in patients with recurrence risk factors, although stim Tg after treatment is undetectable or very low.

Nothing to Disclose: JMH, JHY, WBK, EYK, WGK, TYK, J-SR, GG, SJH, YKS

sort_order 2726
Pub # P3-657
Session Information POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)
Title Recurrence Rate of Papillary Thyroid Cancer over a 5-Year Period in Disease-Free Patients
Author String B O Donnell, I Lukacova-Zib, G Gopalakrishnan
Alpert Medical School of Brown University, Providence, RI
Body **Introduction:** In general, papillary thyroid cancer has an excellent prognosis. In this retrospective chart review, we evaluated the 5-year recurrence rate of papillary thyroid cancer in patients identified as disease free.
Methods: The charts of patients with papillary thyroid cancer who were identified as disease free based on a stimulated thyroglobulin and neck ultrasound were reviewed. Five year follow-up data on recurrence was collected.
Results: A total of 304 charts of patients with papillary thyroid cancer were reviewed. Patients were identified to be disease free based on a stimulated thyroglobulin and neck ultrasound. 117 of these patients had 5-years of follow-up data at our institution. The average age of this population was 43.9 years. A majority of the study subjects were women (77.8%) and Caucasian (85.5%). During the five years of follow-up, the recurrence rate was 4.3%. In the group of patients that experienced recurrence, two of the patients had Stage III or Stage IV disease at diagnosis, and those with Stage I all had lymph node involvement at the time of diagnosis. All patients with low risk papillary thyroid cancer continued to be disease free after 5 years of follow-up.
Conclusion: Considering the 5-year recurrence rate in our cohort, the study investigators would support monitoring tumor recurrence with yearly clinical examination and thyroglobulin measurement on thyroid hormone replacement for disease free low risk papillary thyroid cancer patients as suggested by the American Thyroid Association. However, individuals with intermediate or high risk PTC (Stage III, IV, and any patient with N1a or N1b disease) may require more frequent and rigorous testing.

Nothing to Disclose: BO, IL-Z, GG

sort_order

2727

Pub #

P3-658

Session Information

POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)

Title

The Risk of Breast Cancer Is Reduced in Thyroid Cancer Patients after Radioactive Iodine Therapy

Author String

HY Ahn, AR Kang, Y Hwang Bo, KW Kim, YJ Park, DJ Park, BY Cho
Seoul National University College of Medicine, Seoul, Korea

Body

Background: Both thyroid and breast cancer are common malignancies in women. Recent studies suggested a possible association between breast and thyroid cancer. Also high cumulative amount of radioactive iodine (RAI) increased the risk of secondary primary malignancies in thyroid cancer patients. In this study, we investigated the effect of radioactive iodine therapy to development of secondary breast cancer in women with thyroid cancer.

Methods: Total 2109 female thyroid cancer patients were included who underwent thyroidectomy from 1960 to 2009 in our institute. Among them, 1164 (55.2%, median follow up 8.9 ± 6.8 years) patients were received RAI therapy. The rest of them, 943 (44.8%, median follow-up 9.6 ± 7.3 years) patients were not treated with RAI.

Results: Secondary cancer was occurred in 70 among 2109 patients. Among these secondary cancers, breast cancer was most common ($n = 38$). However the incidence of secondary breast cancer is lower in RAI therapy group than no RAI therapy group (0.9% vs 3.0%, OR 0.283, 95% CI [0.137-0.587], $P < 0.05$). When we adjusted age, RAI therapy was also lowers incidence of secondary breast cancer (OR 0.292, 95% CI [0.140-0.606], $P = 0.001$). There was no significant clinicopathologic difference between RAI therapy and no RAI therapy group in secondary breast cancer patients such as age at diagnosis of breast cancer, tumor size, positive rate of hormone receptors and recurrence rate.

Conclusion: The incidence of secondary breast cancer developing after diagnosis of thyroid cancer was high. However, RAI therapy seems to reduce the risk of secondary breast cancer.

Nothing to Disclose: HYA, ARK, YHB, KWK, YJP, DJP, BYC

sort_order

2728

Pub #

P3-659

Session Information

POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)

Title

TSH and Thyroid Antibody, as Predictors of Thyroid Cancer

Author String

YJ Kim, HY Kim, HJ Yoo, SJ Yang, JH Kim, DS Choi, MJ Cho, SG Kim, KM Choi, SH Baik, HY Choi, JA Seo, NH Kim, CR Eun
Korea University Anam Medical Center, Seoul, Korea; Korea University Kuro Medical Center, Seoul, Korea; Korea University Anam Medical Center, Ansan, Korea

Body

Background: Recently, serum thyrotropin (TSH) level has been suggested as a possible predictor of thyroid cancer. However, there has been several conflicting data in terms of the association between autoimmune thyroiditis and thyroid cancer. The purpose of this study was to compare biochemical markers and ultrasonography (US) characteristics between benign thyroid disease and thyroid cancer, as well as to investigate what factors are independently associated with thyroid cancer.

Methods: Six hundred and forty patients who underwent thyroidectomy at our institution between January 2006 to December 2007 were included in this study. We divided these patients into 2 groups by postoperative histopathologic features; group1 (G1) consisted of 251 patients with benign thyroid disease, group2 (G2) consisted of 389 patients with thyroid cancer. We compared age, sex, serum TSH levels, thyroid antibodies and US characteristics between the two groups. Thyroid autoimmunity was assessed by measuring thyroglobulin antibody (Tg Ab) and microsomal Ab. Additionally, we also evaluated the existence of Hashimoto's thyroiditis based on histopathologic features between two groups.

Results: G2 had higher serum TSH levels and positive thyroid antibodies more frequently than Gr 1. In US characteristics, G2 had smaller nodule, lower echogenicity, higher calcification rate, irregular margins, solid components more frequently than G1. The risk of malignancy rose in parallel with the serum TSH level ($p=0.0009$). Logistic regression analysis revealed significantly increase adjusted odds ratios (AORs) for diagnosis of malignancy in subjects with serum TSH levels more than 1.8mU/L (AOR 2.44(CI 1.01-5.88, $p=0.047$), compared with TSH less than 0.4 mU/L. And thyroid antibodies (AOR 2.19 (CI 1.00-4.79, $p=0.050$)), microcalcifications (AOR 2.10 (CI 1.11-3.98, $p=0.022$)), macrocalcification(AOR 5.01 (CI 1.23-20.37, $p=0.024$)) and irregular margins of nodules in US characteristics(AOR 1.80 (CI 1.01-3.19, $p=0.045$)) were also associated with an increased risk of thyroid cancer. No association was observed between Hashimoto's thyroiditis and thyroid cancer.

Conclusions: Increased serum TSH levels and the presence of thyroid antibodies were independent risk factors in thyroid malignancy, but not Hashimoto's thyroiditis. This data suggests that serum TSH and thyroid autoantibodies can independently serve as predictors for thyroid malignancy.

Nothing to Disclose: YJK, HYK, HJY, SJY, JHK, DSC, MJC, SGK, KMC, SHB, HYC, JAS, NHK, CRE

sort_order 2729
Pub # P3-660
Session Information POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)
Title Does Reoperation for Cervical Lymph Node Metastases Cure Papillary Thyroid Cancer Patients?
Author String JR Chintaparthi, VM Konala, JE Langer, AA Chalian, DL Fraker, SJ Mandel, AA Silpasuvan
Pennsylvania Hospital, Philadelphia, PA; University of Pennsylvania School of Medicine, Philadelphia, PA; University of Pennsylvania School of Medicine, Philadelphia, PA; University of Pennsylvania School of Medicine, Philadelphia, PA; University of Pennsylvania School of Medicine, Philadelphia, PA
Body After thyroidectomy (thyrx) and I131 ablation ~20% of patients (pts) with papillary thyroid cancer (PTC) will be found to have cervical lymph node (CLN) recurrence for which recent guidelines recommend surgery. Our aim was to evaluate persistent disease defined by serum thyroglobulin (Tg) or ultrasound (US) after reoperative central (CND) or lateral cervical lymph node (LND) dissections for CLN metastases.
Methods: Retrospective chart review of pts of a single endocrinologist who underwent reoperation (compartmental CND and/or LND) by 1 of 3 experienced thyroid surgeons between 1997-2010 at a University hospital after initial thyrx and I131 ablation. Tg antibody positive pts and pts with distant metastases were excluded. We recorded detection method for CLN metastases, serum Tg levels (on thyroxine (T4Tg) or after stimulation (stimTg)), and postoperative US results.
Results: 87 PTC pts (F 71%, M 29%) underwent 103 surgeries (37 CND, 43 LND, 23 CND/LND) at a median of 24months (range 5months-24yrs) after thyrx. Initial AJCC TNM classification was: Stage I 59%, II 5%, III 15%, IV 10% (11% unknown). 56 pts had positive LNs at initial thyrx. Initial recurrent metastatic CLNs were detected by US (80pts), US/MRI (4pts), US/PET (1pt), and PET/MRI/CT (2pts). 79 pts had fine needle aspiration (FNA) biopsy; positive cytology-74pts; positive FNATg-5pts. Preop T4Tg levels were undetectable-8pts, detectable but <1ng/ml-17pts, 1-2ng/ml-13pts; and >2ng/ml-48pts. Pts were followed for a median of 2 yrs postop (range 1-13 yrs). Postop T4Tg levels became undetectable in 8/17pts (47%) with preop detectable Tg <1ng/ml, 7/13pts (54%) with preop Tg 1-2ng/ml, 13/48pts (27%) with preop Tg >2ng/ml. Second and third CND/LND were performed in 12pts and 4pts respectively when additional metastatic CLNs were detected by US. Correlating with postop T4Tg, additional reop was required in 1/34pts if Tg undetectable, 4/20pts with detectable Tg <1ng/ml, 1/14 pts with Tg 1-2ng/ml, and 6/17pts with Tg >2ng/ml. Correlating with postop stimTg (available in 64pts), additional reoperation was needed in 0/11pts if Tg undetectable, 1/19 if detectable Tg <1ng/ml, 1/5 if Tg 1-2ng/ml, 5/29 if Tg >2ng/ml.
Reoperation for CLN metastases by experienced surgeons achieves undetectable T4Tg in 50% pts with preop detectable T4Tg \leq 2ng/ml and 27% pts with preop T4Tg >2ng/ml. Only a small proportion (3%) may require additional surgery. In addition, the 17% with undetectable stimTg appear to be disease-free.

Nothing to Disclose: JRC, VMK, JEL, AAC, DLF, SJM, AAS

sort_order 2730
Pub # P3-661
Session Information POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)
Title Response to Initial Therapy Can Be Determined as Early as 1 Month after Primary Surgery in Medullary Thyroid Cancer
Author String G Rondeau, R Zeuren, AR Shaha, RM Tuttle
Memorial Sloan-Kettering Cancer Center, New York, NY; Memorial Sloan-Kettering Cancer Center, New York, NY
Body **BACKGROUND:** Because serum calcitonin (Ct) is a reliable marker of the presence, volume and extent of disease in medullary thyroid cancer (MTC), both the ATA and NCCN guidelines use the 2-3 month post-operative Ct value as the primary response to therapy variable that determines the type and intensity of follow up evaluations. Patients with an undetectable Ct are presumably in remission and can be followed with expectant observation. Conversely, patients with modestly elevated values (measurable, < 150pg/mL) are evaluated with repeat neck ultrasonography to detect loco-regional disease while patients with higher levels (\geq 150pg/mL) are considered for additional imaging to rule out distant metastasis. Even though serum Ct may take months to reach its nadir after surgical resection for MTC, we hypothesized that the 1 month post-operative Ct value would accurately identify patients destined to have 2-3 month Ct values that were either undetectable, < 150pg/mL, or \geq 150pg/mL; thereby allowing follow-up management recommendations and response to therapy assessments to be made at an earlier time point.
METHODS: This retrospective review identified 44 patients with sporadic MTC who had at least two serial basal Ct measurements done in the first three months after primary surgery.
RESULTS: By 3 months after surgery, 14/44 patients demonstrated an undetectable serum Ct. Interestingly, the serum Ct was already undetectable in 13/14 of these patients by 1 month after surgery (1 patient had a 1 month Ct of 5pg/mL that fell to undetectable levels by 3 months). At the 1 month time point, 11/44 patients had a serum Ct that was measurable but < 150pg/mL. While 8 of 11 patients had a 29% median decline in Ct values, only 1 patient (described above) achieved an undetectable serum Ct by 3 months. Finally, the 1 month serum Ct was \geq 150pg/mL in 20/44 patients. Even though 10/20 of these patients had a 16% median decline in serum Ct over the next 2 months, none fell below the 150pg/mL threshold.
CONCLUSION: Serum Ct obtained 1 month after initial surgery for MTC appropriately risk stratified 98% (43/44) of patients as either likely to be in remission (undetectable Ct), likely to have persistent loco-regional disease (Ct measurable, < 150pg/mL) or possibly having distant metastases (Ct \geq 150pg/mL). Thus, the 1 month Ct value is a reliable marker of response to therapy that allows earlier risk stratification than the currently recommended 2-3 month Ct measurement.
Disclosures: GR: Research Funding, Genzyme Corporation. RMT: Research Funding, Genzyme Corporation; Consultant, Abbott Laboratories; Veracyte, Inc.; Novo Nordisk. Nothing to Disclose: RZ, ARS

sort_order 2731
Pub # P3-662
Session Information POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)
Title Predictive Factors of Lymph Node Metastases in Patients with Papillary Thyroid Cancer
Author String U Ozuguz, S Isik, F Gokay, G Akkaba, YA Tutuncu, FK Kucukler, D Berker, S Guler
Ministry of Health, Ankara Numune Research and Training Hospital, Ankara, Turkey
Body
Objective: Regional lymph node metastases may alter relatively benign course of papillary thyroid carcinoma (PTC). The objective of this study was to evaluate predictive factors of lymph node (LN) metastases of PTC.
Methods: Three hundred and eight patients who underwent total thyroidectomy and servical lymph node dissection for PTC who are at follow-up in our department between May 2003 to December 2010 were retrospectively analyzed. Patients with PTC are divided into three groups according to tumor size: Group 1 (n=163) [le] 10 mm, group 2 (n=94) 10 - 20 mm, and group 3 (n=51) [ge]20 mm. Group 1 is further analyzed in two subgroups as <5 (Group 1a) mm and [ge]5mm (Group 1b).
Results: Of the patients, 54 was male (17.5%) and 254 was female (82.5%). Mean age was 44.5±12.2 years. The mean follow-up for the patients with PTC was 23.7±22.4 months. Multifocality and bilaterality were similar between the groups. The vascular and capsule invasion, extrathyroideal extention and LN metastases were significantly higher in the groups 2 and 3 than those in the group 1 (p<0.001, p<0.001, p=0.007, p<0.001). In group 1, there was no significant difference in the terms of multifocality, bilaterality, vascular invasion, capsular invasion and extrathyroideal extension between Groups 1a and 1b. But, LN metastases was significantly lower in the 1a subgroup than the 1b and groups 1 and 2 while it was similar between groups 1b, 2 and 3. Lymph node metastases was significantly positively correlated with tumor size, capsul invasion, vascular invasion, multifocality, bilaterality, and hypoechogenicity, solid structure and presence of microcalcification in US, and negatively correlated with age. In regression analysis, age (<34.5 year), capsule invasion, multifocality and tumor size (>6.5 mm) was important determinant of LN metastases, but ultrasonographic features were not (B=4.28 p=0.001, B=-5.15 p=0.001, B=11.51 p=0.001, B=11.40 p=0.03, respectively).
Conclusion: According to our data patient age <34.5 years, capsule invasion, multifocality, and tumor size greater than 6.5 mm are independent risk markers for lymph node metastasis in PTC.
Nothing to Disclose: UO, SI, FG, GA, YAT, FKK, DB, SG

sort_order 2732
Pub # P3-663
Session Information POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)
Title Predictive Value of Metastatic Lymph Node Ratio in Papillary Thyroid Carcinoma Recurrence
Author String J Yip, S Orlov, D Orlov, D Etarsky, D Tam, A Ganguly, C Hu, A Vaisman, J Freeman, PG Walfish
Mount Sinai Hospital and University of Toronto, Toronto, Canada; Mount Sinai Hospital and University of Toronto, Toronto, Canada
Body **Background:** Lymph node (LN) metastases are associated with increased recurrence of papillary thyroid carcinoma (PTC)(1). Currently, the AJCC (TNM) staging system for well-differentiated thyroid carcinoma (WDTC) categorizes nodal status (TNM NS) as either absent (N0), central (N1) or lateral (N2) LNs(2). Recently, the proportion of metastatic LNs resected (metastatic LN ratio; MLNR) has been shown to have prognostic value in survival for WDTC(3). However, the value of MLNR in PTC recurrence remains unknown.
Purpose: To determine the predictive value of MLNR in PTC recurrence.
Methods: We retrospectively analyzed a cohort of 197 consecutive PTC patients (74% female) with a median follow-up of 3.4 years (range: 0.2-13.2 yrs). All patients underwent total thyroidectomy and therapeutic central neck dissection with a minimum of one LN resected. MLNR and TNM NS were determined for each patient. Patients were selectively treated with radioactive remnant ablation (RRA) when indicated. Stimulated thyroglobulin measurements (Stim-Tg) were performed 3-months post-operatively. All patients were anti-thyroglobulin antibody negative. Recurrence was defined as the need for additional surgery or radioiodine therapy. Logistic regression analyses examined the association of TNM NS and MLNR with recurrence of PTC. The results were expressed as odds ratios (OR) with 95% confidence intervals (CI) and associated p-values. Receiver-operator characteristic (ROC) curves with area under the curve (AUC) calculations were used to evaluate all regression models.
Results: Twenty (10.2%) patients had recurrent PTC. There was no significant difference in recurrence between patients treated with and without RRA ($\chi^2(1, N=197)=3.15$, NS). There was a significant positive correlation between MLNR and Stim-Tg levels ($r=0.15$, $p<0.05$). A multivariable (MLNR and TNM NS) logistic regression model determined that MLNR independently predicted PTC recurrence such that for every unit increase in MLNR, the odds of recurrence was 5.17 (CI 1.20, 22.28, $p=0.027$). TNM NS also predicted PTC recurrence with an OR of 2.21 (CI 1.15, 4.23, $p=0.017$) in the multivariable model and an OR of 2.80 (CI 1.60, 4.91, $p<0.001$) when considered alone. ROC curves showed AUCs of 0.767 and 0.738 for the multivariable and univariable models, respectively, in predicting PTC recurrence.
Conclusion: Metastatic lymph node ratio is an independent predictor of PTC recurrence and enhances the predictive value of TNM nodal status alone.
(1) Beasley NJ et al., Arch Otolaryngol Head Neck Surg 2002;128(7):825-8.
(2) Greene FL, American Cancer Society., American College of Surgeons., American Joint Committee on Cancer. AJCC cancer staging manual. 6th ed / ed. New York: Springer-Verlag; 2002.
(3) Beal SH et al., Am Surg 2010;76(1):28-32.
Sources of Research Support: Mount Sinai Hospital Foundation of Toronto, the Da Vinci Gala Fundraiser; Genzyme Canada Incorporated; Temmy Latner/Dynacare Family Foundation.
Nothing to Disclose: JY, SO, DO, DE, DT, AG, CH, AV, JF, PGW

sort_order 2733
Pub # P3-664
Session Information POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)
Title Ultrasonographically Detected Small Thyroid Bed Nodules Identified after Total Thyroidectomy for Differentiated Thyroid Cancer Seldom Show Clinically Significant Structural Progression
Author String G Rondeau, S Fish, LE Hann, JA Fagin, RM Tuttle
Memorial Sloan-Kettering Cancer Center, New York, NY
Body **BACKGROUND:** High-resolution ultrasound (US) is the primary tool used to identify loco-regional recurrences in differentiated thyroid cancer (DTC). While small thyroid bed (TB) nodules are a commonly reported sonographic finding, their natural history, regardless of whether they are benign or malignant, has not been well characterized. This study was designed to determine the likelihood, magnitude and rate of growth of small TB nodules identified on routine surveillance neck ultrasound following thyroidectomy for DTC as well as to identify ultrasonographic and clinical predictors of growth. **METHODS:** This retrospective review identified 191 patients with at least one TB nodule (≥ 11 mm) on the first post-operative US performed at a comprehensive cancer center. Change in size of each TB nodule was determined using serial US studies over time. Clinico-pathologic and sonographic characteristics were analyzed as possible predictors for growth of the TB nodules. **RESULTS:** Over a median clinical follow up of 5 years, 9% (17/191) of patients had increase in size of at least one TB nodule. Median size of the TB nodules was 5 mm (range 2-11 mm). Suspicious US features (microcalcifications, hypoechogenicity and increased vascularity) were seen in 63% (121/191) of patients with TB nodules identified on initial US and in 31% (21/67) of those with TB nodules detected on subsequent follow up US. The rate of growth was 1.3 mm/year in those nodules showing an increase in size and thus demonstrated a significant increase in size only after several years of follow-up. The negative predictive values (NPV) associated with the absence of any suspicious US features (0.97), the absence of abnormal cervical lymph nodes (0.94), the lack of a rising serum thyroglobulin (Tg) (0.93) and the combination of these three factors (0.96) provided clinically useful information regarding the likelihood that nodules would not increase in size. Definitive pathological diagnosis for a TB nodule was obtained in only 9/191 patients and most demonstrated no clinically significant increase in size over many years of follow up. **CONCLUSION:** Most TB nodules do not show clinically significant growth over several years of follow-up. Thus, TB nodules can be followed with cautious observation and serial ultrasonography using an approach similar to that recommended by the American Thyroid Association Thyroid Cancer guidelines for the management of small abnormal cervical lymph nodes.

Disclosures: GR: Research Funding, Genzyme Corporation. RMT: Research Funding, Genzyme Corporation; Consultant, Abbott Laboratories; Veracyte, Inc.; Novo Nordisk. Nothing to Disclose: SF, LEH, JAF

sort_order 2734
Pub # P3-665
Session Information POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)
Title Detection of BRAFV600E Mutation in May-Grunwald Stained Thyroid FNA Samples Can Help in Identification of Cancers with a High Risk of Extra-Thyroidal Extension and Metastases
Author String V Hoperia, A Larin, J Gwiedzka, K Jensen, A Patel, A Bauer, V Vasko
Center for Endocrine Surgery, Kiev, Ukraine; Washington Hospital Center, Washington, DC; Uniformed Services University, Bethesda, MD
Body
Background: The BRAFV600E mutation is specific for thyroid papillary cancer (PTC) and correlates with invasiveness.
Purpose: This study investigated whether the BRAF mutation could be detected upon analysis of DNA extracted from May-Grunwald stained fine needle aspiration biopsies (FNABs). We examined if detection of the BRAF mutation might improve the cytological diagnosis of suspicious FNABs. In malignant FNABs we studied the utility of this test for the identification of patients at risk for metastatic disease.
Methods: FNABs samples were classified as suspicious (30 cases) or malignant FNABs (104 cases). Among suspicious FNABs there were 10 benign and 20 malignant tumors by histology. All malignant FNABs were PCs by histology. DNA was isolated from stained FNABs samples using Pinpoint Slide DNA Isolation System. BRAF mutation was detected by PCR and by sequencing.
Results: DNA was successfully extracted from all examined FNABs. In suspicious FNABs, BRAF mutation was found in 2/30 (6%) of cases (2 PTC). In malignant FNABs, BRAF mutation was detected in 47/104 (45.2%) of cases. BRAF mutation was detected with the same frequency in males (8/21) and females (39/83), (p=0.63). The mean age of patients with BRAF mutation positive and negative PTCs was not different (42.4 vs 40.3 years; p=0.49). The tumor size in BRAF positive PTCs was not different from tumors harboring wild type BRAF (2.3±1.2 vs 1.94±1.1 cm; p=0.62). Multifocal growth was more frequently detected in BRAF positive (21/47) than in BRAF negative (16/57) PTCs, however, the difference was not statistically significant (44.6% vs 28%, p=0.1). There was a significant association of BRAF mutation with the presence of extra-thyroidal extension and lymph node metastases. Histological examination revealed the presence of extra-thyroidal extension in 35/47 (74.4%) of BRAF positive FNABs and in 24/57 (42.1%) of BRAF negative FNABs (p=0.001). Lymph nodes metastases were detected in 37/47 (78.7%) of BRAF positive and in 28/57 (49.1%) of BRAF negative cases (p=0.002).
Conclusion: Routinely stained FNAB specimens can be used for DNA extraction and assessment for the presence of aBRAF mutation. Detection of a BRAF mutation has limited value in the diagnosis of malignancy in cases of suspicious FNABs. In malignant FNABs, detection of BRAF mutation could be a useful adjunct for preoperative identification of tumors with a high risk of extra-thyroidal extension and metastases.

Nothing to Disclose: VH, AL, JG, KJ, AP, AB, VV

sort_order 2735
Pub # P3-666
Session Information POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)
Title Serum VEGF, VEGF-C and Galectin-3 May Help Identify Malignancy
Author String MA Marcello, A Calixto, EC Etchebehere, MB Martins, B Geloneze, AL Carvalho, LS Ward
State University of Campinas, Campinas, Brazil; State University of Campinas, Campinas, Brazil; Hospital de Cancer de Barretos, Barretos, Brazil
Body Thyroid nodules may be diagnosed in half of the population examined through ultrasonography. However, only 0.1% of those nodules are cancer. This fact creates an urgent need for new markers that might be used in a large scale to diagnose thyroid nodules malignancy. In order to investigate the clinical usefulness of some serum markers for CDT, we studied 165 patients, 31 patients with thyroid benign nodules and 216 controls. Serum VEGF, VEGF-C and Galectin-3 were identified by ELISA. Galectin-3 serum levels differed in subjects with DTC, benign nodules and controls (Kruskal-Wallis, $p = 0.005$) and distinguished malignant nodules from controls (Mann-Whitney, $p = 0.002$). However, serum Galectin-3 did not differentiate benign nodules from controls (Mann-Whitney test, $p = 0.197$) neither identified malignancy among thyroid nodules (Mann-Whitney test, $p = 0.884$). Serum VEGF expression could differentiate patients with DTC from both controls ($p = 0.015$) and benign nodules ($p = 0.041$). However, a ROC curve did not present any point of high specificity and sensitivity for the diagnosis of malignancy: a cutoff point of 193.18 pg/mL had a sensitivity of 4.8%, specificity of 82.3 %, positive predictive value of 83% and negative predictive value of 4.3% for the diagnosis of malignancy. Serum VEGF-C levels distinguished patients with benign nodules, malignant tumors and controls ($p = 0.025$). Patients with DTC differed from controls ($p = 0.046$), but did not differ from benign nodules ($p=0.242$). A cutoff of 7.2 ng/mL had a sensitivity of 11.1%, specificity 89.9%, positive predictive value of 84.8% and negative predictive value of 16.7% for malignancy. We conclude that serum VEGF, VEGF-C and Galectin-3 may help identify malignancy but do not appear to be promising markers from a clinical or epidemiological perspective.

Nothing to Disclose: MAM, AC, ECE, MBM, BG, ALC, LSW

sort_order 2736
Pub # P3-667
Session Information POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)
Title Skeletal-Related Events Are Common and Clinically Significant in Thyroid Cancer Patients with Bone Metastases
Author String V Leung, A Farooki, M Tuttle
MSKCC, New York, NY
Body
Introduction: In oncology, the clinical impact of metastatic bone disease is conveyed via a composite endpoint termed skeletal-related event (SRE) defined as either a new pathologic fracture, spinal cord compression, hypercalcemia, or the need for surgical or radiation therapy to an osseous metastasis. Moreover, reduction in SREs and prolongation of time to first SRE are endpoints required by the FDA for approval of antiresorptive agents in advanced cancers involving the bone. For example, intravenous bisphosphonates have been shown to reduce the 2-year incidence of SREs from 68% to 53%, and delay the time to first SRE from 7 months to 13 months in metastatic breast cancer. While bone metastases are known to occur in 2-13% of thyroid cancer patients and confer a poorer prognosis, the risk and rate of SREs following diagnosis of bone metastasis have not been previously described.
Methods: This was a retrospective chart review of 119 thyroid cancer patients with bone metastases evaluated at a tertiary care center designed to define the risk and rate of SREs over time.
Results: Out of 119 patients, 44% were female. Mean age at diagnosis was 53 yrs. 67% were stage M1. Poorly differentiated thyroid cancer was the most common histology (31%), followed by follicular thyroid cancer (24%), classical papillary thyroid cancer (15%), Hurthle cell carcinoma (14%) and follicular variant of papillary thyroid cancer (24%).
90/119 (76%) patients with documented bone metastases experienced a total of 277 SREs over a follow-up period of 1,063 patient-years. In total, 80/119 (67%) of the patients either presented with or developed at least one SRE within 2 years of the diagnosis of bone metastasis. The median time from identification of bone metastasis to first SRE was 6 months (excluding the 45 in whom an SRE occurred at the time of bone metastasis diagnosis). Out of the 90 patients who had an initial SRE, 64/90 (71%) went on to have a subsequent SRE at a median of 11 months later.
Conclusions: The 2-year incidence of SREs and median time to first SRE in metastatic thyroid cancer to the bone are very similar to those reported in breast cancer. These data confirm that bone metastases from thyroid cancer are associated with significant morbidity and provide preliminary data needed for the design of prospective clinical trials to assess the efficacy of antiresorptive agents such as IV bisphosphonates and RANKL inhibitors in metastatic thyroid cancer to the bone.

Disclosures: MT: Research Funding, Genzyme Corporation; Consultant, Abbott Laboratories; Veracyte, Inc.; Novo Nordisk. Nothing to Disclose: VL, AF

sort_order

2737

Pub #

P3-668

Session Information

POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)

Title

Therapeutic Implications of Diffuse Hepatic Uptake after Iodine-131 Therapy for Differentiated Thyroid Cancer

Author String

HA Ferris, G Williams, JA Parker, JR Garber
Beth Israel Deaconess Medical Center, Boston, MA; Beth Israel Deaconess Medical Center, Boston, MA

Body

Diffuse hepatic uptake (DHU) of I-131 seen on whole-body scans (WBS) following remnant ablation or treatment of scan-positive metastatic thyroid cancer is generally thought to represent hepatic metabolism of I-131-labeled thyroid hormone and its metabolites or thyroglobulin (TG). DHU may also be seen on post therapy scans in patients who have previously undergone remnant ablation with otherwise negative WBS. In this case DHU has been postulated to reflect either a potential therapeutic benefit of the therapy or alternatively merely represent metabolism of iodinated plasma proteins. The purpose of this study is to determine if diffuse hepatic I-131 uptake has any prognostic implications in otherwise scan negative patients.

Methods: This is a retrospective medical records review of patients treated for differentiated thyroid cancer at BIDMC between January 1990 and June 2006. This group included patients receiving therapy to ablate presumed remnant tissue as well as treatment for persistent disease as measured by TG or imaging. All patients included in the study had no remnant uptake and otherwise negative post-therapy scans. A total of 57 patients with 63 scans met these criteria. These scans were then scored for the extent of DHU on a scale of 0 to 5 with 0 being no uptake and 5 being intense uptake. Results: Twelve of the 57 patients were male. Average age was 52.1 years. 16 of 63 treatments were for remnant ablation. 10 of 57 patients had positive TG antibodies. Average liver uptake was similar in the ablation and the therapeutic groups (1.9 vs. 2.3, $p=0.3$). For 23 scans there were TG levels before and 6 months post-therapy. The change in TG post-therapy did not correlate with the degree of liver uptake. There was also no correlation with either I-131 dose or the presence of TG antibodies. There was a difference based on the intensity of the uptake in the rate of clinical cure, (negative TG and no radiographic evidence of metastasis) with a 46% cure rate for a liver score of 0-2 and only 15% cure for scores of 3-5 ($p=0.02$). The average length of follow up for cured patients was 4.6 years.

Conclusion: In patients with DHU with otherwise negative whole-body scans following I-131 treatment more intense hepatic uptake is associated with a reduced chance of complete response to radioactive iodine treatment.

Nothing to Disclose: HAF, GW, JAP, JRG

sort_order 2738
Pub # P3-669
Session Information POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)
Title Trends in the Incidence of Differentiated Thyroid Cancer over a Period of 15 Years in a Single Portuguese Institution (1996-2010)
Author String E Rodrigues, L Matos Lima, A Sousa, T Pimenta, D Carvalho
Hospital São João e Faculdade de Medicina do Porto, Porto, Portugal; Hospital São João, Porto, Portugal
Body
Background: In the last few years it has been reported, both in Europe and North America an increased incidence of differentiated thyroid cancer, mainly due to small papillary thyroid carcinoma.
Aims: The purpose of this study was to investigate the relation between rates of detection, tumour size, age and sex of patients diagnosed with thyroid cancer at a large university hospital in the north of Portugal during a period of 15 years (1996-2010)
Methods: We evaluated retrospectively the pathology reports of all patients with a definitive diagnosis of thyroid cancer submitted to thyroid surgery in our institution during the last fifteen years. Tumours were classified by size, according to TNM classification 7th edition. Statistical analysis was done with SPSS 18.0 for Windows.
Results: During this period a total of 1885 patients had a pathological diagnosis of thyroid cancer, 1614 women and 271 men with a mean age of 49,9±14,5 and 51,9±15,2 years old, respectively. The tumour size was [≤] 1 cm in 870 (44,8%), 1-2 cm in 553 (28,5%), 2-4 cm in 362 (18,6%), > 4 cm in 157 (8,1%) and unknown in 3 cases. Age at diagnosis was [≤] 45 years in 691 (36,7%) and > 45 years in 1194 (63,3%) patients. As expected the number of cases increased over this period of time. The proportion of small tumours ([≤] 2cm) increased from 46% in 1996 to 74,1% in 2010 (p=0,039). When we examined differences in tumour detection rate by age at diagnosis and sex we found a significant increase in the number of tumours detected in patients older than 45 years (50,9% in 1996 vs 71,4% in 2010).
Conclusions: Our findings suggest an increased detection rate of small, subclinical tumours, which in turns probably reflects the widespread use of diagnostic imaging and greater detection of small, nonpalpable thyroid nodules.

Nothing to Disclose: ER, LML, AS, TP, DC

sort_order

2739

Pub #

P3-670

Session Information

POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)

Title

Thyroglobulin Stimulation with Recombinant Human TSH in the Follow-Up of the Differentiated Thyroid Carcinoma: Evaluating the Results

Author String

C Sanabria, AM Ramos-Levy, E Gomez-Hoyos, I Runkle
San Carlos Clinic Hospital, Madrid, Spain

Body

Routine monitoring after initial surgery and radioactive iodine (¹³¹I) therapy in patients with differentiated thyroid cancer (DTC) includes periodic cervical ultrasound (US) and measurement of serum thyroglobulin (Tg) with an ultrasensitive assay every 6-12 months after recombinant human TSH (rhTSH) stimulation. This stimulation is a good predictor of remission, and there are a few cases of false-positive, excluding those patients with anti-tg antibodies positives. The rhTSH stimulation includes two consecutive days (4th and fifth after the administration) for the measuring of TSH, Tg and the anti-bodies.

OBJECTIVES: To compare the biochemical results for TSH, Tg, Anti-bodies (Tg and TPO) the days 4th 1 and fifth 2 after the administration of rhTSH and to know the utility of the measure of the two days in the follow-up of the patients with DTC.

PATIENTS AND METHODS: We studied 72 patients (19 men, 53 women), with a mean age at diagnosis of 44.85 (16-76) and an actual mean age of 51.64 (23-84), diagnosed of DTC. 13 patients had stage T3-T4. Levels of TSH were measured with IRMA (INMUNOTECH), r 0.3-5 mcUI/ml, S 0.02; Tg with IRMA (MEDIPAN), r 2-70 mcg/ml, S 0.3; Tg anti-bodies with RIA (IDS), <80 UI/ml, S 6; TPO anti-bodies with RIA (MEDIPAN), <40 UI/ml, S 6. SPSS 15.0 was used for the statistical analysis, with non parametric methods.

RESULTS: The median values obtained were: TSH1 69.0 mcUI/ml (± 19.1) and TSH2 27.8 mcUI/ml (± 16.4), with a significant difference (p < 0.0001); Tg1 0.001 (0.01-17.7) and Tg2 de 0.001 mcg/ml (0.01-16.5) (7 patients had Tg [ge] 2 in both Tg1 and Tg2); Tg anti-bodies1 8.5 UI/ml (0.001-50) and Tg anti-bodies2 8.0 UI/ml (0.01-70); TPO anti-bodies1 0.001 UI/ml (0.001-281), TPO anti-bodies2 0.001 (0-001-314) (p 0.036). There was a negative correlation between the median levels of Tg1 and Tg anti-bodies1 (p 0.2) and between Tg2 and Tg anti-bodies2 (p 0.08). We found a positive correlation between Tg1 and Tg1 (p < 0.0001).

CONCLUSIONS: The significant difference between TSH1 and TSH2, shows that the highest TSH response to rhTSH stimulation occurs on the fourth day. The strong positive correlation between Tg1 and Tg2 and the negative one between Tg and Tg anti-bodies, could mean that the biochemical results on the fifth day are unnecessary in the follow-up of DTC.

Nothing to Disclose: CS, AMR-L, EG-H, IR

sort_order 2740
Pub # P3-671
Session Information POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)
Title Utility of Pre-Therapy Whole Body Scans in Management of Well-Differentiated Thyroid Cancer
Author String P Santhanam, A Yaqub
Joan C Edwards School of Medicine, Huntington, WV
Body
Introduction
The utility of a pre-therapy radioiodine whole body scan (WBS) prior to Radioiodine (RAI-131) ablation of the remnant thyroid tissue in post-thyroidectomy patients with differentiated thyroid cancer is not yet clearly defined. The objective of our study was to evaluate the utility of pre-therapy WBS scan in influencing the decision to treat or to modify the dose of RAI-131 for thyroid remnant ablation in post-thyroidectomy patients with differentiated thyroid cancer.
Methods
This was a retrospective case-control study review. Patients were seen at the Marshall University endocrinology clinic. We reviewed patients records for the following variables: age, diagnosis, type of surgery, TNM stage, size of the tumor, multifocality, lymphovascular invasion, extrathyroidal extension, thyroglobulin at withdrawal, peak TSH achieved, pre-therapy WBS, dose of I-131 administered, post-therapy scan, recurrence/persistence rates, location of recurrence, follow-up ultrasound, thyroglobulin and duration of follow up. We used student t-test to compare the I-131 dosage between persons who had a pretreatment scan (cases) group and those who did not (controls).
Results
84% of patients were females. Family history of thyroid cancer was present in 12.5 %, multifocality in 44.6 %, lymphovascular invasion in 24.2 %, recurrence in 9.7 % and persistence in 23.2 % of patients. The most common location of recurrence was neck (thyroid bed and cervical lymph nodes combined together had 70% of all recurrences). The mean I-131 doses in the case and control groups were 93.14 mCi (+/- 31.7) and 101.26 mCi (+/- 28.1) respectively. Of the data available, 58.3 % (56/96) of patients had pretherapy scan while 41.7 % (40/96) of patients did not. There was no difference in the I-131 dose administered in the persons who had a pretreatment scan as compared to those who did not (p=0.127). There was no difference in the tumor burden (sum total of sizes of all foci of tumor in cases with multifocality) in patients with or without a pretreatment scan (p=0.176). The size of the tumor did not influence the decision to do the pretherapy scan.
Conclusions
Results of pre-therapy WBS scans did not influence either the physicians' decision to treat with RAI-131 or the recommended dose of RAI-131 for thyroid remnant ablation. The dose of I-131 administered for remnant ablation of thyroid tissue did not differ among patients who have had pretreatment scan as compared to those who did not.
Nothing to Disclose: PS, AY

sort_order 2741
Pub # P3-672
Session Information POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)
Title A Comparison of Iodine-131 Postoperative Ablation in Stage 1 Differentiated Thyroid Cancers in Norman Regional Hospital in 2008 vs. 2009 To Assess Practice Change after 2009 American Thyroid Association Guidelines Regarding Use of I 131 A
Author String L Mirza
Norman Regional Hospital, Norman, OK
Body
Background:
Radioactive iodine has been used to treat thyroid cancer since 1946. Radioactive iodine treatment is given after thyroidectomy to ablate the remnant thyroid tissue and to treat metastatic thyroid cancer. Studies have shown regional differences in opinions on adjuvant radioactive iodine treatment of thyroid carcinoma within Canada and the United States. (1) According to the American thyroid association guidelines 2009, I 131 is not indicated in stage 1 differentiated thyroid carcinoma unless patients have multifocal disease, nodal metastases, vascular invasion or more aggressive histological features. I 131 treatment is associated with both long and short term complications such as nausea, vomiting, ageusia, pain, recurrent sialadenitis, xerostomia, dental caries, pulmonary fibrosis, nasolacrimal outflow obstruction and second primary malignancies. (2,3)
Methods:
We obtained data for Norman Regional Hospital Thyroid cancer cases which were diagnosed and treated in 2008 and 2009, including age, gender, stage and type of Thyroid cancers, mode of treatment post-op I 131 treatment, cancer histology and behavior and use of chemotherapy. This data was compared to other hospitals in the state and nationwide. Percentages of stage 1 thyroid cancer patients who received adjuvant radioactive iodine in 2008 and 2009 were compared.
Results:
There were 26 cases of thyroid cancer cases in 2008 which increased to 32 in 2009. There were 20/26 (76%) stage 1 thyroid cancer cases in 2008 and 24/32 (75%) in 2009. We noted that 11/20 (55%) patients with stage 1 thyroid cancer were treated with adjuvant radioactive iodine in 2008 which reduced to 10/32 (31%) in 2009.
Conclusion:
A higher percentage of thyroid cancer patients at NRH received adjuvant treatment with I 131 as compared to all other hospitals nationwide in 2008. Fewer patients with stage 1 thyroid cancer were treated with adjuvant radioactive iodine in 2009 which reflects a change in local practice after the release of 2009 American thyroid association guidelines.

1-Sawka AM et al.,Thyroid Dec;17(12):1235-42
2-Lee SL et al.,J Natl Compr Canc Netw. 2010 Nov;8(11):1277-86
3-Van Nostrand D.,Oral Dis. 2010 Oct 28

Nothing to Disclose: LM

sort_order

2742

Pub #

P3-673

Session Information

POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)

Title

Metabolic Syndrome in Patients with Thyroid Cancer

Author String

K Komarovskiy, SJ Winters, S Krishnasamy
University of Louisville, Louisville, KY; Robley Rex VA Medical Center, Louisville, KY

Body

Patients with metabolic syndrome (MetS), a state of insulin resistance and hyperinsulinemia, are at increased risk for several types of cancer including colorectal, vaginal, endometrial and breast cancer possibly via insulin activation of IGF-I receptor (IGF-IR) signaling. Thyroid progenitor cells express IGF-IR and IGF-IIR, and thyroid cancer cells have predominance of IGF-IIR and insulin receptor isoform A. In a prospective study of 549944 Europeans, the incidence of thyroid cancer increased with hyperglycemia in men but not women. Among residents of mild-moderate iodine-deficient area, thyroid volume was greater and nodules occurred more often in those with MetS. In this study we investigated the association between thyroid cancer, MetS and its components in a population of U.S. veterans.

We conducted a retrospective cohort study of patients who had thyroidectomy or lobectomy from 2000 to 2010 at Robley Rex VA Medical Center. We identified 21 patients (19 M, 2 F) with histology confirmed thyroid cancer (1 anaplastic, 3 lymphomas, 1 medullary, 3 FTC, 13 PTC). 21 age/gender matched patients who had thyroidectomy for nodular disease but no thyroid cancer represented the controls. We evaluated TSH and modified ATP III criteria for MetS: BMI [ge] 30 kg/m², BP [ge] 130/85 mmHg or treatment for HTN, fasting glucose [ge] 110 mg/dl or treatment for DM, TG [ge] 150 mg/dl, HDL-C < 40 mg/dL (men) or < 50 mg/dL (women) at time of thyroidectomy. MetS was identified when 3 or more components were present.

The mean (\pm SD) age of cases was 65.19 \pm 14.34 and in controls was 63.76 \pm 12.17 (p = 0.73); 90% were Caucasians. The BMI in cases was similar to controls (31.48 \pm 5.86 vs 31.43 \pm 6.04 kg/m²; p = 0.97). MetS was present in 14/21 cases and 11/21 controls (p = 0.8); mean number of MetS components in the cases was 3.23 \pm 1.30 vs controls 2.95 \pm 1.39 (p = 0.67). 9/21 cases had diabetes vs 10/21 controls (p = 1.0). Cancer stage was unrelated to the number of MetS components: stage I 3.2 \pm 1.54, stage II 3.0 \pm 1.0, stage III 2.5 \pm 2.1, stage IV 2.6 \pm 1.2 (p = 0.93). TSH level in study group was not significantly (p = 0.065) higher in cases than controls: 2.51 \pm 2.46 vs 1.35 \pm 1.37U/L. PTC stage was similar (p = 0.49) in obese (BMI [ge] 30 kg/m²) and non-obese cases (2.5 \pm 1.38 vs 2.0 \pm 1.15).

In this cohort, there was no relationship between thyroid cancer and the components of MetS. Kentucky adults have a high prevalence of obesity (>30.9%) and diabetes (>10.6%); and thus may not be representative of other populations.

Nothing to Disclose: KK, SJW, SK

sort_order 2743
Pub # P3-674
Session Information POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)
Title Complementary and Alternative Medicine and Thyroid Cancer: Some Patients Use Kelp as Part of Their Treatment for Thyroid Cancer
Author String JE Rosen, P Gardiner, R Saper, G Bloom, EN Pearce, SL Lee
Boston Medical Center, Boston, MA; Boston Medical Center, Boston, MA; Thyroid Cancer Survivors' Association, New York, NY; Boston Medical Center, Boston, MA
Body **Background:** This report presents characteristics of kelp users among patients with papillary thyroid cancer.
Methods: Data were collected using a web-based online anonymous survey under IRB approval. This report is based on 1324 responses from subjects with thyroid cancer.
Results: Twenty one subjects reported using kelp during the last twelve months. Kelp users on average used 5.7 additional complementary and integrative medicine (CAM) modalities (range 0-18). The two most commonly used forms of CAM were multivitamins (18/21) and special diets (14/21). Next to these, the five most commonly used CAM practice therapies were prayer (12), yoga (10), meditation (9), acupuncture (8) and massage (8); the five most commonly used CAM biologic therapies were herbal supplements (13), herbal tea (12), naturopathy (11), homeopathy (10), garlic and ginger (10). Kelp was most often used with the intention of treating thyroid cancer (8/12, 75%). The majority of subjects used kelp ten or more times in the past 12 months (83%) and spent more than \$20/month on kelp (91%). In fact, 13% of subjects spent \$50 or more per month on CAM therapies. Eighty-three percent of respondents felt that kelp was helpful, none felt that kelp was harmful to their health. Thirty-three percent of kelp users reported their CAM use was not told to their physicians, and 67% reported that their physicians did not ask.
Conclusions: This survey is the first to describe the characteristics of kelp users in patients with thyroid cancer. The majority of the kelp users felt it was part of their thyroid cancer treatment. Some patients used kelp within 12 months of their radioactive iodine treatment. Dietary seaweeds or kelp contains variable amounts of iodine up to 6,571 mcg/g. This level of iodine intake is sufficient to block iodine uptake into malignant tissue rendering diagnostic whole body radioactive scans and therapeutic radioiodine therapies ineffective. In comparison to national surveys of CAM use, patients with thyroid cancer used CAM therapies twice as often as the general U.S. population; a significant proportion of them are neither asked by nor report their use of CAM to their physicians. Physicians who treat patients with thyroid cancer should be aware of these data to further assist in their assessment and care of these patients.
Nothing to Disclose: JER, PG, RS, GB, ENP, SLL

sort_order 2744
Pub # P3-675
Session Information POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)
Title A Case Series of Metastases to the Thyroid Gland
Author String C Moran, D Broderick, A Cahalane, D O'Shea
St Vincent's University Hospital, Dublin, Ireland
Body Thyroid metastases are clinically rare. The most commonly primary sites are breast, kidney and lung (1). We have identified only 4 cases of metastasis to the thyroid gland at our institution over the previous 15 years. Here we describe the clinical features and outcome of these cases.
A 38 year old male underwent an excision of a 22 cm liposarcoma from the left thigh and was subsequently found to have lesions consistent with metastases in his lungs, liver, sacral ala and thyroid on whole body PET imaging. Fine needle aspirate (FNA) of the thyroid nodule revealed abundant pleomorphic neoplastic cells, cytologically similar to the previous sarcoma. The patient is currently undergoing systemic chemotherapy.
A 60 year old male was diagnosed with Stage IV non small cell carcinoma of the lung after a mass was found on chest X-Ray. FDG-PET scanning revealed multiple pulmonary nodules, extensive lymphadenopathy and a left sided thyroid nodule. FNA of the thyroid revealed malignant cells similar to that seen in a mediastinal lymph node biopsy and the cells were TTF1 positive, however the morphology and clinical picture favoured a lung primary. He underwent six cycles of systemic chemotherapy with carboplatin and paclitaxel with partial response.
A 59 year old female was diagnosed with rectal carcinoma which was resected. She underwent lobectomy for pulmonary metastasis six years later. A FDG-PET scan ten years after her initial diagnosis revealed a thyroid lesion. FNA of this nodule revealed carcinomatous cells, consistent with metastatic colorectal cancer. She was subsequently diagnosed with metastatic disease in the bone, brain and cavernous sinus. Having received external beam radiotherapy, she is now being managed palliatively.
Lastly a 57 year old male presented 3 years following diagnosis of squamous cell carcinoma of the pyriform fossa. Again, his thyroid nodule was identified by FDG-PET scanning and FNA was consistent with metastatic keratinised squamous cell carcinoma.
Consistent with published data, all our patients had metastatic disease elsewhere at the time of diagnosis of thyroid metastases. However, all our patients were diagnosed following FDG PET scanning and had not presented with a clinically palpable thyroid nodule. The possibility of a thyroid metastasis should be borne in mind when investigating a focal thyroid abnormality on PET imaging, especially in the presence of a history of previous carcinoma elsewhere.

(1) Wood et al. Metastases to the Thyroid Gland: the Royal Marsden Experience, Eur J Surg Onc 30 (6) 583-8

Nothing to Disclose: CM, DB, AC, DO

sort_order 2745
Pub # P3-676
Session Information POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)
Title A Retrospective Evaluation of Papillary Thyroid Carcinoma Patients Followed in an Endocrinology Outpatient Clinic
Author String MS Gonen, SH Ipekci, M Ozturk, G Gonulalan, M Cakir, A Kaya, M Kulaksizoglu, F Aksoy, M Erikoglu, G Tastekin, H Esen
Selcuk University, Meram School of Medicine, Konya, Turkey; Selcuk University, Meram School of Medicine, Konya, Turkey; Selcuk University, Meram School of Medicine, Konya, Turkey; Selcuk University, Meram School of Medicine, Konya, Turkey; Selcuk University, Meram School of Medicine, Konya, Turkey
Body
Objective: The incidence of thyroid cancer has increased in the last decades. It is not clear if this increase is due to the improved diagnostic procedures or increased cancer frequency. Among all thyroid malignancies, papillary thyroid carcinoma (PTC) frequency is clearly more increased (1). Iodination programs may have a role in this acceleration (2).
Materials and Methods: Data of thyroid cancer patients who were followed in our endocrinology outpatient clinic were evaluated for this study. Four hundred twenty four patients (98.1%) had differentiated thyroid cancer (93.4% PTC, 4.5% follicular carcinoma, 2.1% hurtle cell carcinoma), 1 patient had undifferentiated (anaplastic) thyroid cancer, 7 (1.6%) patients had medullary thyroid cancer. Demographic and histopathological features, treatment type and metastases history were collected from the subgroup of PTC patients.
Results: Among PTC patients 63 (15.9%) were male, 333 (84.1%) were female and mean age was 53.3±14.3 years for men and 47.3±12.5 years for women (p=0.001). Body mass index (BMI) was 31.89±5.99 kg/m² for women and 28.56±6.22 kg/m² for men (p=0.005). Obesity (BMI[ge]30 kg/m²) rate was 59.2% overall.
A lump in the neck was the initial complaint in 196 (72.1%) patients, while 49 (18%) patients had thyroid incidentelomas. Thyroid hormone status was euthyroid in 78.3%, hyperthyroid in 9.6%, subclinical hyperthyroid in 8.1% and hypothyroid in 4%. Among the subjects who had preoperative ultrasonographic evaluation (n=158), 44 (27.8%) patients had a solitary nodule, while the rest had multiple nodules.
At the time of diagnosis, 71.1% of patients were stage T1, 73.3% of patients were stage N0. Eleven (2.8%) patients had distant metastases. Two patients had bone, 1 patient had brain, 11 patients had lung metastases. Eighty seven (22%) patients had multifocal disease in the thyroid. On the other hand, 72.1% versus 23.9% of patients had classical and follicular variant of PTC, respectively. Two hundred seventy three patients (76.9%) received radioactive iodine (I-131) therapy (100-200 mCi).
Conclusions: PTC composes 80% of all thyroid cancers (3). In our study group, PTC was seen in 91.7% of the patients while mean age was 48.5 years and it was 5.3 times more common in women than men. Significantly higher BMI values in female patients combined with increased PTC frequency may suggest a role for insulin resistance in carcinogenesis, however this issue needs further clarification.

1- Cramer JD, Fu P, Harth KC, Margevicius S, Wilhelm SM. Analysis of the rising incidence of thyroid cancer using the Surveillance, Epidemiology and End Results national cancer data registry. Surgery 2010;148:1147-52.
2- Feldt-Rasmussen U. Iodine and Cancer. Thyroid 2001;11:483-6.
3- Aschebrook-Kilfoy B, Ward MH, Sabra MM, Devesa SS. Thyroid Cancer Incidence Patterns in the United States by Histologic Type, 1992-2006. Thyroid 2011;21:1-10.

Nothing to Disclose: MSG, SHI, MO, GG, MC, AK, MK, FA, ME, GT, HE

sort_order 2746
Pub # P3-677
Session Information POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)
Title Advanced Hurthle Cell Carcinoma in a Belizean Woman: Treatment Options in Central America
Author String E Lawler, G Fareau
The Medical College of Wisconsin, Milwaukee, WI; The Medical College of Wisconsin, Milwaukee, WI
Body
Introduction: Hurthle cell thyroid carcinoma is an uncommon malignancy that often presents with evidence of distant metastasis. We report a fascinating case of a Belizean woman, and discuss the state of thyroid cancer care in Central America.
Clinical Case: A 51 year old woman was met by a traveling medical group doing missionary work in rural Belize. The woman was living with her 14 children in a small village in the jungle, and had limited healthcare access. She described a five year history of goiter, but noted that the goiter had doubled in size over the preceding six months. She was experiencing worsening hoarseness and dysphagia, and arrangement was subsequently made by the missionary group for her to come to the US for treatment of her goiter. A computerized tomographic (CT) scan of the neck identified a very large heterogeneous thyroid gland with evidence of tracheal deviation. She underwent a thyroidectomy at a community hospital, the pathology of which was remarkable for an 18.5 cm widely invasive Hurthle cell thyroid carcinoma. She was subsequently referred to the local academic medical center for surgery to remove significant residual tumor in the neck. She received adjuvant radioactive iodine, with uptake noted in the thyroid bed and vertebral spine on post-treatment imaging. She was started on levothyroxine to suppress her TSH below 0.1 IU/ml, and continues to return to the US for ongoing follow up.
Discussion: The recent publication of consensus guidelines has improved the standardization of thyroid cancer care in much of the world. However, application of these guidelines requires sufficient resources and access to specialist care, which are frequently limited in developing countries. We discuss the state of thyroid cancer management in various Central American countries.
Nothing to Disclose: EL, GF

sort_order 2747
Pub # P3-678
Session Information POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)
Title Mucinous Metaplasia: A New Feature of Aggressive Papillary Thyroid Carcinoma?
Author String A Schneider, G Leiman
University of Vermont Medical Group at Fletcher Allen, Burlington, VT; University of Vermont Medical Group at Fletcher Allen, Burlington, VT
Body
Background
The cytodiagnosis of papillary thyroid cancer is based on cellular morphology emphasizing key nuclear and cytoplasmic features. Intracytoplasmic mucin globules usually eliminate papillary thyroid carcinoma from the diagnostic differential. Presented is a case with an aggressive pattern of invasion which had the typical cellular features but also intracytoplasmic mucin.
Clinical Case
A 79-year old man presented with a 2 cm thyroid mass and cervical lymphadenopathy. On-site rapid interpretation of the lymph node fine needle biopsy (FNB) provided the preliminary diagnosis of papillary thyroid carcinoma.
Microscopic examination of the permanent slides showed a massive population of neoplastic cells with rare lymphocytes in the background. The malignant cells were arranged in large monolayer sheets with numerous stromal cores and poorly formed papillary architecture. The cells were of medium size with a moderate amount of cytoplasm and enlarged nuclei with pale chromatin and numerous nuclear grooves. Rare intranuclear inclusions were also noted. Papanicolaou stain revealed the presence of intracytoplasmic mucin concretions raising uncertainty about the origin. The case was signed out as metastatic adenocarcinoma to lymph node, origin indeterminate.
In search for the primary tumor a PET scan redirected focus to the patient's thyroid. The thyroid mass itself was subjected to FNB and demonstrated identical cellular findings as the lymph node. Surgical pathology confirmed papillary carcinoma, with focal tall cell features, mucin and an aggressive pattern of invasion.
Clinical Lessons
Making the cytopathologic diagnosis of papillary thyroid carcinoma from FNB frequently does not pose many challenges. Key cellular features including enlarged nuclei, pale chromatin, nuclear grooves and nuclear pseudo-inclusions will point to papillary thyroid carcinoma. All of these characteristics were present in this case; complicating the diagnosis was the presence of intracytoplasmic mucin globules.
Mucin is a rare and not well-recognized feature of papillary thyroid carcinoma as evident by the small number of case reports in the literature. One source described very similar features in an aggressive tumor and termed this [ldquo]mucinous metaplasia[rdquo] (1). It would appear, therefore, that from a purely morphological standpoint, intracytoplasmic mucin vacuoles can be seen in papillary thyroid carcinoma. Additionally, this feature may characterize an aggressive variant.

(1) Morrison C, Wakely P, Jr., Mod Pathol. 2001;14(4):361-365.

Nothing to Disclose: AS, GL

sort_order 2748
Pub # P3-679
Session Information POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)
Title Initial Therapy with Either Thyroid Lobectomy or Total Thyroidectomy without Radioactive Iodine Remnant Ablation Is Associated with Very Low Rates of Structural Disease Recurrence in Properly Selected Patients with Differentiated Thyroid Cancer
Author String F Vaisman, A Shaha, S Fish, R Tuttle
Universidade Federal do Rio de Janeiro and Instituto Nacional do Cancer, Rio de Janeiro, Brazil; Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan Kettering Cancer Center, New York, NY
Body **Background:** Individualized and risk stratified approach to the management of patients with differentiated thyroid cancer is an ongoing trend over the past few years. In this context, the role of less aggressive approach in selected patients is still controversial.
Objective: To describe the risk of structural disease recurrence in a cohort of differentiated thyroid cancer patients selected for treatment with either thyroid lobectomy or total thyroidectomy without radioactive iodine remnant ablation (RRA).
Design and Patients: This is a retrospective review of 289 patients were selected for either thyroid lobectomy (n=72) or total thyroidectomy (n=217) without RRA and followed with modern disease detection tools in a tertiary referral center. Most patients had papillary thyroid cancer (89%) without clinically evident lymph node metastases (91%). However, 55% (156/289) of patients had primary tumors that greater than 1 cm, and 10% (28/289) had minor extrathyroidal extension. The primary endpoint was detection of recurrent/persistent structural disease.
Results: After a 5 year median follow up, structural disease recurrence was detected in 2.3% (5/217) of patients treated with total thyroidectomy without RRA, and in 4.2% (3/72) of patients treated with thyroid lobectomy. Size of the primary tumor, the presence of cervical lymph node metastases, and ATA risk category were all statistically significant predictors of recurrence. Changes in serum thyroglobulin were not helpful in identifying the presence of persistent/recurrent structural disease. Importantly, 88% (7/8) of the patients that had recurrent disease were rendered clinically disease free with additional therapies.
Conclusions: Initial risk stratification is able to identify a cohort of patients with differentiated thyroid cancer with a very low risk of structural disease recurrence following treatment with either thyroid lobectomy or total thyroidectomy without RRA. Our data strongly support a selective approach to the initial management of thyroid cancer.

(1) Cooper DS et al Thyroid(2009);1167-1214
(2) Shaha AR et al Ann Surg Oncol (1997);328-333
(3) R. Michael Tuttle et al Thyroid(2010);1341-1349

Disclosures: RMT: Research Funding, Genzyme Corporation; Consultant, Abbott Laboratories, Veracyte, Inc., Novo Nordisk. Nothing to Disclose: FV, AS, SF

sort_order 2749
Pub # P3-680
Session Information POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)
Title Intraoperative Ultrasound-Guided Needle Localization (IOUSNL) of Malignant Lymph Nodes in the Management of Recurrent Differentiated Thyroid Cancer
Author String CD Uy, KC Kort, JM Hsu, RE Izquierdo
State University of New York Upstate Medical University, Syracuse, NY; State University of New York Upstate Medical University, Syracuse, NY
Body Introduction: Patients with well-differentiated thyroid cancer have excellent survival after near-total thyroidectomy and I-131 ablation. However, lymph node metastases at diagnosis may be difficult to eradicate (1). Two recent studies commented on the benefits of ultrasound (US) guided hook needle localization of malignant lymph nodes in papillary thyroid cancer (PTC) (2,3). Objective: This retrospective study examines the outcome of intraoperative US-guided needle localization (IOUSNL) in patients with recurrent PTC. Methods: Ten patients with PTC presented with cervical lymph node recurrence or disease persistence. They all had previous neck operations. Neck US detected locoregional recurrences in patients with elevated serum thyroglobulin levels that were non-radioactive iodine avid. Suspicious lymph nodes were aspirated and patients with FNA-proven malignant lymph nodes were localized intraoperatively under US guidance with a Hawkins needle and guidewire and underwent resection. Follow-up imaging and laboratory values after 3 to 5 years were reviewed. Results: IOUSNL successfully identified and guided resection of 23 metastatic lymph nodes. Within six months post-operatively, basal serum thyroglobulin level decreased to <1ng/mL in three of 10 patients. In another patient, the basal serum thyroglobulin level decreased to <1ng/mL after a second intraoperative needle localization procedure. Six patients had persistent disease after the procedure. After three to five years of follow-up, three patients remained disease-free. In the 7 patients with persistent disease or recurrent disease, only two had progressive disease. There was only one minor complication associated with IOUSNL (puncture of the internal jugular vein). Conclusions: IOUSNL of metastatic lymph nodes in recurrent thyroid cancer facilitated the successful resection of malignant lymph nodes with minimal risks. As compared to modified radical lateral and central neck dissection, IOUSNL and focal neck excision of malignant lymph nodes required less OR time, resulted in a much smaller scar, and was associated with a lower complication rate. Despite that only 30% of patients with recurrent thyroid cancer were disease free at 3 years, only two patients in our cohort demonstrated disease progression. The usefulness of this procedure may be limited to selected patients, i.e. those with recurrent disease localized to a specific area and in whom a more extensive surgery would be too morbid.

(1) Al-Saif et al., J Clin Endocrinol Metab, 2010; 95(5):2187
(2) Duprez et al., Eur J Radiol, 2010; 73:40
(3) Triponez et al., J Clin Endocrinol Metab, 2006; 91 (12):4943

Nothing to Disclose: CDU, KCK, JMH, REI

sort_order 2750
Pub # P3-681
Session Information POSTER SESSION: CLINICAL - Thyroid Cancer (1:30 PM-3:30 PM)
Title MALT Thyroid Lymphoma: An Unusual Case of Thyroid Cancer with Uncertain Prognosis
Author String PG Nikolopoulos, M Peppas, K Pinelopi, D Lapatsanis, G Dimitriadis, D Hadjidakis
Attikon University Hospital Athens, Athens, Greece; Athens University Medical School, Athens, Greece; Patision General Hospital, Athens, Greece; Attikon University Hospital Athens, Athens, Greece
Body
Background: Primary thyroid lymphoma represents 2-8% of all thyroid malignancies and 1-2% of all extranodal lymphomas. The majority of cases are non-Hodgkin's lymphomas of B cell origin. However, Hodgkin's, T cell and mucosa-associated lymphoid tissue (MALT) thyroid lymphomas have been also reported, which are often difficult to be diagnosed based on the morphological and clinical criteria. A number of factors have been associated with the pathogenesis of thyroid lymphoma, including autoimmune Hashimoto's thyroiditis, Epstein-Barr virus and radiation. Herein, we describe the case of a 44-year-old female who was diagnosed with MALT thyroid lymphoma in the background of multinodular goiter of autoimmune origin.
Clinical case: A 44 year-old woman, with autoimmune thyroiditis on L-thyroxine treatment (100[μg/d]), was referred to our department for further evaluation of a rapidly growing mass of the thyroid gland, associated with gradually increased pain and dyspnea. The hormonal investigation revealed normal TSH levels and positive thyroid antibodies, indicating a properly treated autoimmune thyroiditis. A Doppler ultrasound of the thyroid gland revealed multiple hypoechoic nodules (max. diam. 2cm) with microcalcifications and increased peripheral and central vascularity, suspicious for malignancy based on the fine needle aspiration (FNA) findings. Due to the suspicious ultrasound and cytologic findings and the positive for thyroid cancer family history (mother and sister), total thyroidectomy was performed. The pathology showed monoclonal plasma cells infiltration with the presence of big epithelial histiocytes, indicative of MALT thyroid lymphoma on the background of autoimmune thyroiditis. Further evaluation with scanning tomography of the neck, thorax and pelvis, bone biopsy, gastroscopy and colonoscopy, were negative. The patient was referred for radiotherapy and currently is adequately replaced with L-thyroxine.
Discussion/Conclusion: Primary MALT thyroid lymphoma is a rare thyroid neoplasm with an uncertain prognosis. Radiotherapy and/or chemotherapy are considered as possible therapeutic options. However, the proper timing but also the impact of the therapeutic intervention on the recurrence rate and the prognosis of patients with primary MALT thyroid lymphoma has not been fully addressed and needs further investigation.

Nothing to Disclose: PGN, MP, KP, DL, GD, DH

sort_order 2751
Pub # P3-682
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Diabetes, Obesity, Thyroid, Calcium/Bone & Miscellaneous (1:30 PM-3:30 PM)
Title Nationwide Study of Nephrogenic Diabetes Insipidus in Japan
Author String M Fujimoto, N Miyahra, R Nishimura, T Hanada, Y Kawashima, S Okada, K Hanaki, S Kanzaki
Faculty of Medicine Tottori University, Yonago, Japan; Faculty of Medicine Tottori University, Yonago, Japan
Body Nephrogenic diabetes insipidus (NDI) is an incurable disease with mental retardation, growth disorder, renal dysfunction and other complications. In some cases with NDI, it reported the difficulty in diagnosis because of mild symptoms. Moreover, the actual details of clinical course on NDI were still unknown. Accordingly, we performed a questionnaire about NDI to members of the Japanese Society for Pediatric Endocrinology, for Pediatric Nephrology, for Endocrinology and Nephrology from Dec. 2009 to Feb. 2010. We would like to present the results of those: the etiology, complication, and therapy and gene mutation of NDI.
Number of reported NDI in the survey was 155 cases; 124 cases were congenital NDI, and 36 cases were secondary. Most of secondary NDI were induced by lithium carbonate preparation. In 56 patients (36%) of NDI, structural abnormality of the kidney and urinary system were accompanied. Moreover, 23 cases (19%) of congenital NDI had mental retardation which appeared to be caused by hypernatremia and hyperosmolality. NDI patients mainly received thiazide diuretics, and some patients responded to treatment with desmopressin (DDAVP). 78 cases (60.4%) of NDI were performed gene analysis, and 56 patients of those were detected arginine vasopressin receptor type 2 (AVP2R) mutation and 7 patients (9.0%) of those had aquaporin-2 (AQP2) mutation. The case with AVPR2 mutation (D85N) showed a mild NDI phenotype and DDAVP was effective. We performed the first largest investigation about clinical course of NDI in Japan. Those findings suggest that early diagnosis and the cautious examination for abnormality of the urinary system are critically important to prohibit severe complication. Our results provide an important information on clinical course of NDI, and valuable information for managing patients with NDI.
Nothing to Disclose: MF, NM, RN, TH, YK, SO, KH, SK

sort_order 2752
Pub # P3-683
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Diabetes, Obesity, Thyroid, Calcium/Bone & Miscellaneous (1:30 PM-3:30 PM)
Title The Prevalence of Celiac Disease in the Type 1 Diabetes Mellitus Patient Population at Children's Hospital Medical Center of Akron
Author String TS Musick, A Salvator, W Riley
Children's Mercy Hospitals and Clinics, Kansas City, MO; Children's Hospital Medical Center of Akron, Akron, OH; The University of Texas Medical Branch at Galveston, Galveston, TX
Body
Objective: Patients with type 1 diabetes mellitus have an increased incidence of celiac disease. This study was performed to determine the prevalence of celiac disease and the impact of the gluten free diet on diabetes control.
Methods: A retrospective chart review was performed on all type 1 diabetes mellitus patients seen in the Diabetes Center at Children's Hospital Medical Center of Akron (CHMCA) in Akron, Ohio between 01/10/06 and 11/09/07. Patients were selected based on the ICD 9 codes for type 1 DM and/or DKA, which resulted in a total of 722 patients. A total of 645 patients met the inclusion criteria. Patients were excluded if they did not have type 1 diabetes, had not been seen in the selected time frame, had only been seen in the inpatient setting, or the chart could not be located. Serum IgA transglutaminase antibody was measured to screen the patients for celiac disease. Endoscopic biopsy of the small bowel was required to confirm the diagnosis.
Results: 7% of the patients had positive antibodies for celiac disease. 4% of the total population, which is 65% of the antibody positive population, was confirmed to have celiac disease. The patients with both disease states were diagnosed with diabetes earlier in life with a mean age at diagnosis of 6.1 years (p value of 0.01). 37% of patients were diagnosed with celiac disease within one year of diagnosis of type 1 diabetes mellitus. Hemoglobin A1c did not significantly change with the introduction of the gluten free diet. Height and weight percentiles were maintained after the patients were started on a gluten free diet.
Conclusion: The prevalence of celiac disease in type 1 diabetes mellitus at Children's Hospital Medical Center of Akron of 4% correlates with the national average of 1-5%. Children diagnosed with both disease states were younger at the age of diagnosis of type 1 diabetes. Glycemic control as evident by Hemoglobin A1c, growth rate, and weight gain were maintained once the gluten free diet was initiated.
Nothing to Disclose: TSM, AS, WR

sort_order 2753
Pub # P3-684
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Diabetes, Obesity, Thyroid, Calcium/Bone & Miscellaneous (1:30 PM-3:30 PM)
Title BMI Z-score but Not Pancreatic Antibody Status Is Associated with Insulin and C-peptide Levels at Diabetes Presentation in African-American Children
Author String P Gumus, R Gomez, A Vargas, JM Hempe, SA Chalew
Louisiana State University Health Sciences Center and Children's Hospital, New Orleans, LA; The Children's Hospital Research Institute for Children, New Orleans, LA
Body
We previously reported that there were no differences in age, HbA1c, BMI, blood glucose (BG), insulin and C-peptide levels at the time of diagnosis or HbA1c one year post diagnosis distinguishing GAD-65 antibody (Ab) positive from Ab negative obese African American (AA) children with diabetes. In this study we extended our observations to include lean AA children with diabetes. Our expectation was that Ab positive patients would have lower levels of insulin and C-peptide at presentation and hence higher HbA1c.
Records of lean and obese children self-identified as AA and diagnosed with diabetes were retrospectively analyzed. Patients had to have initial presentation of diabetes at Children's Hospital of New Orleans, and be under 19 years of age. Anti-GAD65, anti-insulin, ICA-512, islet cell antibodies (Ab) as well as HbA1c, BG, insulin and C-peptide levels were drawn at the time of diagnosis. Patients were classified as Ab positive if any anti-pancreatic Ab titer was positive. The initial clinical diagnosis of the patient whether type 1 or type 2 was also noted. HbA1c, insulin and C-peptide levels were considered as dependent variables in statistical models which included Ab status, gender, age, BMI z-score, BG as independent covariates. Log transformation of variables was performed when necessary.
Records of 54 AA children were available for analysis. There was no statistical association of Ab status nor initial clinical diagnosis with HbA1c, insulin or C-peptide level. BMI z-score was strongly associated with insulin ($p=0.0012$) and C-peptide ($p<0.0001$) levels. Gender and age also influenced C-peptide. In general, higher BMI z-score, female gender and age were associated with higher C-peptide levels.
Although potentially helpful in determining etiology, pancreatic autoantibody levels do not have an association with HbA1c, insulin or C-peptide levels in AA children with new onset diabetes. However, BMI has the most robust association with insulin and C-peptide levels at presentation.
Nothing to Disclose: PG, RG, AV, JMH, SAC

sort_order 2754
Pub # P3-685
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Diabetes, Obesity, Thyroid, Calcium/Bone & Miscellaneous (1:30 PM-3:30 PM)
Title Sexual Dimorphisms in the Associations of BMI and Body Fat with Pubertal Development in Boys and Girls
Author String MK Crocker, EA Stern, LB Shomaker, SA Brady, AH Ali, M Tanofsky-Kraff, VS Hubbard, JA Yanovski
National Institutes of Health, Bethesda, MD; Uniformed Services University of the Health Sciences, Bethesda, MD; Department of Health and Human Services, Washington, DC
Body **Background:** Recent studies suggest obesity accelerates breast development in females but conversely slows testicular development in males. To investigate this phenomenon, we examined pubertal development and body composition in a large cohort of carefully phenotyped youth enriched for presence of obesity (BMI [ge] 95th percentile standard for age and sex). **Methods:** 1067 youth (59% female, 51% obese) ages 5-17y were assessed to determine breast Tanner stage (BTS), pubic hair Tanner stage (PHTS), testicular size (TS), BMI (to calculate BMI z score), percent fat mass (%FM) by DEXA or by air displacement plethysmography in 257 participants where DEXA was not performed, bone age (BA), estradiol (E2), testosterone (T), and androstenedione (A4). **Results:** 45.3% of boys and 20.5% of girls were prepubertal. Adjusting for age and race, there was a significant interaction between sex and body composition (BMI z or %FM) in the prediction of pubertal status (p<0.05). Among girls only, BMI z (p<0.001, OR=1.86) and %FM (p<0.001, OR=110.98) were associated with a higher odds of being pubertal (vs. pre-pubertal). Accounting for age and race, girls' BMI z and %FM were related to greater BTS, BA, BA advancement (p's<0.001), and PHTS (p's<0.05). Girls' BMI z and %FM were not associated with E2 and A4. Conversely, among boys, adjusting for age and race, there was an inverse relationship between BMI z (p=0.01) or %FM (p<0.001) and TS. Average TS for boys with a BMI z <2 was 9.2cc (CI 8.6-9.8) compared to 7.1cc (CI 6.5-7.8) for boys with a BMI z [ge]2 (p<0.001). In boys, BMI z (p=0.01) and %FM (p<0.001) were also negatively associated with PHTS; however, boys' BTS, BA, and BA advancement were all positively associated with BMI z and %FM (p's<0.001). Among boys, BMI z and %FM were positively associated with E2 (p's=0.02), while %FM was negatively associated with A4 (p=0.03) and T (p<0.001). **Discussion:** There are marked sexual dimorphisms in pubertal development between boys and girls with high adiposity. Obese girls have uniformly advanced BTS, PHTS, and BA; obese boys have smaller testes, lower PHTS, lower T, and lower A4 despite their increased BTS, BA, and higher E2 concentrations. We hypothesize these obesity-related differences are caused by increased peripheral aromatization of androgens to estrogens in adipose tissue, stimulating breast development and BA advancement directly in both obese girls and boys, but inhibiting the gonadotropins that promote testicular development.

Sources of Research Support: Intramural program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, DNRC, NIDDK, and the National Institute on Minority Health and Health Disparities.

Nothing to Disclose: MKC, EAS, LBS, SAB, AHA, MT-K, VSH, JAY

sort_order 2755
Pub # P3-686
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Diabetes, Obesity, Thyroid, Calcium/Bone & Miscellaneous (1:30 PM-3:30 PM)
Title Waist Circumference as a Potential Indicator of Insulin Resistance in Prepubertal Girls with Premature Adrenarche
Author String C Capone, AT Gerken, DJ McMahon, SE Oberfield, AB Sopher
Columbia University Medical Center, New York, NY; Columbia University Medical Center, New York, NY
Body **Background:** Premature adrenarche (PA) is the appearance of sexual hair associated with the production of adrenal androgens in girls before the age of 8 years in the absence of enzymatic defects of steroidogenesis, and is associated with insulin resistance (IR). Waist circumference (WC) has been shown to identify obese children at risk for IR; however, few studies have addressed whether prepubertal girls with PA have greater WC, or if WC predicts IR in this group.
Objective: To determine if prepubertal girls with PA have greater WC than controls and if there is a difference in the relationship between WC and IR in PA girls compared to controls.
Methods: 44 prepubertal girls (5-9 yr), 30 PA (BMIz:1.4±1.5, WC:62.4±9.1cm) and 14 controls (BMIz:1.4±1.1, WC:64.8±11.5cm) had a 1.75g/kg body weight (max75g) OGTT with glucose and insulin obtained at 0, 30, 60, 90 and 120 min. WBIS and HOMA (IR cutoff>2.72 (1)) were calculated to determine IR. WC, height, and weight were measured. BMI, BMI and WC z-scores (BMIz,WCz) were calculated. Baseline characteristics were evaluated by t-tests. The accuracy of WC in predicting IR by WBIS and HOMA was assessed by receiver operator curve (ROC) analysis and by comparing the areas-under-the-curve (AUC); a 95% confidence interval was used for statistical significance. Pearson correlations were used to assess the relationship between IR and anthropometric measures in PA and controls.
Results: PA and control subjects did not differ in age, BMIz, WC or WCz. Correlations among WBIS or HOMA and anthropometric measures did not differ between PA and controls. WC did not discriminate IR by HOMA in controls (AUC=0.58, p=0.59), but showed good discrimination in PA (AUC = 0.89, p<0.046). However, there was no difference between the groups in comparison of the ROCs for WC. Spline fit of WC against WBIS showed lower WBIS for a given WC in PA compared to controls, particularly at the lower values of WC.
Conclusions: In this pilot study, prepubertal girls with PA did not have greater WC for BMIz, but did have greater IR at lower WC when compared to controls. Our findings show that evidence of insulin resistance manifests at a lower WC in PA girls as compared to controls, suggesting that prepubertal girls with PA have a disproportionate risk of IR at a lower WC compared to their unaffected peers.

(1) Hirschler et al., Arch Pediatr Adolesc Med 2005; 159:740

Nothing to Disclose: CC, ATG, DJM, SEO, ABS

sort_order 2756
Pub # P3-687
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Diabetes, Obesity, Thyroid, Calcium/Bone & Miscellaneous (1:30 PM-3:30 PM)
Title Favorable Metabolic Syndrome Parameters and Serum YKL-40 Levels in Children Born after Intracytoplasmic Sperm Injection (ICSI)
Author String A Gkourogianni, A Margeli, I Kosteria, M Konsta, D Loutradis, G Mastorakos, I Papassotiriou, C Kanaka-Gantenbein, G Chrousos
Athens University Medical School, Athens, Greece; Aghia Sophia Children's Hospital, Athens, Greece; Athens University Medical School, Athens, Greece; Athens University Medical School, Athens, Greece
Body We previously reported that children conceived with conventional in vitro fertilization (IVF) have increased arterial blood pressure and circulating triglycerides, both early components of the metabolic syndrome (MS). No discrete studies have been done in children conceived with intracytoplasmic sperm injection (ICSI). YKL-40 (also called human cartilage glycoprotein 39 or CH3L1) is a new potential biomarker of acute and chronic inflammation. It is mainly produced by macrophages and neutrophils and, like CRP, its production is stimulated by proinflammatory cytokines. Increased circulating levels of YKL-40 have been reported in various conditions characterized by inflammation such as bacterial infections, inflammatory rheumatic and gastrointestinal diseases and cancer. Recently, it was proposed that YKL-40 might be implicated in the low-grade inflammation of atherosclerosis, while it was found elevated in patients with insulin resistance, as well as patients with diabetes type 1 and 2. We investigated the presence of metabolic syndrome parameters, including circulating YKL-40 levels, in children conceived by ICSI and naturally conceived (NC) children. Eighty-four pre-pubertal children were included in the study: 42 born after ICSI and 42 NC children, matched for age and sex. Along with anthropometric parameters (height, weight, BMI-z score, blood pressure, WHR, etc) and biochemical parameters (glucose, lipids, hormones, HOMA, hs-CRP, hsIL-6, etc), we determined serum levels of YKL-40 with a specific immuno-enzymatic technique. The main results of the study showed: a) No significant differences in anthropometric and biochemical parameters between the two groups of children studied, while ICSI children had significantly lower SBP and hs-CRP values than NC ones ($p<0.03$ and $p<0.02$, respectively), b) YKL-40 levels were significantly lower in ICSI than NC children (15.0 ± 8.8 vs. 27.5 ± 15.4 ng/mL, $p<0.001$), c) in NC children, YKL-40 correlated positively with BMI-z score ($p<0.01$), while d) in ICSI children YKL-40 correlated positively with SBP ($p<0.03$). These findings indicate that children conceived with ICSI, in contrast to those conceived with conventional IVF, have a favorable metabolic profile. Whether this discrepancy is due to the different assisted reproduction method employed and/or because these children were studied at a younger, prepubertal age, is not yet known. Prospective follow-up studies will be informative on this issue.

(1) Catalán V et al., J Clin Endocrinol Metab. 2011;96(1):200-9.
(2) Miles HL et al., J Clin Endocrinol Metab. 2007;92(9):3441-5.
(3) Kanaka-Gantenbein C, Chrousos GP et al., Fertil Steril. 2010;94(5):1693-9.

Sources of Research Support: Grant of the Hellenic Endocrine Society.

Nothing to Disclose: AG, AM, IK, MK, DL, GM, IP, CK-G, GC

sort_order

2757

Pub #

P3-688

Session Information

POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Diabetes, Obesity, Thyroid, Calcium/Bone & Miscellaneous (1:30 PM-3:30 PM)

Title

The Correlation of Insulin-Like Growth Factor Binding Protein-3 Proteolysis with Insulin Resistance in Obese Adolescents

Author String

KE Kim, SE Hyun, H-W Chae, AR Kwon, YH Shin, HJ Shin, YJ Lee, WJ Lee, JH Kim, DH Kim, H-S Kim
CHA Gangnam Medical Center, CHA University College of Medicine, Seoul, Korea; Yonsei University College of Medicine, Seoul, Korea; National Medical Center, Seoul, Korea

Body

Purpose: Recent studies have proposed the metabolic roles of insulin-like growth factor binding protein-3 (IGFBP-3) on glucose homeostasis. This study was performed to investigate the role of IGFBP-3 proteolysis in insulin resistance in obese adolescents.

Methods: A total of 197 adolescents aged 12 to 13 years were included in this study. They were classified into the control group (group I, $n=100$, M:F=49:51), the overweight group (group II, $n=41$, M:F=19:22), and the obesity group (group III, $n=56$, M:F=25:31) according to body mass index (BMI) for age and gender. Measurements for anthropometric profiles and blood pressure were taken. Lipid profiles, and levels of AST/ALT, high sensitivity C-reactive protein, fasting insulin and glucose were measured. Homeostatic model assessment-insulin resistance (HOMA-IR) was calculated. IGFBP-3 proteolytic fragments were obtained by Western immunoblot assay.

Results: Weight, height, waist circumference, BMI, systolic BP, and diastolic BP were higher in the group II and III than in the group I ($P < 0.01$). The levels of triglycerides, LDL-cholesterol, ALT, fasting glucose, and fasting insulin were increased in the group II and III compared to the group I ($P < 0.01$), while the level of HDL-cholesterol was decreased in the group III compared to the group I and II ($P < 0.01$). HOMA-IR was significantly increased in the group II and III (group I vs. group II, 1.5 ± 0.8 vs. 2.9 ± 3.2 , $P < 0.001$; group I vs. group III, 1.5 ± 0.8 vs. 3.6 ± 2.2 , $P < 0.001$). The optical densities of the IGFBP-3 proteolytic fragments were significantly increased in the group II and III (group I vs. group II, 2.09 ± 1.32 (100%) vs. 3.83 ± 0.37 (183%), $P < 0.001$; group I vs. group III, 2.09 ± 1.32 (100%) vs. 3.85 ± 0.63 (184%), $P < 0.001$). The degree of IGFBP-3 proteolysis was correlated with weight ($r = 0.599$, $P < 0.001$), fasting glucose ($r = 0.295$, $P = 0.001$), fasting insulin ($r = 0.307$, $P = 0.001$), BMI ($r = 0.651$, $P < 0.001$), waist circumference ($r = 0.608$, $P = 0.001$), and HOMA-IR ($r = 0.313$, $P < 0.001$).

Conclusion: The degree of IGFBP-3 proteolysis was increased in overweight and obese subjects and positively correlated with parameters associated with insulin resistance. These results suggest that the proteolysis of IGFBP-3 may be involved in the pathogenesis of insulin resistance and IGFBP-3 fragments could be considered as surrogate markers of insulin resistance in obesity.

Nothing to Disclose: KEK, SEH, H-WC, ARK, YHS, HJS, YJL, WJL, JHK, DHK, H-SK

sort_order 2758
Pub # P3-689
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Diabetes, Obesity, Thyroid, Calcium/Bone & Miscellaneous (1:30 PM-3:30 PM)
Title Diet Combined with Desserts with a Low Glycemic Index/Glycemic Load Has a Positive Effect on Metabolic Syndrome Parameters in Overweight/Obese Children
Author String A Dastamani, N Philippas, N Papadopoulou, P Pervanidou, C Kanaka-Gantebein, GP Chrousos
Athens University, School of Medicine, Athens, Greece
Body **Background:** Studies have suggested a positive effect of low glycemic index (GI) /glycemic load (GL) diets on body weight regulation and insulin resistance. Here we investigated the effect of consumption of food products (desserts) with a low GI/GL on Metabolic Syndrome (MS) parameters in overweight/obese children.
Materials-Methods: We studied 29 girls, aged 10-14 years, with body mass index ([Beta][Mu][Iota]) [ge]85th percentile, divided into 2 groups: 1) Group A (15 girls) who followed a diet (carbohydrates 45%, fats 35%, proteins 20%) including 4 times/week desserts with a low GI/GL, 2) Group B (14 girls) who followed the same diet including a once/week desserts of their choice. Each participant underwent physical (Weight, Height, Body Mass Index/BMI, Waist-to-Hip Circumference/WHR, Blood Pressure/BP) and biochemical (fasting glucose, fasting insulin, cholesterol, triglycerides, HDL, LDL, Uric Acid, SGOT, SGPT, γ GT, HbA_{1c}, leptin, andiponectin, cortisol, hsCRP, IL-6) evaluation before and after 3 months of diet. HOMA index was calculated as a marker of insulin resistance.
Results: We detected significant improvement in Group A at weight ($p=0,001$), BMI ($p=0,001$), systolic BP ($p=0,011$), fasting insulin ($p=0,021$) and leptin ($p=0,002$). In Group B we detected significant improvement at BMI ($p=0,011$), diastolic BP ($p=0,031$) and γ GT ($p=0,002$). We revealed significant improvement in Group A compared with Group B at the following parameters: i) Weight ($p=0,001$), ii) BMI ($p=0,037$), iii) Systolic Blood Pressure ($p=0,027$), iv) fasting insulin ($p=0,004$), v) HOMA Index ($p=0,009$) and vi) leptin ($p=0,04$).
Conclusions: Dietary treatment including desserts with a low GI/GL helped overweight-obese children to adapt a balanced diet and improved MS parameters, such as BMI and Systolic Blood Pressure and the biochemical markers of insulin resistance, such as fasting insulin and HOMA index.
Nothing to Disclose: AD, NP, NP, PP, CK-G, GPC

sort_order 2759
Pub # P3-690
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Diabetes, Obesity, Thyroid, Calcium/Bone & Miscellaneous (1:30 PM-3:30 PM)
Title Metabolic Syndrome and Its Individual Components Are Strongly Associated with a Pro-Inflammatory and Insulin-Resistant State in Pediatric Population
Author String H Garcia, G Andrea, C Campino, R Bancalari, M Aglony, A Martinez-Aguayo, C Carvajal, C Avalos, B Lillian, C Loureiro, P Arnaiz, J Cerda, C Fardella
Pontificia Universidad Cat[oaacute]lica de Chile, Santiago, Chile; Pontificia Universidad Cat[oaacute]lica de Chile, Santiago, Chile
Body Endothelial inflammation and Insulin resistance (IR) begin in childhood. Cardiac and metabolic risk factors are both components of Metabolic Syndrome (MS), whose diagnosis has increased in children. Inflammation markers such as highly sensitive C-reactive protein (hsCRP), plasminogen activator inhibitor 1(PAI-1) and IR markers as insulin (Ins), Alanine aminotransferase (ALT) and Microalbuminuria (MA), have been associated with MS in adults, but has not been studied in children. **Aim:** To correlate the presence of MS and their individual components with inflammatory and IR markers in children and adolescents. **Subjects and Methods:** A cross sectional study of 337 children (52.5% males) of 10.9 ± 9.7 years, BMI 1.03 ± 2.11 SDS (33.2% overweighted and 25.5% obese) were performed. MS was defined by the Cook[acute]s criteria: waist circumference (WC) and blood pressure $> p90$ (BP), Triglycerides (TG) > 110 mg/dl, HDL Cholesterol (HDL) < 40 mg/dl and Glycemia (GL) > 99 mg/dl. Plasma levels of hsCRP, PAI-1, Ins, ALT, and urinary MA were determined and their association with the presence of MS and its individual components were calculated. Results were expressed as median and were compared with Kruskal Wallis test. **Results:** MS was present in 37 children (10.9%). The frequency of individual components of MS were: 38.5% WC, 21.3% BP; 17.8% TG; 21.3% HDL and 1.4% GL. Median hsCRP, PAI-1, Ins and ALT were significantly higher ($p < 0.01$) in the presence of MS and increased progressively when a increasing number of MS components was present. Inflammatory markers (hsPCR and PAI-1) increased from 0.3 mg/l and 16 ng/ml to 3.6 mg/l ($p < 0.02$) and 58.8 ng/ml ($p < 0.01$) with one or four components respectively. Ins and ALT increased from 6.8 [micro]U/ml and 13 U/L to 16 [micro]U/ml ($p < 0.03$) and 21 U/l ($p < 0.02$) with one and four components respectively. In contrast, MA was no correlated with MS or its components.
Conclusions: 1) Pediatric population with MS has a higher concentration of hsCRP, PAI-1, ALT and Ins but not MA. 2) Levels increase proportionally as MS components are added, suggesting that even before reaching the diagnostic criteria for MS, a proinflammatory and/or an insulin resistant state exists.
Sources of Research Support: FONDECYT (1100356), FONDEF (D0811087) and NMII (P07/088-F) Chilean Grants.
Nothing to Disclose: HG, GA, CC, RB, MA, AM-A, CC, CA, BL, CL, PA, JC, CF

sort_order 2760
Pub # P3-691
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Diabetes, Obesity, Thyroid, Calcium/Bone & Miscellaneous (1:30 PM-3:30 PM)
Title ACTH and Cortisol Are Differently Associated with Metabolic Syndrome (MS) Components in a Large Cohort of Caucasian Obese Children and Adolescents
Author String F Prod'ham, S Bellone, R Ricotti, G Walker, A Petri, S Savastio, G Genoni, V Agarla, G Bona
A Avogadro University, Novara, Italy; A Avogadro University, Italy
Body
Introduction. Higher cortisol levels and, in particular, hyperactivity of the hypothalamic-pituitary adrenal axis (HPA) might play a role in the development of MS at both central and peripheral level at least in adults. Data on the pediatric age are scanty.
Aim of our study was to evaluate ACTH and cortisol association with MS, its components, phenotypic parameters, family history of metabolic derangements and birth weight in pediatric obesity.
Methods. The design was cross-sectional. 271 Caucasian overweight or obese children and adolescents (age range: 1.8-18.0 yrs) were evaluated for: family and birth history, detailed clinical examinations, fasting morning ACTH, cortisol, glucose, insulin, lipid profile and OGTT test; HOMA, ISI and QUICKI were calculated. We divided patients according to pediatric NCEP criteria for MS. An overnight dexamethasone tests were performed when needed.
Results. In the whole group 62.4% of the subjects had MS (73.9% had hypertension, 58.4% HDL-cholesterol <10th percentile, 23.1% triglycerides > 90th percentile, and 8.2% IFG, IGT or type 2 diabetes). Children and adolescents with MS presented higher ACTH (mean±SEM: 31.1±2.0 vs 21.9±1.5 pg/ml, p<0.0001) and cortisol levels (13.1±0.6 vs 11.0±0.4 [micro]g/dl; p<0.03) than those without MS. Increasing numbers of features of MS were associated with higher ACTH, but not cortisol, also when adjusted for confounding factors (p<0.001). Subjects with IFG, IGT or type 2 diabetes, or altered HDL-cholesterol or triglycerides respect to the MS cut-offs had higher ACTH, but not cortisol levels (p<0.01). Subjects with hypertension had increased levels of both ACTH and cortisol levels (p<0.02) if the cut-off was 95th percentile, and only cortisol (p<0.05) if the cut-off was reduced to 90th percentile as suggested by MS criteria. ACTH and cortisol levels were associated with insulin resistance. Acanthosis index and the presence of striae rubrae were not dependent by these hormones. Subjects with a family history of hypertension (p<0.003) or low birth weight had higher cortisol, but not ACTH levels. The other family histories for metabolic impairments are independent by ACTH and cortisol levels.
Nothing to Disclose: FP, SB, RR, GW, AP, SS, GG, VA, GB

sort_order 2761
Pub # P3-692
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Diabetes, Obesity, Thyroid, Calcium/Bone & Miscellaneous (1:30 PM-3:30 PM)
Title Effect of Obesity on Sexual Maturation in Girls with Precocious Puberty
Author String HS Lee, JS Hwang
Ajou University School of Medicine, Suwon, Korea
Body
Objective: Girls with precocious puberty have high LH levels and advanced bone age more than 1 year above chronological age. Obese children enter puberty at earlier ages than nonobese children. The mechanisms whereby obese children grow faster since early childhood are not well defined. We analyzed the effects of obesity on luteinizing hormone secretion to gonadotropin-releasing hormone (GnRH) tests in girls with precocious puberty.
Methods: Clinical data was collected retrospectively by chart review from the Pediatric Endocrine Unit at Ajou University Hospital. A total of 673 subjects with precocious puberty who completed a gonadotropin-releasing hormone stimulation testing between 2008 and 2010 were included in the study. Subjects included 462 nonobese girls, 120 overweight girls (BMI [ge]85th percentile and [le]95th percentile), and 91 obese girls (BMI >95th percentile), ranging from pubertal stage 2 to stage 5.
Results: In Tanner 2 girls, peak stimulated LH levels on GnRH test were 8.5 ± 7.2 , 7.1 ± 5.5 , and 5.0 ± 4.9 mIU/mL among normal weight, overweight, and obese subjects, respectively ($P < 0.001$ for all comparisons). In Tanner 3 girls, peak stimulated LH levels were 13.4 ± 11.9 , 8.8 ± 7.4 , and 7.6 ± 7.2 mIU/mL, respectively ($P = 0.019$ for all comparisons). However, in Tanner 4 and 5 girls, peak stimulated LH levels were not significantly different among normal, overweight, and obese children. On univariate analysis, BMI was significantly and negatively associated with peak LH ($r = -0.532$, $P < 0.001$).
Conclusion: In girls with precocious puberty, obesity affects peak stimulated LH levels. In addition, obesity may directly modulate skeletal growth and sexual maturation in early puberty.
Nothing to Disclose: HSL, JSH

sort_order 2762
Pub # P3-693
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Diabetes, Obesity, Thyroid, Calcium/Bone & Miscellaneous (1:30 PM-3:30 PM)
Title Peculiar Case of Hyperthyroidism in a Young Girl with Down Syndrome
Author String PJ Patel, CK Buckway
Stanford University, Stanford, CA
Body
Background: Autoimmune diseases are not uncommon in Down syndrome. It has been postulated that in children with Down syndrome, autoimmune hypothyroid disease presents at a younger age, have a less severe course, and have association with other autoimmune diseases [1]. Paraneoplastic hyperthyroidism has been reported because high levels of beta hCG interact with the TSH receptor by increasing cAMP activity [2]. It has not yet been reported that paraneoplastic hyperthyroidism has higher incidence in Down Syndrome children.
Clinical Case: 2-year-old female with Down syndrome presented for abnormal thyroid function tests, TSH 0.009 (range 0.34-6 mIU/ml), Free T4 2.8 (range 0.6-1.6 ng/dL), Total T3 485 (range 70-180 ng/dL), Anti TPO positive, Anti Tg negative, TSI 1.3 (normal [le]1.3). She was started on methimazole at 0.45 mg/kg/day. She underwent total thyroidectomy at 4 years old and was started on levothyroxine post operatively.
At 6 years of age she presented with intermittent polyuria, polydipsia, and nocturia. She was re-evaluated because of poor weight gain, poor height velocity, and intermittent polyuria, polydipsia with nocturia. She underwent a pituitary work up showed stimulated cortisol 11 mcg/dL, HgA1c 4.9%, Na 138 mmol/L, TSH 0.01 and Free T4 1.2 ng/dL, IGF1 70 ng/mL (normal for age 82-292 ng/mL), IGFBP3 1.8 mg/L (normal for age 1.5-3.4 mg/L).
Due to concerns for pituitary dysfunction, an MRI was obtained to rule out intracranial process. The MRI showed enhancing sellar and suprasellar mass which measures 2 cm SI x 1.2 cm AP x 1.7 cm left-to-right. MRI concerning for mixed germ cell tumor with metastasis. She underwent further testing which showed serum prolactin 45 ng/mL (elevated), beta hCG 7,964 mIU/mL (normal <5), alpha-fetoprotein 10 ng/mL (normal <10). The patient was referred to neuro-oncology for radiation and chemotherapy.
Conclusion: The presentation of pituitary dysfunction can be varied from thyroid disease to growth failure. While Down syndrome is associated with an increased rate of autoimmune diseases, a high clinical index of suspicion will help prevent delay in diagnosis and treatment of other serious causes of pituitary dysfunction.
1. De Luca F, et al., Peculiarities of Graves' disease in children and adolescents with Down's syndrome. *Eur J Endocrinol.* 2010. Mar 1. **162**(3): p. 591-5.
2. Yoshimura M and Hershman JM, Thyrotropic action of human chorionic gonadotropin. *Thyroid.* 1995. Oct. **5**(5): p. 425-34.

Nothing to Disclose: PJP, CKB

sort_order 2763
Pub # P3-694
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Diabetes, Obesity, Thyroid, Calcium/Bone & Miscellaneous (1:30 PM-3:30 PM)
Title Transient Hyperthyroidism Associated Chronic Lymphocytic Thyroiditis in Adolescence
Author String HR Chung, CH Shin, SW Yang
Body Seoul National University Bundang Hospital, Seongnam, Republic of Korea; Seoul National University Children's Hospital, Seoul, Republic of Korea
Purpose: Chronic lymphocytic thyroiditis (CLT) which presents with hyperthyroidism makes confusion among clinician. The aim of this study is to know the frequency and clinical characteristics in hyperthyroid CLT in children and adolescence.
Methods: Medical records of patients who showed thyroid autoimmunity between 2005 and 2010 in pediatric endocrinology clinic of Seoul National University Bundang Hospital were reviewed. Clinical data in terms of sex, age at diagnosis, variation in thyroid functions were investigated among the patients of hyperthyroid CLT.
Results: Of 255 patients who showed thyroid autoimmunity, 177 patients were diagnosed as CLT and 50 were Graves' disease. Of 177 patients of CLT, 9 showed hyperthyroid state at diagnosis or during follow-up. All the 9 patients were female and their median age was 12.1 years. Technetium-99m scan of 6 patients showed thyroid with decreased uptake and durations of hyperthyroidism were between 2 and 6 weeks. Change in thyroid functions was markedly variable. Four patients showed recurrent hyperthyroidism and 4 patients showed subclinical or overt hypothyroidism during follow-up.
Conclusions: Hyperthyroid CLT is one of important causes of hyperthyroidism in adolescents and long term follow-up after resolution of hyperthyroidism is necessary because of a diverse clinical course.
Nothing to Disclose: HRC, CHS, SWY

sort_order 2764
Pub # P3-695
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Diabetes, Obesity, Thyroid, Calcium/Bone & Miscellaneous (1:30 PM-3:30 PM)
Title Attention-Deficit/Hyperactivity Disorder Treatment and Weight Outcome: A Population-Based Birth Cohort Study
Author String RL Aguirre, SK Katusic, RG Voigt, CL Leibson, WJ Barbaresi, AL Weaver, JM Killian, S Kumar
Mayo Clinic College of Medicine, Rochester, MN; Mayo Clinic College of Medicine, Rochester, MN; Mayo Clinic College of Medicine, Rochester, MN; Children's Hospital Boston, Boston, MA; Mayo Clinic College of Medicine, Rochester, MN
Body **BACKGROUND:** Psychostimulant medications have been shown to be effective in the treatment of patients with Attention-Deficit/Hyperactivity Disorder (AD/HD). Decreased appetite and weight loss are recognized side effects in short term studies that sometimes limit their use. Long term prospective data regarding the effect of psychostimulants on weight is limited.
OBJECTIVE: To determine and compare the body mass index (BMI) status amongst AD/HD persons treated and not treated with psychostimulants at baseline and follow-up.
METHODS: Subjects included 339 research identified AD/HD incident cases from a birth cohort of all children born during 1976-1982 remaining in Rochester, MN after age five (n=5718). A model combining three categories of information (DSM-IV criteria, ADHD-specific questionnaire, and clinical diagnoses) was used to define cases. BMI percentiles for age and sex and BMI (subjects >20 years) were used to determine BMI categories (normal, overweight, obese). BMI categories were compared between treated vs not treated with stimulants using the chi-square test. We evaluated the relative change (["a"] between a) last BMI percentile before the onset of stimulant medication and b) last BMI percentile before age 20. For cases never on stimulants, the BMI percentile prior to the average age when cases started stimulants was used. The relative change was compared between treated vs non treated using the Wilcoxon rank sum test.
RESULTS: Among 339 AD/HD cases, 251 had used psychostimulant medication (194/254 boys; 57/85 girls). 90% of both males and females were not on stimulant medication at the time of the last BMI measurement (mean 24.6 years in stimulant group, 22.2 years non stimulant group). There was no difference in the BMI category between the stimulant and non stimulant group at last BMI measurement (p=0.53 girls, p=0.79 boys). The relative change in BMI percentile was not significant for boys when stimulant vs non stimulant groups were compared. Among girls, the median change in the non stimulant group was significantly greater compared to the stimulant group (1.4 vs -0.7, p<0.01).
CONCLUSION: There was no significant change in the BMI percentile between treated and untreated boys. However, girls treated with stimulants did not demonstrate the rise in BMI percentile seen in not treated girls. Additional studies are warranted to investigate the impact of stimulant medications and associated comorbidities on long term weight outcomes in AD/HD children.
Nothing to Disclose: RLA, SKK, RGV, CLL, WJB, ALW, JMK, SK

sort_order 2765
Pub # P3-696
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Diabetes, Obesity, Thyroid, Calcium/Bone & Miscellaneous (1:30 PM-3:30 PM)
Title Low Iodine Content in the Diets of Hospitalized Preterm Infants
Author String MB Belfort, EN Pearce, LE Braverman, X He, RS Brown
Children's Hospital Boston, Boston, MA; Boston University Medical Center, Boston, MA; Children's Hospital Boston, Boston, MA
Body
Introduction
Iodine is critical for normal thyroid function and neurodevelopment in infants. Preterm infants are particularly vulnerable to the effects of inadequate iodine intake, and dietary intake may not meet the recommended 30 [mu]g/day, even in iodine sufficient regions such as the U.S. Our aim was to measure the iodine content of enteral and parenteral nutrition products commonly used for hospitalized preterm infants, and to estimate the total dietary iodine intake for a hypothetical 1 kg infant.
Methods
We used mass spectroscopy to measure the iodine concentration of 7 commercially available preterm infant formulas; 10 samples of pooled donor human milk; 2 commercial human milk fortifiers (HMF's); and the enteral supplements medium chain triglyceride (MCT) oil, Beneprotein[reg], and Polycose[reg]. We also measured the iodine concentration of a parenteral nutrition (PN) solution of Trophamine[reg] and dextrose and Intralipid[reg], an intravenous lipid emulsion. Using a hypothetical 1 kg infant with a daily fluid intake of 150 mL/kg, we calculated the iodine provided daily by typical diets from formula, donor human milk, and PN with Intralipid[reg].
Results
The iodine concentration in preterm formula ranged from 109 to 190 (median 157) [mu]g/L. The pooled donor human milk contained less iodine than formula (range 33 to 118 [mu]g/L, median 46 [mu]g/L). The PN solution contained 2.5 [mu]g/L of iodine and the Intralipid[reg] 15 [mu]g/L. Preterm formula-based diets provided 16.4 to 28.5 (median 23.6) [mu]g/day of iodine, whereas HMF provided 5.0 to 17.6 (median 6.9) [mu]g/day. 2 servings (6 packets) of Similac HMF increased the iodine intake by 11.7 [mu]g/day to a maximum of 29.4 [mu]g/day, whereas 2 servings of Enfamil HMF increased the iodine intake by only 0.9 [mu]g/day to a maximum of 18.5 [mu]g/day. The enteral supplements MCT oil, Beneprotein[reg], and Polycose contained almost no iodine. For a 1kg infant receiving exclusively PN and Intralipid[reg], the daily iodine intake was only 0.6 [mu]g.
Conclusions
Typical enteral diets for hospitalized preterm infants provide less than the recommended 30 [mu]g/day of iodine, and parenteral nutrition provides almost no iodine. Human milk contains variable amounts of iodine, and may be lower in iodine than formula. Commercial human milk fortifiers vary widely in the additional iodine they provide. Hospitalized preterm infants may be at risk for iodine deficiency, particularly if environmental iodine exposure from iodinated skin cleansers is low.

Sources of Research Support: NIH grant K23 DK083817 to Dr. Belfort.

Nothing to Disclose: MBB, ENP, LEB, XH, RSB

sort_order 2766
Pub # P3-697
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Diabetes, Obesity, Thyroid, Calcium/Bone & Miscellaneous (1:30 PM-3:30 PM)
Title Lowering Thyrotropin Cutoff for Newborn Screening: Additional Cases of Congenital Hypothyroidism Are Identified, but What Do They Really Have?
Author String J Deladoey, J Ruel, Y Giguere, G Van Vliet
Sainte-Justine Hospital/University of Montreal, Montreal, Canada; Laval University, Quebec City, Canada
Body
Context: An increased global incidence of congenital hypothyroidism (CH) has been reported from the United States over the past two decades. This may in part reflect changes in screening methods. In Québec, by contrast, the same initial whole blood thyrotropin cutoff (i.e. 15 mU/L) has been used for the last 20 years; the only change occurred in 2001, when the thyrotropin threshold was decreased from 15 to 5 mU/L on the second screening test, which is requested in cases with an intermediate thyrotropin (15-30 mU/L) on the first sample.
Objectives: To determine whether the increased global CH incidence is artefactual (i.e., changes in screening practices) or real, we assessed the impact of the change in our screening procedure on the incidence of CH, globally and by subcategory.
Design, Setting, Patients, and Main Outcome: This is a population-based retrospective study. The Québec provincial newborn screening database was analyzed from January 1990 to December 2009. Incidences of CH were grouped by etiology (i.e., thyroid ectopy, athyreosis, goiter, normal-size gland in situ and unknown diagnosis) and time was categorized in two periods (i.e. 1990-2000 and 2001-2009).
Results: Of 1,660,857 screened newborns over the 20-year period, 621 had confirmed CH (overall incidence: 1:2,674). Of these, 390 had thyroid dysgenesis (291 had ectopy, 99 had athyreosis, overall incidence 1:4,259); 53 had goiter (1:31,337); 115 had a normal-size gland in situ (1:14,184) and 63 had no reported diagnosis (1:26,212). Between 1990-2000 and 2001-2009, the incidence remained stable for dysgenesis ($p=0.33$; 1:4102 to 1:4,485) and goiter ($p=0.41$; 1:28,719 to 1:35,656). However, the incidence of normal-size gland in situ and CH without diagnosis more than doubled ($p=0.0015$; 1:22,565 to 1:9,769 and $p=0.0037$; 1:43,079 to 1:17,393, respectively). Consequently, the global incidence of CH increased ($p=0.02$; 1:2,889 to 1:2,433). The new screening algorithm identified 48 additional cases (25 normal-size gland in situ, 11 no reported diagnosis, 10 ectopies, 2 goiters).
Conclusion: The slightly increased incidence of CH observed in the past two decades resulted from a change in the repeat screening threshold which led to detecting more cases of non-goitrous non-dysgenetic CH, whereas the incidence of dysgenetic and goitrous CH remained stable. Whether the additional cases detected since 2001 were at risk of intellectual impairment and have transient or persistent CH remains to be determined.
Nothing to Disclose: JD, JR, YG, GVV

sort_order 2767
Pub # P3-698
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Diabetes, Obesity, Thyroid, Calcium/Bone & Miscellaneous (1:30 PM-3:30 PM)
Title Utility of the Random Urine Calcium-to-Creatinine Ratio as a Screening Tool for Vitamin D Deficiency in Infants and Toddlers
Author String MR Benson, K Black, R Olney
Nemours Children's Clinic, Jacksonville, FL; University of Florida College of Medicine Jacksonville, Jacksonville, FL
Body Vitamin D deficiency (VDD) is estimated to affect over one billion people at this time. In recent reviews, 9-12% of healthy US children were deficient in vitamin D. In children, VDD leads to nutritional rickets, which is considered to be the most common non-communicable disease of children worldwide. Renal calcium excretion in healthy people is a sensitive indicator of total body calcium balance. Renal calcium excretion correlates with blood levels of 25-hydroxyvitamin D levels in older children and urine calcium-to-creatinine ratios (Uca/Ucr) have been shown to distinguish children with active rickets from healthy controls in Nigeria. We explored the possibility of using Uca/Ucr as a biomarker of VDD.
We studied infants and toddlers with one or more risk factors of VDD: 1) exclusively breastfed for one month or more, 2) darkly pigmented, 3) born prior to 32 weeks gestation, 4) recently immigrated from developing country, 5) weight/height < 10%, 6) significant genu varus or valgus deformities. Subjects were recruited from March-December 2010. Anthropometric data was obtained and a physical exam was done to assess for presence of overt rickets. A questionnaire was completed to detail subject's skin pigmentation, sunlight exposure and dietary history including frequency of vitamin supplementation of both mother and child. We obtained total calcium, phosphorous, magnesium, intact PTH, 25-hydroxyvitamin D (LC/MS/MS), alkaline phosphatase, and serum creatinine. A random urine sample was collected to measure calcium, phosphate and creatinine.
To date, a total of 49 healthy children have been studied. Mean age of the subjects were 1.4 (range 0.5 to 2.9) years. We found a prevalence of VDD (25-hydroxyvitamin D < 20 ng/mL) of 4%, while insufficient (< 32 ng/mL) was 26% and sufficient (> 32 ng/mL) was 69%. Only 11% of children were regularly given vitamin D supplements. Of the two subjects deficient in vitamin D, one had biochemical but not radiographic evidence of rickets. Linear regression analysis showed a weak but significant correlation between 25-hydroxyvitamin D levels and random Uca/Ucr ($R^2 = 0.11$, $P = 0.035$). PTH and 25-hydroxyvitamin D showed a positive correlation ($R^2 = 0.09$, $P = 0.04$), which was striking ($R^2 = 0.81$, $P < 0.005$) in VDD insufficient subjects. We identified a correlation between vitamin D levels and renal calcium excretion in infants at risk for VDD. More subjects are needed to determine if this will prove to be a clinically useful biomarker of VDD.
Nothing to Disclose: MRB, KB, RO

sort_order 2768
Pub # P3-699
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Diabetes, Obesity, Thyroid, Calcium/Bone & Miscellaneous (1:30 PM-3:30 PM)
Title Pseudohypoparathyroidism Type Ia: A Regional Clinical and Biological Study of Eleven Cases
Author String S Kayemba-Kay's, C Tripon, C Boniface, S Troller, A Zelinsky, R Hankard
Poitiers University Teaching Hospital, Poitiers, France; Lausanne University Teaching Hospital, Lausanne, Switzerland; Centre Hospitalier de Saintes, Saintes, France; Centre Hospitalier de La Rochelle, La Rochelle, France; Centre Hospitalier de Niort, Niort, France
Body Pseudohypoparathyroidism (PHP) is a rare genetic disease with autosomal dominant transmission and parental imprinting, characterized by multiple hormone resistance. Its prevalence is under estimated, classic phenotype is termed as Albright Osteodystrophy. Diagnosing PHP may be difficult; this study was undertaken to remind clinicians of signs that should lead to diagnosis. We insist on subclinical hypothyroidism as an early sign in children aged < 2 years of age.
Methods: retrospective study of medical records of children diagnosed and followed up for PHP Ia. Clinical and biological signs that led to diagnosis along with patients' epidemiological characteristics were extracted and analyzed.
Results: eleven cases of PHP Ia were identified, mean age at diagnosis was 3.7 years (0.4 to 13 yrs), diagnostic signs **before age 2yrs** [obesity 70%, subcutaneous calcifications 60%], **in older children** brachydactily 60% (table I). Biological signs: before age 2 yrs (6 cases) hypocalcemia 17%, hyperphosphoremia 50%, increased PTH 83%, subclinical hypothyroidism (high TSH normal or low FT4) 70%. Results of Gsa activity and GNAS1 gene study (table II).
Comments:
[diams] The association of subclinical hypothyroidism, rapidly growing body weight (early obesity), subcutaneous calcifications and lunar face are early signs that should raise suspicion in children aged < 2 years.
[diams] seizures occurred in older children (cases 2, 4, 5 and 9 respectively), this late occurrence may be due to systematic supplementation in Vitamin D in children < 2 years of age in France. Brachymetacarpia is rare before the age of five years.
[diams] Hypocalcemia, hyperphosphoremia and increased serum PTH are rare before age two years.
[diams] In those children who were tested, the most frequent mode of transmission was maternal, but in three cases (2, 6 and 7) GNAS1 gene mutations were De novo.
[diams] GHD was diagnosed only in one child (case 6), GH testing should be part of biological follow-up in children with poor statural growth (rhGH therapy has shown beneficial results in a recent study by Montovani et al. JCEM 2010).
Diagnosing PHP can be difficult, only sharp clinical suspicion can lead to early diagnosis, with the association between subclinical hypothyroidism and obesity as early signs to consider.

(1) Gelfand IM et al., J Pediatr 2006;149:877-80
(2) Montovani G et al., JCEM 2010;95:5011-7
(3) Kottler ML. Pathol Biol (paris) 2010;58:367-71

Nothing to Disclose: SK-K, CT, CB, ST, AZ, RH

sort_order 2769
Pub # P3-700
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Diabetes, Obesity, Thyroid, Calcium/Bone & Miscellaneous (1:30 PM-3:30 PM)
Title Loss of Gastrointestinal Endocrine Cells in Patients with Autoimmune Polyendocrine Syndromes and Gastrointestinal Dysfunction
Author String C Posovszky, T Barth, G Lahr, J Schnurbein, S Buderus, A Findeisen, C Schutz, C Schroder, A Schulz, KM Debatin, M Wabitsch
Body University of Ulm, Ulm, Germany; University of Ulm, Ulm, Germany; University of Ulm, Ulm, Germany; St Marien-Hospital, Bonn, Germany; University of Greifswald, Greifswald, Germany
Autoimmune polyendocrine disorders are defined by multiple endocrine failures and an underlying genetic defect. Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is a rare autosomal recessive disorder typically presenting with chronic mucocutaneous candidiasis, hypoparathyroidism, adrenal failure and is caused by a mutation in the autoimmune regulator gene (AIRE). Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is an extremely rare X-linked disorder with fulminant widespread autoimmunity, such as early onset type 1A diabetes caused by a mutation in the FOXP3 gene. These disorders may be accompanied by gastrointestinal (GI) symptoms such as malabsorption, constipation, watery diarrhea or steatorrhea. The pathogenesis of GI dysfunction in these patients is largely unknown. Here, we report on four patients with APECED, and one with IPEX-like syndrome with severe diarrhea, vomiting, malabsorption, and constipation. Immunohistological analysis of biopsies along the GI tract (stomach, duodenum, colon) immunostained with chromogranin A and serotonin revealed a widespread loss of gastrointestinal endocrine cells (GIECs). We propose a diagnostic algorithm for these patients integrating clinics, genetics and immunohistology.
Nothing to Disclose: CP, TB, GL, JS, SB, AF, CS, CS, AS, KMD, MW

sort_order 2770
Pub # P3-701
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Diabetes, Obesity, Thyroid, Calcium/Bone & Miscellaneous (1:30 PM-3:30 PM)
Title Development of the EMR (Electronic Medical Record) Growth Chart Program for Hallym University Medical Center
Author String PS Oh
Hallym University Medical Center, Chuncheon, Republic of Korea
Body **Background:** In the EMR (electronic medical record) system, the convenient growth chart program is essential for the pediatric endocrinology clinic. So recently we did our best to develop the EMR growth chart program that can simply show chronological age with bone age, father's and mother's heights with automatically calculated mid-parental height on the growth chart.
Methods: We used the programs of Delphi 7.0 version and Sybase 12.5 version with some tools.
Results: In our EMR growth chart program, the bone age can be shown even a range of age lining from A to B on the EMR growth chart. So you can see the bone age at a glance on the growth chart. And also we can conveniently describe the age of menarche, the duration of treatment injections and drugs on the growth chart.
Conclusions: We developed the convenient EMR growth chart program for Hallym University Medical Center in Korea.

Nothing to Disclose: PSO

sort_order

2771

Pub #

P3-702

Session Information

POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)

Title

LH Pulses Are Associated with Slow-Wave Sleep in Pubertal Children

Author String

ND Shaw, SM McKinney, JP Butler, SA Nelson, K Gannon, JM Ellenbogen, JE Hall
Massachusetts General Hospital, Boston, MA; Children's Hospital Boston, Boston, MA; Massachusetts General Hospital, Boston, MA; Brigham and Women's Hospital, Boston, MA; Massachusetts General Hospital, Boston, MA

Body

Context: The transition from the quiescence of the reproductive axis in childhood to its reactivation during puberty is characterized by sleep-specific augmentation of GnRH/LH activity. We hypothesized that LH secretion would be specifically associated with deeper stages of sleep, as is the case for growth hormone. Further investigation of this relationship is important to our understanding of the control of GnRH secretion during puberty and will address the question of whether obstructive sleep apnea (OSA), which affects 1% of children, interferes with normal maturation of the reproductive axis.

Methods: Children in early to mid-puberty with OSA being treated with continuous positive airway pressure (CPAP) were studied. Subjects underwent 2 studies, spaced 1-2 months apart, consisting of frequent blood sampling (q10x 8hr) and polysomnography. Subjects were studied on their prescribed settings of CPAP or off CPAP, in random order. The onset of LH pulses was indexed to sleep records to determine the relationship between pulse initiation and sleep stage. ANOVA was used to compare pulse characteristics in each sleep stage, controlled for time in that stage, and chi-square was used to compare the distribution of each sleep stage within an interpulse interval (IPI).

Results: 4 subjects (3 boys, 1 girl), 11.8-14.4 yr-old, in Tanner stages II-IV, were studied. One was of normal weight and 3 were obese (BMI > 95th %). LH pulses occurred most frequently during stage N3 (slow-wave sleep) compared to N2, N1, REM, or wake following sleep onset (1.5 ± 0.3 [mean \pm SE] vs 0.4 ± 0.1 , 0.1 ± 0.1 and 0 pulses/hr of sleep stage, respectively; $p < 0.001$). There was no effect of treatment (CPAP) on this relationship. In studies on CPAP, there was a predominance of N3 (60%) in the last quarter of the IPI ($p < 0.005$), while the other sleep stages were more evenly distributed across the IPI. The 4th quarter-N3 predominance was present but diminished (49%) in studies off CPAP ($p = 0.2$). LH pulse amplitude did not vary by sleep stage or by the use of CPAP.

Conclusion: The presence of deep sleep prior to the onset of LH pulses in studies in adolescents with OSA on CPAP suggests that deep sleep stimulates GnRH secretion during puberty. Further studies will determine whether gonadotropin secretion is diminished in children with untreated OSA and whether the temporal link between deep sleep and LH pulses is attenuated in these children.

Sources of Research Support: 5T32HD007396; 1F32HD062315-01A1; Scholars in Clinical Science Program of Harvard Catalyst; Pediatric Endocrine Society; American Medical Association; Endocrine Fellows Foundation; Thrasher Research Fund; Genentech; and the Charles A. King Trust.

Nothing to Disclose: NDS, SMM, JPB, SAN, KG, JME, JEH

sort_order

2772

Pub #

P3-703

Session Information

POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)

Title

Growth Hormone Is an Important Determinant of Bone Modeling during Puberty Independent of Systemic IGF-1

Author String

M Russell, N Mendes Estella, A Klibanski, M Misra
Massachusetts General Hospital, Boston, MA; Massachusetts General Hospital, Boston, MA

Body

Background: Puberty is associated with increased GH and IGF-1 secretion and the pubertal growth spurt. During this growth phase, bone formation and resorption increase, consistent with increased bone modeling.

Objective: To determine the relationship between pubertal phase, bone modeling and the GH-IGF-1 axis. We hypothesized that bone modeling, as evidenced by increased levels of bone turnover markers, peaks during pubertal growth at the time of greatest GH secretion.

Subjects/Methods: Subjects included 41 girls and 45 boys, 9-17 y (10^{th} - 90^{th} %iles for BMI). Higher endogenous GH secretion is associated with higher nadir GH following a glucose load. We thus used the GH nadir following a 2-h OGTT as indicative of GH status. We also obtained fasting serum IGF-1. Subjects were placed into early (group 1), mid (group 2), or late (group 3) pubertal groups to allow for comparisons based on timing of peak growth, such that group 1 included Tanner 1 girls and Tanner 1-2 boys (period preceding peak growth), group 2 included Tanner 2-3 girls and Tanner 3-4 boys (period of peak growth), and group 3 included Tanner 4-5 girls and Tanner 5 boys (period following peak growth). Bone formation was evaluated using serum procollagen type-1 NH₂-terminal propeptide (P1NP) and bone resorption using serum carboxy-terminal collagen crosslinks (CTX).

Results: GH nadir was highest in mid-puberty (group 2), 0.32 ± 0.27 ng/mL, vs. early and late puberty, 0.12 ± 0.08 and 0.17 ± 0.15 ng/mL ($p=0.0002$). Similar trends were observed for GH AUC. IGF-1 was higher in late vs. early puberty (295 ± 115 vs. 160 ± 59 ng/mL), with mid-puberty levels being 242 ± 131 ng/mL ($p=0.0001$). P1NP and CTX were highest in mid-puberty, 673 ± 304 ng/mL and 2.3 ± 1.0 ng/mL ($p<0.0001$ and $p=0.0002$) respectively, vs. 494 ± 157 ng/mL and 1.6 ± 0.7 ng/mL in early puberty, and 305 ± 260 ng/mL and 1.3 ± 0.7 ng/mL in late puberty. Similar to the group as a whole, GH nadir, P1NP and CTX were highest in group 2 boys and group 2 girls. GH nadir was positively associated with P1NP ($r=0.43$, $p=0.0001$) and CTX ($r=0.30$, $p=0.01$), while IGF-1 was not associated with either. Similar trends were observed within boys and girls. On regression modeling, GH nadir positively predicted P1NP and CTX in the group as a whole and when separated by gender. In contrast, IGF-1 did not predict P1NP or CTX independent of GH.

Conclusion: GH levels are strong determinants of bone modeling markers during puberty in boys and girls, independent of IGF-1.

Nothing to Disclose: MR, NME, AK, MM

sort_order 2773
Pub # P3-704
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)
Title Prepubertal Glucocorticoid Status and Pubertal Timing
Author String L Shi, SA Wudy, AE Buyken, C Maser-Gluth, MF Hartmann, T Remer
Research Institute of Child Nutrition, Dortmund, Germany; Center of Child and Adolescent Medicine, Justus-Liebig-University, Giessen, Germany; University of Heidelberg, Heidelberg, Germany
Body
Context: Whether prepubertal glucocorticoid status impacts on the timing of puberty is not clear.
Objective: To examine the relationship between prepubertal glucocorticoid status and early or late pubertal markers, independent of adrenarchal and nutritional status.
Design and Participants: Prospective cohort study of healthy free-living Caucasian children (n=111, 56 boys) who provided both 24-h urine samples and 3-day weighed dietary records 1 and 2 yrs before the start of pubertal growth spurt (age at take-off, ATO).
Measurements: Major urinary glucocorticoid and androgen metabolites determined by GC-MS analysis were summed to assess daily overall cortisol ([sum]C21) and adrenal androgen ([sum]C19) secretion; urinary free cortisol and cortisone measured by RIA were also summed (UFF+UFE) as an indicator of potentially bioactive free glucocorticoids.
Main outcomes: ATO, age at peak height velocity (APHV), age at menarche/voice break, and ages at Tanner stage 2 for breast (girls) and genital (boys) development (B2_G2) and pubic hair (PH2).
Results: In girls [sum]C21, but not UFF+UFE was associated with pubertal markers after adjusting for [sum]C19, urinary nitrogen (biomarker of protein intake) and body fat. Girls with higher [sum]C21 (4th quartile) reached ATO 0.7 yrs (p=0.01) and menarche 0.9 yrs later (p=0.006) than girls with lower [sum]C21 (1st quartile). [sum]C21 tended to be also positively associated with age at B2 (p=0.1), PH2 (p=0.1), and APHV (p=0.06). In boys, neither [sum]C21 nor UFF+UFE was related to pubertal timing.
Conclusion: An individually higher prepubertal glucocorticoid secretion level even in physiological range appears to delay early and late pubertal timing of healthy girls.

Sources of Research Support: Research grant from the Long-range Research Initiative (LRI) of the European Chemical Industry Council (Cefic).

Nothing to Disclose: LS, SAW, AEB, CM-G, MFH, TR

sort_order 2774
Pub # P3-705
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)
Title Puberty Is Delayed or Absent in Duchenne Muscular Dystrophy Boys on Chronic Glucocorticoid Therapy
Author String MM Rutter, SR Rose, J Collins, H Sucherew, B Wong
Cincinnati Children's Hospital Medical Center and University of Cincinnati, Cincinnati, OH; Cincinnati Children's Hospital Medical Center and University of Cincinnati, Cincinnati, OH; Cincinnati Children's Hospital Medical Center, Cincinnati, OH
Body Background: Duchenne Muscular Dystrophy (DMD) is a progressive neuromuscular disorder affecting 1 in 3500 boys. Chronic glucocorticoid (GC) treatment is considered standard therapy, and slows disease progression. However, GCs cause osteoporosis, growth failure, obesity, insulin resistance and pubertal delay, compromising quality of life. Absent or delayed puberty is an important problem which negatively impacts bone health, growth, self esteem and muscle strength. The prevalence in DMD is not known, and it is frequently under-recognized and untreated.
Objective: To determine the prevalence of delayed or absent puberty in DMD on GC therapy.
Methods: Patients aged 13 to 19 years with confirmed DMD on chronic daily GC treated in the Cincinnati Neuromuscular Comprehensive Care Center were studied. Clinical data was obtained from an IRB-approved database and chart review. Pubertal status was assessed annually by measuring early morning total testosterone concentrations and/ or pubertal examination by an endocrinologist.
Results: Of 64 boys aged [ge] 13 years, 56 (88%) had no evidence of puberty. Of 49 boys aged [ge] 14 years, 41(84%) showed no signs of puberty. Overall, 3 boys had pubertal arrest with very low testosterone levels for age or testicular size. Only 5 boys were in puberty; of these, 2 had 4 mL testes at age 14 years and 2 showed no significant progression over 2 years. Of 22 boys aged [ge] 16 years, 21 (95%) still had absent or arrested puberty. 47/59 (80%) boys with absent/ arrested puberty had severe osteoporosis. Absent puberty was distressing to 25 boys who as a result were treated with testosterone, 14 using topical gel.
Conclusions: Most DMD boys on chronic daily GC do not develop spontaneous puberty, or fail to progress. The problem does not tend to improve with age. Primary providers need an increased awareness to facilitate timely referral to an endocrinologist. We recommend clinical assessment and discussion by age 12 and referral by age 14 years. Management should be proactive and interdisciplinary, with attention to related co-morbidities such as osteoporosis.

Nothing to Disclose: MMR, SRR, JC, HS, BW

sort_order 2775
Pub # P3-706
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)
Title Unfused Epiphyses Due to Unrecognized and Untreated Congenital Hypogonadotropic Hypogonadism (HH): Evidence for an E2 Threshold for Bone Maturation in Men
Author String V Rochira, A Balestrieri, L Zirilli, B Madeo, A Luberto, C Carani
Chair and Unit of Endocrinology & Metabolism, University of Modena and Reggio Emilia, Modena, Italy; Unit of Endocrinology, Bufalini Hospital, Cesena, Italy
Body
INTRODUCTION At puberty, the raise of serum estradiol (E2) [coming from conversion of testosterone (T) is needed to fuse epiphyses and to complete bone maturation in normal boys. Due to severe hypogonadism and very low circulating T, adult men with congenital Hypogonadotropic Hypogonadism (HH) may present with unfused epiphyses and continuing linear growth if androgen deficiency is unrecognized and untreated. In order to establish the minimal amount of sex steroids needed to ensure bone maturation we prospectively studied 28 caucasian men first diagnosed as HH in adulthood (a very rare clinical condition) and we compared 11 adult HH men (mean age+S.D: 22.7+6.1) with fused epiphyses to 17 adult HH men (mean age+S.D: 21.8+4.3) with unfused epiphyses.
METHODS Serum T, E2, LH, FSH were assayed. Bone age, target height, Tanner stage, anthropometrical measurements (height, arm span, upper [U] and lower [L] segments) and bitesticular volume were calculated.
RESULTS Bone age, T, E2, Tanner stage, bitesticular volume were significantly lower in HH men with unfused than with fused epiphyses (p<0.001). Height, arm span, the arm span/height ratio, the U/L segment ratio and the difference between patient's height and his calculated target height were significantly greater in HH men with unfused than with fused epiphyses (p<0.001). All patients with unfused epiphyses had E2<15 pg/mL and all patients with fused epiphyses had E2>20 pg/mL, while T resulted partially overlapped in the two groups.
CONCLUSION A threshold of 20 pg/mL exists for serum E2 above which epiphyseal closure and bone maturation may be reached in men. Setting this threshold is challenging for targeting some kind of treatment for short or tall stature in boys, like aromatase inhibitors or androgens, respectively. Unfused epiphyses, tall stature and eunuchoid skeleton all depend from circulating estrogens rather than androgens not only in genetic diseases due to congenital estrogen deficiency.
Nothing to Disclose: VR, AB, LZ, BM, AL, CC

sort_order 2776
Pub # P3-707
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)
Title Congenital Isolated Hypogonadotropic Hypogonadism: A Detailed Clinical and Molecular Characterization of a Brazilian Patient Cohort
Author String LFG Silveira, MG Teles, AP Abreu, LR Montenegro, C Tusset, D Beneduzzi, M Castro, EMF Costa, A Lofrano-Porto, MTM Baptista, HM Garmes, G Guerra-Jurnior, BB Mendonca, AC Latronico, EB Trarbach
Hospital das Clinicas - FMUSP, São Paulo, Brazil; Hospital das Clinicas - FMRP, Ribeirao Preto, Brazil; Hospital Universitario de Brasilia - FS - UnB, Campinas, Brazil; Hospital das Clinicas - Unicamp, Campinas, Brazil
Body Congenital isolated hypogonadotropic hypogonadism (IHH) is a clinically and genetically heterogeneous disorder characterized by impaired pubertal development, secondary to GnRH deficiency. When associated to anosmia, it is called Kallmann syndrome (KS). We describe the phenotypic and genotypic characteristics of a Brazilian cohort of patients with congenital IHH. Detailed phenotypic characterization of 149 patients, 80 with KS (70 males) and 69 with normosmic IHH (nIHH) (47 males) was performed. *GnRH1/GnRHR*, *KISS1/KISS1R* and *TAC3/TAC3R* were studied in nIHH patients, *KALI* in KS and *FGF8/FGFR1*, *PROK2/PROKR2* and *NDN* in both groups. Median age at diagnosis was 18 yrs in KS and 21.5 in nIHH. 28.7% of KS and 20.2% of nIHH were familial. 14% of KS and 51% of nIHH had spontaneous pubarche. All males had micropenis (median = -5.4 SD, range 1.4-10 cm) and 54% of KS and 23% of nIHH had cryptorchidism. All females had hypoplastic uterus (<30 mL) and ovaries (<3 mL) and 34% had spontaneous telarche. Median testosterone (T) and estradiol (E2) were similar in KS and nIHH patients (T= 32 ng/dL, range <14-239 ng/dL, E2 <13pg/mL, range <13-402). Median LH levels were <0.6 U/L in all groups (<0.6-3.82). 39% of KS patients had synkinesia, 30% had renal malformations and 60.6% abnormal olfactory sulci and/or bulbs on MRI. Genetic defects were found in 34% of all patients, 40% with KS and 27.5% with nIHH. Mutations were more prevalent in familial cases (61% in KS and 71% in nIHH) than in sporadic cases (31% in KS and 16% in nIHH). The most affected genes in KS were *KALI* (16%, males exclusively) and *FGFR1* (14%). Less than 1.5% of KS patients had deleterious mutations in *FGF8*, *PROKR2* and *PROK2*. Synkinesia, renal malformations, cryptorchidism and anatomic olfactory abnormalities were more prevalent in patients with *KALI* mutations. Clef/lift palate was present only in patients with *FGFR1* mutations. In nIHH, the most affected gene was *GnRHR* (10%). *FGFR1* mutations were found in 3% of cases and *KISS1R* and *TAC3* in 1.4%. No phenotypic differences between patients with and without mutations were found in nIHH. Heterozygous variants in *PROK2/PROKR2* and *NDN* were found in 7.4% and 0.7% of all patients, respectively, and in *TAC3* in 1.4% of nIHH. No mutations were found in *KISS1* and *GnRH1*. In conclusion, overall it was not possible to establish a genotype/phenotype correlation. Careful characterization of IHH patients is imperative to increase our understanding of this complex disease.

Sources of Research Support: Fundacao de Amparo a Pesquisa do Estado de Sao Paulo 2005/04726-0.

Nothing to Disclose: LFGS, MGT, APA, LRM, CT, DB, MC, EMFC, AL-P, MTMB, HMG, GG-J, BBM, ACL, EBT

sort_order 2777
Pub # P3-708
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)
Title Clinical and Molecular Analysis of *TAC3* and *TACR3* Genes in Brazilian Patients with Isolated Hypogonadotropic Hypogonadism
Author String C Tusset, E Trarbach, LG Silveira, BB Mendonca, M Castro, G Guerra, A Lofrano, AC Latronico
Hospital das Clinicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil; Universidade de São Paulo, Faculdade de Medicina de Ribeirao Preto, Ribeirao Preto, Brazil; Universidade de Campinas, Campinas, Brazil; Hospital Universitario de Brasilia, Brasilia, Brazil
Body Inactivating mutations of the *TAC3* and *TACR3* genes, which encode the neurokinin B and its receptor, NK3R, respectively, provided compelling evidence for the involvement of this system signaling in the reproduction axis. Recently, Gianetti *et al.* (1) reported a frequency of 5% of the *TAC3* and *TACR3* mutations in a large cohort of patients with congenital isolated hypogonadotropic hypogonadism (IHH), including 60 Brazilians. **Aim:** To update the clinical and molecular data (*TAC3* and *TACR3* gene analysis) in a larger cohort of Brazilian patients with IHH. **Patients and Methods:** Eight-six patients (58 males and 28 women) with normosmic IHH were selected. The diagnosis of IHH was based on the failure to undergo normal sexual maturation by age 18 yr, low serum sex steroid levels in the setting of inappropriately low or normal gonadotropin levels, and normal central nervous system magnetic resonance imaging. A group of 150 Brazilian individuals who had puberty at adequate age was used as controls. Genomic DNA was extracted from peripheral blood and the entire coding region of both *TAC3* and *TACR3* genes were amplified and automatically sequenced. **Results:** Three known distinct inactivating variants (p.G18D, p.W275X, and p.R295S) were identified in the NK3R in four not related males with IHH. Both p.G18D and p.R295S mutations were identified in heterozygous state. The p.W275X, were identified in two of these males, since one in homozygous and in another in heterozygous state in association with the silent mutation (p.L58L). These four variants were not found in any of the control subjects studied. Micropenis without cryptorchidism was detected in two males who carried *TACR3* mutations. Gonadotropin levels were low in these patients, except in one who had normal LH and FSH levels. In addition, three previously known polymorphisms, p.K286R, p.L291L, and p.A449T were identified in the NK3R. No new variant was identified in the *TAC3* gene in patients with IHH **Conclusion:** *TACR3* mutations were identified in approximately 5% of the Brazilian patients with normosmic IHH. The p.W275X mutation was the most frequent *TACR3* variant in this group. The identification of heterozygous mutations in an autosomic recessive condition suggests the presence of an unrecognized second defect or a potential digenic or oligogenic alteration.

(1) Gianetti E *et al.*, JCEM 2010; 95(6):2857-2867.

Sources of Research Support: FAPESP # 2005/04726-0 and CAPES.

Nothing to Disclose: CT, ET, LGS, BBM, MC, GG, AL, ACL

sort_order

2778

Pub #

P3-709

Session Information

POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)

Title

Mutational Analysis of the Necdin Gene in Patients with Congenital Isolated Hypogonadotropic Hypogonadism

Author String

D Beneduzzi, AK Iyer, EB Trarbach, AP Silveira-Neto, LFG Silveira, C Tusset, K Yip, BB Mendonca, PL Mellon, AC Latronico
Hospital das Clinicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil; University of California, San Diego, CA

Body

Context: The human *Necdin* gene (*NDN*) is fundamental for the development, migration, and axonal extension of murine GnRH neurons. In addition, necdin activates GnRH gene expression, potentially playing a role in the hypogonadotropic hypogonadism phenotype in patients with Prader-Willi syndrome. **Aim:** To investigate *NDN* variants in patients with isolated hypogonadotropic hypogonadism (IHH). **Patients and Methods:** We studied 160 Brazilian patients with sporadic or familial IHH, including 68 with normosmic IHH and 92 with Kallmann syndrome. Genomic DNA was extracted and the single *NDN* exon was amplified and sequenced. To measure GnRH transcriptional activity, luciferase reporter plasmids containing rat GnRH regulatory regions were transiently transfected into GT1-7 cells, in the presence and absence of over-expressed wild-type or mutant Ndn. **Results:** A new heterozygous variant of necdin, p.V318A, was identified in a 23 yr-old male with Kallmann syndrome. The p.V318A was also present in one affected aunt and in his father, who had pubertal delay, and was absent in 100 Brazilian control subjects. Previous *FGFR1* gene analysis revealed a missense mutation (p.P366L) in this family. Functional studies revealed a minor difference in the activation of GnRH transcription by mutant necdin compared with wild type in that a significant impairment of the necdin protein activity threshold was observed. Additionally, two previously known polymorphisms, c.11C>T and c.971C>T, were also identified in 80 and 35 patients with IHH, respectively. **Conclusion:** A rare variant of necdin was described in a family with Kallmann syndrome associated with a *FGFR1* mutation. Familial segregation and *in vitro* analysis suggest that the *NDN* variant is a rare alteration most likely without a direct causative role in hypogonadism phenotype.

Sources of Research Support: FAPESP 05/04726-09/52256-3.

Nothing to Disclose: DB, AKI, EBT, APS-N, LFGS, CT, KY, BBM, PLM, ACL

sort_order

2779

Pub #

P3-710

Session Information

POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)

Title

Modified Spectria Testosterone RIA Detects the Same Testosterone Levels in Prepubertal and Pubertal Children as Liquid Chromatography-Tandem Mass Spectrometry

Author String

E Norjavaara, C Ankarberg-Lindgren
Institute of Clinical Sciences, The Sahlgrenska Academy at University, Göteborg, Sweden

Body

Objective: Kulle and co-workers¹ have developed a novel ultra pressure liquid chromatography tandem mass spectrometry for androgen determination in children and reference data for children and adolescents with respect to the entire pediatric age range, sex, and pubertal development. This is a prerequisite for a meaningful biological interpretation of the data. It is also a prerequisite for comparison to other methods. In the present study we have compared the results from Kulle and co-workers on the morning levels of testosterone in prepubertal and pubertal girls and boys at different pubertal stages with results from a modified RIA (Spectria testosterone; Orion Diagnostica, Espoo, Finland), as previously described from us^{2,3} with the aim to compare testosterone levels in children determined by a modified testosterone RIA with mass spectrometry.

Setting: Our modified testosterone RIA (Spectria^{reg} testosterone; Orion Diagnostica, Espoo, Finland) has a lower limit of detection of 0.03 nmol/L with a functional sensitivity of 0.1 nmol/L. The method is an accredited assay by SWEDAC in Sweden, SS-EN ISO 15189 (no 1899).

Design: We are attending an International External Quality Assessment program for laboratory medicine, as the reference method, liquid chromatography-tandem mass spectrometry (Helsinki University Central hospital) and report the results. We have also compared our earlier published data on testosterone in boys and girls using the same pubertal classification for boys and girls as done in the study by Kulle et al¹ using ultra-pressure tandem mass spectrometry.

Results: In the International External Quality Assessment program for laboratory medicine our modified testosterone RIA have participated 9 times and reports similar values ($r=1.00$, $n=18$, $p<0.0001$) on the test samples (range 0.85-24.4 nmol/L) as the reference method, liquid chromatography-tandem mass spectrometry. The pediatric reference values determined by ultra pressure liquid chromatography tandem mass spectrometry and determined by modified testosterone RIA, these both methods deliver similar testosterone values across the different pubertal stages.

Conclusions: Our modified testosterone Spectria RIA is an immunoassay that delivers clinical useful information. This is based on a direct comparison with liquid chromatography-tandem mass spectrometry as well as a comparison to pediatric reference intervals determined by ultra pressure liquid chromatography tandem mass spectrometry.

(1) Kulle A.E et al., JCEM; 95:2399

(2) Ankarberg, C. & Norjavaara, E., JCEM; 84:975

(3) Ankarberg-Lindgren, C. & Norjavaara E., Eur J Endocrinol; 151:747-757

Nothing to Disclose: EN, CA-L

sort_order 2780
Pub # P3-711
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)
Title A Novel Activating Mutation of the LH Receptor in a Family with Familial Male-Limited Precocious Puberty
Author String JE Emerick, M Poth
Uniformed Services University of the Health Sciences, Bethesda, MD; Walter Reed Army Medical Center, Washington, DC
Body
Background: Familial male-limited precocious puberty (FMPP) is caused by an activating mutation of the luteinizing hormone (LH) receptor leading to early sexual development and classically stunted adult height in affected males. Early sexual development may also lead to mood disorders and aggressive behavior in young children.
Clinical Presentation: Our index patient presented at age 6 with precocious sexual development. At presentation his specific diagnosis was not clear. His development continued and he developed significant depression. He was placed on Lupron at age 8 with excellent resolution of his psychiatric symptoms, but his accelerated growth continued. His brother was examined at ages 4 and 5 and appeared normal. However, at age 6, he developed testicular enlargement. The two brothers and their father, who never received treatment for precocious puberty, were all tested for mutations in the LH receptor.
Conclusion: Asp 564 Val mutation of *LHCGR* leading to FMPP was found in both brothers and their father. Retrospectively, the father only describes being tall at an early age, perhaps experiencing puberty before his peers, and having mild behavioral difficulties as a school aged child. The novel Asp 564 Val missense mutation found in our pedigree has resulted in an atypical FMPP phenotype in our patients. The father, who never received any treatment, is of above average adult male height and the sons presented slightly later than the average age of 3-4 commonly seen as the first age of presentation for this disorder. A possible explanation could be that the aspartic acid to glycine amino acid substitution at position 564 causes less activation of the LHCGR than missense mutations at other locations and possibly the specific substituted amino acid, even at the same location, can affect the degree of activation of the receptor. These patients represent the first confirmed cases of this mutation leading to FMPP. Although phenotypic heterogeneity in family members with the same LH receptor mutation has been reported, the very benign course of the father who had not been diagnosed, treated or even evaluated as a child is unusual in patients with this disorder. The knowledge that their father has the same genetic mutation and is successful and an above average height adult has significantly improved the family's stress level and helped in addressing the behavioral difficulties in the proband.

Nothing to Disclose: JEE, MP

sort_order

2781

Pub #

P3-712

Session Information

POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)

Title

A Novel Mutation of the Luteinizing Hormone Receptor Gene in a Compound Heterozygote Child with Hypergonadotropic Hypogonadism

Author String

A Vottero, R Minari, I Viani, M Petraroli, S Bernasconi, L Ghizzoni
University of Parma, Parma, Italy; University of Turin, Turin, Italy

Body

The luteinizing hormone receptor (LHR, NM_000233.1) plays a critical role in reproductive physiology in both males and females. In males, severe inactivating mutations of the LHR was recognized as the cause of Leydig cell hypoplasia, a rare form of male pseudohermaphroditism. In addition, inactivating mutations that partially inactivate LH signaling can cause micropenis, sometimes accompanied by hypospadias and cryptorchidism. Here we report a child who presented at birth with micropenis, cryptorchidism and hypospadias. His karyotype was 46,XY. At 5 yrs of age he underwent surgery for bilateral cryptorchidism. The patient came to our attention when he was 11.6 yrs old and at that time his auxological parameters were: height and weight >97[deg] pct, pubertal status: PH3, TV 4 ml bilaterally, penis length 2 cm (<2.5 SDS for age). Adrenal function was normal, but testosterone levels were low (<0.69 nmol/L) and did not increase after hCG stimulation test, and baseline LH levels were extremely elevated (40.8 mU/ml). The patient was started on testosterone therapy (250 mg i.m. every 3 weeks for 9 months) to increase the penis size with no significant results. A testicular biopsy showed no evidence of Leydig cells. Genetic testing of the LH receptor was performed on peripheral blood sample by PCR and direct automated sequencing. The patient was found to be compound heterozygote for the following mutations: c.29T>C, c.1847C>A and presented the c.1005A>G polymorphism. The mutation c.1847C>A was previously reported to be associated with hypergonadotropic hypogonadism (Lantronico AC, NEJM, 1996, 334:507). c.29T>C is a novel mutation, not described in the Human Genome Mutation Database, whose functional study is underway. Screening of the parents showed heterozygosity for the mutation, indicating autosomal recessive inheritance. Interestingly, the c.1005A>G polymorphism was previously reported to be associated with impaired spermatogenesis, suggesting that in this patient both LHR gene mutations and the c.1005A>G polymorphism may contribute to the impaired fertility that might arise in adult life.

Nothing to Disclose: AV, RM, IV, MP, SB, LG

sort_order 2782
Pub # P3-713
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)
Title *LIN28B* Polymorphisms Are Associated with Central Precocious Puberty in Girls
Author String S Ji, YB Sohn, SY Cho
Samsung Medical Center, Seoul, Korea
Body
Context: SNP markers within *LIN28B* have been reported to be associated with the timing of pubertal growth from the genome-wide association study in normal population. However, no study has investigated the frequency of genetic markers in girls with precocious puberty (PP, puberty before 8 years old) or early puberty (EP, puberty between 8 and 9).
Objective: To determine whether there is an increased or decreased prevalence of putative genetic markers in girls with PP or EP.
Design: Genomic DNAs were obtained from 77 and 109 girls fulfilled the criteria for PP and EP, respectively. Haplotypes were reconstructed using 11 SNPs in *LIN28B* and haplotype association analysis was performed.
Setting: All subjects were evaluated in the outpatient clinic
Interventions: Target SNPs were genotyped
Main Outcome Measures: The haplotype frequencies were compared between cases and controls. Differences in the clinical and laboratory parameters were analyzed according to the haplotype dosage.
Results: Eleven SNPs in *LIN28B* were all located in a linkage disequilibrium block, and haplotype could be reconstructed using two representative SNPs, rs4946651 and rs369065. The AC haplotype was less frequently observed in PP group compared to control (0.069 vs. 0.144; $P=0.010$). The trend was also illustrated even in the patient (EP+PP) group by Kaplan-Meier analysis; girls carrying non-AC haplotypes tend to have earlier pubertal onset ($P=0.037$).
Conclusions: The results of this study showed for first time that non-AC haplotypes of *LIN28B* had significant association with precocious puberty in girls.
Key words: SNP markers, *LIN28B*, precocious puberty, early puberty.

Sources of Research Support: Samsung Genomic Center Research Fund (D-B0-007-1).
Nothing to Disclose: SJ, YBS, SYC

sort_order 2783
Pub # P3-714
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)
Title Novel GnRH Analog Test (Triptorelin) vs. Classical GnRH Test for the Early Diagnosis of Central Precocious Puberty (CPP) in Girls: Comparative Validation Study
Author String AV Freire, ME Escobar, M Gryngarten, A Arcari, MG Ballerini, M Morini, I Bergada, MG Ropelato
Ricardo Gutiérrez Children's Hospital, Buenos Aires, Argentina
Body **Introduction:** The GnRH stimulation test is considered to be the gold standard to detect the activation of the hypothalamic-pituitary gonadal axis (HPG) (1). It is used to differentiate between idiopathic premature thelarche (IPT) and CPP. However, the formulation of GnRH for testing is not readily available. GnRH analogues could be a valid alternative to ascertain differential diagnoses of some HPG axis disorders.
Objectives: To design a novel test using aqueous subcutaneous Triptorelin acetate (TA) to identify girls with CPP in early stage and to determine its diagnostic efficiency (DEF) compared to classical GnRH test.
Methods: We performed a prospective clinical trial, case-control, Phase IV, validation study. Thirty eight girls (5-8.5 y) who presented premature thelarche and accelerated growth or advanced bone age were included. Girls with previous central nervous system illness or suspicion of peripheral precocious puberty were excluded. All girls underwent the two tests in a randomized order: 1) GnRH 100 [micro]g iv, blood sampling 0-30-60 min for LH, FSH and 2) TA 0.1 mg/m[^{sup}2] sc, with blood sampling at 0-3-24 h for LH and FSH (IFMA), and Estradiol (E2, ECLIA). CPP (Case group) diagnosis was made with a peak LH [ge] 6 IU/L in response to GnRH (2). Patients with peak LH < 6 IU/L were considered as IPT (Control group).
Results: Clinical and auxological characteristics were similar in both groups. LH-3h and E2-24 h showed the best diagnostic accuracy under TA test. CPP girls (n=27) presented LH-3h: 11.7±1.6 IU/L (mean±SEM) and E2-24h: 147±19 pg/mL, while IPT (n=11) showed LH-3h: 2.8±0.5 IU/L and E2-24h: 43±10 pg/mL (both p<0.001). When both tests were compared, ROC curve analyses provided a cutoff of LH-3h: 5 IU/L with Sensitivity (S):90%, Specificity (Sp): 90%, DEF: 98% (95% CI, 94-100%) and a Positive Predictive Value (VPP): 96%. The cutoff of E2-24h was 80 pg/mL with S: 78%, Sp: 90%, DEF: 91% (82-100%) and VPP: 95%. Spearman correlation between peak LH (GnRH-test) and LH-3 h (TA-test) was significant (r: 0.73 p<0.001). LH-3 h >5 IU/L on Triptorelin test classified as CPP 24 out of 27 CPP girls identified by classical GnRH test. Two of the three remaining girls showed E2-24h response above its cutoff.
Conclusion: A single LH-3h sample in the Triptorelin Acetate-test efficiently differentiates CPP from IPT. This test constitutes a valid alternative for assessing children with suspicion of CPP when GnRH is not available and allows a full assessment of HPG axis.

(1) Carel JC, Léger J, N Engl J Med 2008; 236:77.
(2) Lee PA, Arch Pediatr Adolesc Med 1994; 148: 369-76.

Nothing to Disclose: AVF, MEE, MG, AA, MGB, MM, IB, MGR

sort_order 2784
Pub # P3-715
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)
Title Evaluation of Puberty by Verifying Spontaneous and Stimulated Gonadotropin Values
Author String V Chin, L Lam, B Shah, P Zhou
Children's Hospital at Montefiore, Bronx, NY; Children's Hospital at Montefiore, Bronx, NY; NYU Langone Medical Center, New York, NY
Body
Background: Due to changes of pharmacological agents and laboratory assay advancements (1), threshold values of the GnRHa stimulation test for puberty should be reevaluated.
Objective: To compare spontaneous and leuprolide-stimulated serum levels of LH, FSH, and E2 with published data (1,2,3,4) to determine whether the thresholds currently used in our institution are appropriate.
Design/Methods: Thirty-five girls (2-year 7 month to 9 year 3 month) were divided into two groups: with (n=20) or without (n=15) central precocious puberty (CPP). The diagnosis of CPP, premature thelarche (PT), or premature adrenarche (PA) were retrospectively determined by 3 pediatric endocrinologists based on clinical information including tanner stages, height percentile, mid-parental height, BMI, growth velocity, basal FSH/LH and E2 levels, skeletal age, pelvic sonogram, and brain MRI. All subjects had leuprolide (20 mcg/kg) stimulation testing completed using the immunochemiluminometric assay, IMMULITE 2000. Spontaneous and stimulated gonadotropin and estradiol values were analyzed using SAS statistical software. CPP was used as the dependent variable while LH, FSH and E2 were used as independent variables. Logistic regression analysis was performed and models are selected based on statistical significance, fit, sensitivity, and specificity. The best single predictor model has a sensitivity of 0.80 and a specificity of 0.87, and uses 3-hour LH level as the predictor that has a threshold of 5.1 mIU/mL. In comparison, using the basal LH level as a predictor gives a sensitivity of 0.65 and a specificity of 0.60 with a threshold of 0.126 mIU/mL. A two-predictor model has an improved sensitivity of 0.95 and a specificity of 0.80, and uses 3 hour LH level and the logarithm of the percentage change between the 3 hour E2 and the 24 hour E2 as its independent variables.
Conclusions: The basal gonadotropin level has poor predictive power. The 3 hour LH level combined with two E2 levels has the best sensitivity. However, a 3 hour LH level provides the best clinical use for its practicality and convenience.

(1) Garibaldi LR et al, J Clin Endocrinol Metab. 1993;76 (4):851 -856
(2) Ibañeta L et al, J Clin Endocrinol Metab. 1994;78 (1):30 -35
(3) Christopher PH et al, Pediatrics. 2009;123(6): e1059-e1063
(4) Neely EK et al, J Pediatr. 1995;127 (1):47 -52

Nothing to Disclose: VC, LL, BS, PZ

sort_order 2785
Pub # P3-716
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)
Title Factors Associated with a Pubertal Response to Leuprolide Stimulation in Females with Suspected Central Precocious Puberty
Author String A Sathasivam, S Shapiro, M Marieta Pehlivanova, R Rapaport
Georgetown University Hospital, Washington, DC; Washington Hospital Center, Washington, DC; MedStar Health Research Institute, Hyattsville, MD; Mount Sinai School of Medicine, New York, NY
Body **Background:** GnRH analogue testing is employed in females (pts) with minimal pubertal signs and non diagnostic baseline (b) levels of LH or estradiol (E2) to help diagnose central precocious puberty (CPP). Previously we reported (Ref) that pts with a pubertal response (PR) to Leuprolide stimulation test (L-stim) are likely to have pubertal progression (PP). It is unclear which clinical or diagnostic factors are associated with PR to L-stim.
Objective: To analyze the factors associated with a PR to L-stim tests.
Methods: Retrospective chart review of 71 pts with suspected CPP who had L-stim done to detect the activation of hypothalamic pituitary gonadal axis (HPGA). L-stim: FSH and LH (ICMA) measured at 0, 60, and 120 after s.c. 20mcg/kg of Leuprolide. E2 measured at baseline and at 24 hrs. All assays were done at Esoterix Lab.CA. Criteria for PR are: stimulated LH [ge] 5 IU/L and/or stimulated E2 [ge] 50 pg/ml. Statistical analysis: Pearson's chi-square test or Fisher's exact test by SAS 9.1.
Results: Six pts with disorders of HPGA were excluded. PR obtained in 24/65 pts. Pelvic sonograms were obtained in 50 pts. All pts with Breast Tanner Stage (BTS) [ge] 3, LH [ge] 0.3 IU/L, E2 [ge] 10 pg/ml and pubertal uterine configuration (UC) had PR. There was substantial overlap in all other parameters.
1) Age < 8 years: PR=13/46; Age [ge] 8 years: PR=11/19 ; P=0.02
2) **BTS 2:** PR=17/58; **BTS 3:** PR=7/7 ; P<0.0001
3) **LH-b** <0.2 IU/L: PR=10/49; LH-b [ge] 0.2 IU/L: PR=14/16; P<0.0001
4) **LH-b** <0.3 IU/L: PR=15/56; LH-b [ge] 0.3 IU/L: PR=9/9; P<0.0001
5) **FSH-b** <3.0 IU/L: PR=6/43; FSH-b [ge] 3.0 IU/L: PR=18/22; P<0.0001
6) **LH/FSH-ratio-b** <0.10: PR= 15/51; LH/FSH-ratio-b [ge] 0.10: PR= 9/14; P=0.01
7) **E2-b** [le] 5 pg/ml: PR=11/50; E2-b > 5 pg/ml: PR=13/15; P<0.0001
8) **E2-b** < 10 pg/ml: PR=14/55; E2-b [ge] 10 pg/ml: PR=10/10; P<0.0001
9) **Average ovarian volume** (Av-Ov) <1 ml: PR=3/16; Av-Ov [ge] 1ml: PR=17/34; P=0.03
10) **Av-Ov** <2 ml: PR=8/33; Av-Ov [ge] 2ml: PR=12/17; P=0.001
11) **Uterine Volume** (UV) <4 ml: PR=12/38; UV [ge] 4 ml: PR=8/12; P=0.04
12) **UC** prepubertal: PR=16/46; **UC** pubertal: PR=4/4; P=0.02
BMI, bone age and uterine length were not statistically associated with a PR (Data not shown).
Conclusion: Among pts with minimal signs of puberty, those with LH-b [ge] 0.2 IU/L, FSH-b [ge] 3.0 IU/L, E2-b > 5 pg/ml and Av-Ov [ge] 2 ml are most likely to have pubertal response to L-stim and therefore to progress in puberty.

A. Sathasivam et al., Clinical Endocrinology (Oxford) 2010 Sep;73(3):375-81

Nothing to Disclose: AS, SS, MMP, RR

sort_order 2786
Pub # P3-717
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)
Title Efficacy of the 50 mg Histrelin Implant in Suppressing Puberty in Boys
Author String LA Silverman, D Chin, B Cerame, J Steelman, MD Wilcutts, P Thornton
Goryeb Children's Hospital, Atlantic Health, Morristown, NJ; Cook Children's Medical Center, Fort Worth, TX
Body
Background: The 50 mg histrelin acetate implant, used for the treatment of central precocious puberty, releases 65 mcg of histrelin daily to suppress the hypothalamic/pituitary/gonadal (HPG) axis. In two published studies, only 3 boys, all of whom had been first treated with a different agonist, were studied; all had continued suppression of LH <4mIU/mL after a GnRH α stimulation test. Because of the small number of male patients studied, questions remain as to the implant's efficacy in boys. Clinical experience with other GnRH analogues and anecdotal reports suggest that boys, even without underlying CNS abnormalities, may be more difficult to suppress than girls.
Design: We performed a retrospective chart review to assess the efficacy of the histrelin implant in suppressing puberty in boys. A total of 25 charts from 2 sites were reviewed. Treated boys ranged in age from 6.4 to 12.9 years, and had a variety of underlying diagnoses, including off-label treatment for height augmentation. 5 had a CNS lesion and 3 were born SGA. 2 boys with CAH and 3 who had prior treatment with other GnRH α were excluded. The primary measure of suppression analyzed in the remaining 20 was the combination of random or GnRH α stimulated LH and testosterone (T) level.
Results: Of the 20 boys, 18 were judged by the treating physician to have adequate HPG axis suppression by the implant. An 11 year old boy treated for rapidly progressive puberty was suppressed at 2 months post implant, but escaped suppression by 6 months. He had a similar pattern with a second implant, initially showing a suppression of T, which then rose. A 10 year old boy had suppression of LH, but not of T at 4 weeks, was judged equivocal. In all of the suppressed boys, testicular volumes either stayed the same or decreased slightly, but not to pre-pubertal volumes. There did not appear to be a correlation of CNS anomalies and lack of suppression.
Conclusions: In this largest series of boys reported to date, we found the histrelin implant to be an effective treatment to suppress puberty in the majority of boys. As lack of suppression is possible, there is a need for close monitoring after the placement of the histrelin implant. If a random LH and T level are insufficient to define adequacy of treatment, a GnRH α test may be indicated. The highly sensitive T assay (LCMSMS) may be necessary to define suppression. Further studies are needed to evaluate those patients deemed to have inadequate suppression.

Disclosures: LAS: Consultant, Endo Pharmaceuticals; Speaker Bureau Member, Endo Pharmaceuticals; Investigator, Endo pharmaceuticals. DC: Study Investigator, Endo Pharmaceuticals. BC: Teacher, Endo Pharma. PT: Consultant, Endo Pharmaceuticals; Speaker Bureau Member, Endo Pharmaceuticals. Nothing to Disclose: JS, MDW

sort_order 2787
Pub # P3-718
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)
Title Sex Steroids and Gonadotropins during Treatment with Yearly Histrelin or Monthly Leuprolide Acetate in Youth
Author String ML Klein, MO Regelman, R Annunziato, E Chacko, L Jazzeiti, E Wallach, S Hyman, D Chia, R Rapaport
Mount Sinai School of Medicine, New York, NY; Fordham University, Bronx, NY
Body **Background:** During Gonadotropin-Releasing Hormone (GnRH) analogue treatment (Tx) of central precocious puberty (CPP) with monthly Leuprolide Acetate (LA) or yearly Histrelin (HT), GnRH stimulated gonadotropin levels have been used to monitor efficacy of Tx. We are unaware of studies evaluating the effects of HT and LA on non-stimulated gonadotropins, Estradiol (E) and Testosterone (T).
Objective: Evaluate the effect of LA and HT on non-stimulated LH, E and T.
Methods: Retrospective chart review of pts Tx with HT (n=29, F=14) and LA (N=22, F=12) for CPP or early and/or rapidly advancing puberty naïve to Tx. LH, E, and T were measured before (pre) and [ge]90 days after (post) Tx (ultrasensitive, Esoterix, CA). Biochemical suppression was defined as prepubertal LH <0.3 mIU/mL, E <2.0 ng/dL and T <20 ng/dL. Clinical suppression was defined as lack of progression or reversal of breast development in F and testicular volume in M. Bone ages (BA) were obtained pre and [ge]6 months post Tx. Statistical analysis was done with Univariate analysis of variance (ANOVA) repeated measures of ANOVA, and Chi squared. Data are reported as mean±SD, age in yrs. LH values in mIU/mL, E in ng/dL and T in ng/dL.
Results: The age at the start of Tx was similar in both groups: HT (10.8±1.9 in F, 12.3±1.9 in M) and LA (10.0±3.6 in F, 12.7±2.0 in M). BA/CA, LH, and E were not different between LA and HT. T was greater in M with LA than HT (p=0.04). In HT, LH decreased from 2.8±3.2 to 0.3±0.2 in F and from 1.7±0.5 to 0.5±0.3 in M. In LA, LH decreased from 2.6±1.8 to 0.4±0.3 in F and from 1.6±0.6 to 0.6±0.4 in M.
All had clinical evidence of pubertal suppression. LA and HT resulted in similar suppression of E and T to prepubertal levels.
In the HT group, post LH was significantly lower in F (0.3±0.2) than M (0.5±0.3) (p=0.01) but similar in the LA group. Post LH was >0.3 in 43% of F and 60% of M with HT and 58% of F and 70% of M with LA. When comparing post LH >0.3 and LH <0.3, there were no differences between E and T in both LA and HT.
There was no significant difference between BA/CA pre and post in both HT and LA suggesting that BA/CA did not significantly advance during Tx. This was also true in those with post LH >0.3 in both groups.
Conclusion: Both HT and LA resulted in clinical and biochemical suppression in M and F. E and T were suppressed in all despite variable suppression of LH in both the HT and LA groups. Therefore, E and T may better reflect clinical suppression than LH in both HT and LA Tx pts.
Nothing to Disclose: MLK, MOR, RA, EC, LI, EW, SH, DC, RR

sort_order

2788

Pub #

P3-719

Session Information

POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)

Title

Danazol Therapy-Induced Central Precocious Puberty in a Patient with Hereditary Angioedema

Author String

BA Aulsebrook, PF Backeljauw
Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Body

Background: Hereditary angioedema (HAE) is an autosomal dominant disorder affecting approximately 10,000 people in the US and has a prevalence of 1 in 50,000. HAE is characterized by severe and painful inflammation that can even become life-threatening. Attenuated androgens, such as danazol, have been the main therapy option until recently. A single study has addressed side-effects of danazol therapy in children with HAE. In this study of 11 patients treated with danazol, there was one case of delayed menarche, but no effects on skeletal growth or maturation, secondary sexual characteristics, weight gain, or abnormal hair growth were reported.

Case Presentation: An 8 year-old male with HAE presented with premature adrenarche. He had a one-and-a-half year history of accelerated linear growth, acne, body odor, progressive pubic hair growth (Tanner II), and increased moodiness. The HAE had been treated with danazol 50 mg orally daily, but this was administered intermittently to specifically treat HAE exacerbations. Skeletal maturation was advanced to 11 years. Laboratory evaluation showed normal thyroid function, testosterone (7 ng/dL, nl <20), dehydroepiandrosterone sulfate (66 mcg/dL, nl 13-83), and sex hormone binding globulin (51 nmol/L, nl 28-190). Leuprolide acetate stimulation yielded a pubertal response: baseline LH was <0.02 mIU/mL and stimulated values were 5.01, 6.86, and 8.04 mIU/mL (nl <1.41) after respectively 30, 60, and 90 minutes. Corresponding FSH values were 0.31, 1.06, 1.64, and 1.87 mIU/mL (nl <3.00). This response is consistent with hypothalamic-pituitary-gonadal axis activation. Danazol therapy was discontinued and HAE exacerbations were treated conservatively with anti-inflammatory agents. During the next year the patient's pubertal development did not progress, acne improved and linear growth normalized.

Conclusion: Virilization is a documented adverse effect of danazol therapy in adults, but this has not been reported in children. We believe that the intermittent or pulsatile administration of the danazol therapy primed the HP-gonadal axis causing pubertal development in this boy. Physicians should be aware of the potential side effect of central precocious puberty (CPP) with danazol and consider alternative therapies, not containing androgens, for HAE prophylaxis/therapy in childhood. Danazol therapy can cause CPP, associated with psycho-emotional consequences and compromise of obtaining normal height potential.

Nothing to Disclose: BAA, PFB

sort_order 2789
Pub # P3-720
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)
Title Prediction of Growth Velocity in Girls with Precocious Puberty during GnRH Agonist Treatment by Measurement of Growth Velocity at 3 Months after Treatment
Author String S Yang, IT Hwang
Kangdong Sacred Heart Hospital, Hallym University, Seoul, Korea
Body
Objectives: The aim of this study was to assess the usefulness of growth velocity at 3 months after GnRH agonist treatment as a predictive value of 1 year growth velocity after treatment in girls with precocious puberty.
Subjects and Methods: We studied 26 Korean girls with precocious puberty whose chronologic and bone age were less than 9 years and 11 years old, respectively at diagnosis. They treated with a 4 week interval GnRH agonist subcutaneous injections for at least more than 1 year. The patients who were treated with GH simultaneously excluded for this study. Data were collected from chart review retrospectively. We measured heights and calculated growth velocities of the subjects at 3 months and 12 months after GnRH agonist treatment.
Results: The mean chronologic and bone age of the subjects were 8.1 ± 0.9 and 10.5 ± 0.6 years, respectively. The growth velocities at 3 months and 12 months after GnRH agonist treatment were 9.6 ± 5.2 , 7.1 ± 1.6 cm/year, respectively. The positive correlation between the growth velocity at 3 months and 12 months after GnRH agonist treatment was shown ($P=0.046$, $R=0.394$).
Conclusions: In this study, the growth velocity at 12 months after GnRH agonist treatment may be predicted by the growth velocity at 3 months after treatment. It may be helpful to decide early combined treatment with growth hormone for improvement of their final heights in patient with precocious puberty treated with GnRH agonist.
Nothing to Disclose: SY, ITH

sort_order

2790

Pub #

P3-721

Session Information

POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)

Title

Serum Kisspeptin and Bisphenol A Levels in Girls with Central Precocious Puberty

Author String

A Kwon, H Chae, KH Lee, H-S Kim, YJ Rhie
Yonsei University College of Medicine, Seoul, Republic of Korea; Korea University College of Medicine, Seoul, Republic of Korea

Body

Objectives: Central precocious puberty (CPP) is caused by premature activation of hypothalamic GnRH secretion. Kisspeptins, the peptide products of the KISS1 gene, and their putative receptor, GPR54 are the essential gatekeepers of the reproductive system, playing a key role in the activation of the gonadotropic axis at puberty. Bisphenol A (BPA) is supposed to be associated with precocious puberty. The objectives of this study were to determine serum kisspeptin and BPA levels in girls with CPP and prepubertal controls.

Methods: Serum kisspeptin and BPA levels of girls with CPP (n=31) and prepubertal age-matched healthy controls (n=30) were assayed with a competitive ELISA.

Results: Serum kisspeptin levels were significantly higher in CPP group compared with control group (6.19 ± 2.50 vs. 2.52 ± 1.07 ng/mL, $P < 0.0001$). Also, serum BPA levels were significantly higher in CPP group (4.97 ± 1.05 vs. 4.01 ± 1.13 , $P = 0.026$). Serum kisspeptin levels were positively correlated with peak LH levels during GnRH stimulation test ($r = 0.345$, $P = 0.022$), but not related to age, height, weight, BMI, peak FSH and serum BPA. Serum BPA levels were not related to age, height, weight, BMI, peak LH and FSH and serum kisspeptin.

Conclusions: Our findings suggest that CPP is triggered by premature increase of kisspeptin and subsequent activation of hypothalamic-pituitary-gonadal (H-P-G) axis. BPA level has no influence on kisspeptin level. BPA may induce CPP by different mechanism from kisspeptin. Further studies on other environmental factors or the KISS1 gene polymorphisms leading to higher risk of premature increase of kisspeptin are needed.

Nothing to Disclose: AK, HC, KHL, H-SK, YJR

sort_order 2791
Pub # P3-722
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)
Title Endocrine Disruptors in the Pubertal Transition: Bisphenol A Is Negatively Correlated with Testosterone in Early Puberty
Author String MB Baker, I Hernandez, F Stanczyk, C Azen, Y Hsu, D Spruijt-Metz
University of Southern California, Los Angeles, CA; University of Southern California, Los Angeles, CA
Body **Background:** Bisphenol A (BPA) is an endocrine disruptor with known estrogen-mimetic properties that has been implicated in young girls reaching puberty earlier. In addition, it has been implicated in having a role in androgen metabolism. In vitro studies have indicated that BPA may lead to increased testosterone concentrations, and in vivo studies have suggested a positive correlation of BPA with androgens. However, the impact of BPA on hormonal and metabolic parameters in young girls is lacking.
Objective: To determine if there is a correlation between BPA and gonadotropins, androgens, estrogens, and SHBG in normal young girls.
Materials & Methods: Prospective cohort analysis of 74 subjects, n=53 Latino and n=21 African-American girls, ages 8-11. Clinical examination was performed upon enrollment, and all subjects were either Tanner stage 1 or 2. Baseline blood samples were obtained for measurement of serum levels of BPA, LH, FSH, DHEAS, 3 α -androstenediol glucuronide (3 α -diol G; a marker of peripheral androgen action) and SHBG by direct immunoassays, and testosterone, androstenedione, E₁ and E₂ by RIAs with preceding purification steps. Spearman correlations were carried out between BPA and the various hormones and SHBG.
Results: Baseline hormone levels (mean \pm SD) were: LH, 0.91 \pm 1.72 mIU/ml; FSH 2.96 \pm 2.08 mIU/ml; testosterone, 11.2 \pm 6.86 ng/dL; androstenedione, 0.44 \pm 0.28 ng/ml; DHEAS, 54.7 \pm 31.1 [mu]g/ml; 3 α -diol G, 1.23 \pm 0.69 ng/ml; E₁, 18 \pm 10 pg/ml; E₂, 17 \pm 18 pg/ml; SHBG, 37 \pm 20 nM. For BPA, the levels were 0.38 \pm 0.33 ng/ml. There were no statistically significant correlations seen with BPA and LH (r=-0.0629, p=0.59), FSH (r=-0.082, p=0.49), DHEAS (r=0.068, p=0.57), androstenedione (r=-0.167, p=0.16), 3 α -diol G (r=-0.027, p=0.82), E₂ (r=-0.141, p=0.23), or SHBG (r=-0.018, p=0.87). BPA levels were statistically and negatively correlated with testosterone (r=-0.258, p=0.03) and E₁ (r=-0.425, p=0.002).
Conclusions: BPA is negatively correlated with testosterone and estrone in early pubertal stages. These data do not support the positive correlation between BPA and androgens seen in other studies, suggesting that in early puberty this effect is not yet apparent.
Nothing to Disclose: MBB, IH, FS, CA, YHH, DS-M

sort_order 2792
Pub # P3-723
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)
Title An Ovarian Germ Cell Tumor Causing Rapidly Progressing Precocious Puberty and Virilization
Author String M Marinkovic, KL Jones
University of California San Diego, San Diego, CA; Rady Children's Hospital, San Diego, CA
Body
Introduction/Background
Ovarian tumors are rare neoplasms in childhood, occasionally producing precocious puberty but rarely adrenarchal changes.
Clinical Case
This previously healthy 5 10/12 year old girl had a 6 month history of breast development with pubic hair and a growth spurt. She was referred immediately to our endocrine service when large pelvic mass and clitoral enlargements were also noted. She had no exogenous exposure to estrogen or androgen containing products.
Her breasts measured 4 cm in diameter (Tanner 3), pubic hair was early Tanner 2, vaginal mucosa showed estrogen effect and her clitoris measured 1.5 cm in length. Abdominal examination revealed a pelvic mass measuring approximately 10 cm in diameter.
Pelvic sonography demonstrated a multicystic right ovarian mass (10.8 x 10.8 x 8.5 cm), a pubertal uterus (5.8 x 2.8 x 1.6 cm) and an enlarged left ovary without cysts (2 x 2 x 1.3 cm). Adrenals were unremarkable. Her bone age was advanced 1 year. Pelvic/abdominal MRI confirmed the presence of a large cystic/solid right abdominal mass. The patient's gonadotropins were undetectable and androgens were elevated: testosterone 252 ng/dL (<7); 17OHP 299 ng/dL (<90); DHEAS 36 mcg/dL (<=34); androstenedione 188 nd/dL (6-15). Estradiol (E2) was mildly increased to 17 pg/mL (<16) HCG and α -fetoprotein (AFP) were elevated at 2.5 IU/L (<0.7) and 88 ng/mL (<6), respectively.
Removal of the mass resulted in gradual disappearance of tumor markers and return to normal of estrogens and androgens. Pathologic examination of the tumor (stage 1) reported it was 85% immature teratoma and 15% dysgerminoma. The tumor contained tissues representing ectoderm, mesoderm, and endodermal derivatives. Tissue resembling adrenal and Leydig-like cells (noted within dysgerminoma) were probably responsible for androgen production.
Two months postoperatively a small amount of breast tissue was present only on right side, with clitoral size decreased to <1cm. Follow up MRI of her pelvis and abdomen showed no residual tumor or evidence of metastases.
Clinical Lesson(s)/Conclusion:
Rapidly progressing precocious puberty should always raise a concern for a hormone-secreting tumor. This tumor, primarily germ cell component, stimulated E2 secretion and also contained androgen secreting cells complicating the clinical presentation.

Nothing to Disclose: MM, KLJ

sort_order

2793

Pub #

P3-724

Session Information

POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)

Title

Detection of the P.R201H Mosaic Mutation of the GNAS1 α , Associated with McCune-Albright Syndrome, Using Genotyping Real-Time PCR

Author String

BMP Mariani, RA Toledo, ET Barbosa, MCBV Fragoso, BB Mendonca

Hospital das Clinicas, School of Medicine, University of São Paulo, São Paulo, Brazil; School of Medicine, University of São Paulo, São Paulo, Brazil

Body

Background McCune-Albright syndrome (MAS) is a sporadic disorder characterized by the classic triad of polyostotic fibrous dysplasia, cafe[acute]-au-lait skin pigmentation, and endocrine dysfunction, in particular, peripheral precocious puberty (PB) in girls. MAS has a large spectrum of clinical presentation: beyond the classic triad, a number of atypical or partial presentations have been reported. Other hyperfunctional endocrinopathies have been reported such as pituitary adenomas, hyperthyroidism, autonomous adrenal hyperplasia, and hypophosphatemic osteomalacia. These endocrine disorders occur alone or in combination and encompass a wide range of severity peripheral precocious puberty and are due to postzygotic activating mutations of arginine 201 in the guanine-nucleotide-binding protein (G protein) α subunit (Gs α), leading to a mosaic distribution of cells bearing constitutively active adenylate cyclase. This mosaic distribution makes MAS molecular diagnosis, technically difficult to analyze, once the percentage of mutant cells can be as low as 2, 5 % in blood. Objective: To evaluate the sensitiveness of Genotyping Real Time PCR in the detection of the p.R201H mosaic mutation in affected tissues of classic and non-classic MAS patients. Subjects: One male patient with classic MAS presenting with acromegaly and cafe[acute]-au-lait skin pigmentation, which was used as a positive control for the mutation and two patients with non-classic MAS, an eight year-old girl with gonadotropin-independent precocious puberty with no clinical diagnosis established, and a forty year old woman, presenting with polyostotic fibrous dysplasia. Five controls were also genotyped. Methods: DNA was extracted from tumor tissue samples. The p.R201H was genotyped by PCR-Real Time using Taqman SNP Genotyping Assay Results: The technic used on this study was able to detect the p.R201H mosaic mutation in all three patients here analyzed, including those patients with the non-classic form. The control group did not have the p.R201H mutation, as expected. Conclusions This technic appears to be sensitive to detect the p.R201H mosaic mutation in affected tissues were the percentage of mutant cells should not be low. This method could bring an improvement in establishing MAS diagnosis and consequently in the management of patients that present no classical signs of MAS.

Sources of Research Support: CNPq - 130285/2010-2.

Nothing to Disclose: BMPM, RAT, ETB, MCBVF, BBM

sort_order 2794
Pub # P3-725
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)
Title Down-Regulation of Lymphocyte Apoptosis in Girls with Precocious Puberty
Author String MC Maggio, M Todaro, G Stassi, G Corsello
University of Palermo, Palermo, Italy; University of Palermo, Palermo, Italy
Body
The effects of sexual hormones secretion in children with precocious puberty induce significant somatic and psychological changes, with systemic implications on several organs and tissues. Besides immune system and blood cells are involved in these changes.
Recent studies on mice lymphocytes have demonstrated a protection of estrogens against apoptosis Fas-FasL pathway. These data could partially elucidate why autoimmune diseases are more frequent in females adolescents, whereas males have higher mortality associated with infectious diseases.
We studied ten girls (age: 4-7 years) affected by idiopathic precocious puberty, with pubertal stage B3-PH3-4. All presented increased bone age/chronological age, increased growth velocity, echographic signs of ovarian and uterine maturation, enhanced FSH, LH and 17- β -estradiol levels. In all the patients pituitary MNR was normal.
We also evaluated 10 control girls matched for age, with pubertal stage B1PH1.
We studied apoptosis of peripheral lymphocytes, using the technique of stratification on Ficoll.
Lymphocytes sensitization to apoptotic death mediated by receptors CD95 and TRAIL (tumour necrosis factor-related apoptosis-inducing ligand) was induced. Lymphocytes were incubated for 24 hours with 11 [mu]g/ml of PHA and for 4 days with 25U/ml of IL-2. Therefore 2x10⁵ lymphocytes were cultured in 96-well plates and incubated for 24 hours with 200 ng/ml of CD95, 800 ng/ml of TRAIL and with negative control medium alone.
Apoptotic death was detected by MTT and lecture by Orange Acridine.
We relieved a reduced lymphocytes apoptosis in girls with precocious puberty versus lymphocytes of control subjects both with CD95 and with TRAIL.
Our results support the role of pubertal activation by sex hormones on the immune response and the potential incidence of autoimmune diseases in children with precocious puberty, linked to estrogens protection of lymphocytes against apoptosis.

Nothing to Disclose: MCM, MT, GS, GC

sort_order 2795
Pub # P3-726
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)
Title Comparison of Transdermal and Oral Estrogens in Adolescents with Ovarian Failure
Author String S Shah, N Forghani, EK Neely
Stanford University, Stanford, CA
Body
Background: Estrogen replacement in adolescents with Turner Syndrome (TS) or other forms of ovarian failure is necessary to induce feminization and deliver other important physiologic effects. Studies in adults have demonstrated differential safety profiles among various forms of estrogen, but the ideal route and form of estrogen delivery have not been adequately explored in this adolescent population.
Objective: Our primary objective was to evaluate the metabolic profiles of three forms of estrogen: oral conjugated equine estrogen (OCEE), transdermal 17 β estradiol (TDE), and oral 17 β estradiol (OBE). Our secondary objective was to evaluate the three forms of estrogen in efficacy of feminization. We hypothesized that TDE would have a better metabolic profile than OCEE and OBE.
Methods: Adolescent females >12 years old with ovarian failure were enrolled in a randomized controlled open label study and assigned to 1 of 3 forms of estrogen. Estrogen replacement was initiated at a low dose (0.15 mg/d OCEE, 0.25mg/d OBE, or 0.012 mg/wk TDE) and doubled every 6 months to a maximum dose of 0.625mg/d (OCEE), 1mg/d (OBE), or 0.05mg/wk (TDE) at 18 months, when progesterone (Prometrium) was added to induce menstrual cycles. Biochemical markers including CRP, fibrinogen, liver enzymes, coagulation factors, lipids, growth factors, sex hormones, and insulin were obtained at baseline and 6 month intervals.
Results: 14 females, including 9 with TS, have enrolled in the study to date. The mean (SD) serum estradiol concentrations at baseline were similar: OCEE 3.8(3.5) pg/mL; OBE 1.3(0.5) pg/mL; TDE 6.3(8.5) pg/mL. At 18 months the mean (SD) estradiol concentrations were: OCEE 9.6(7.2) pg/mL; OBE 6.3(6) pg/mL; TDE 53(33) pg/mL (p=0.024). Mean (SD) serum concentrations of CRP were higher in the OCEE and OBE groups at baseline and at 18 months (OCEE 7.4(10.5) mg/L; OBE 0.45(0.3) mg/L; TDE 0.16(0) mg/L), but did not reach statistical significance. Other biochemical markers were not significantly different between groups at 18 months. Feminization occurred more rapidly in TDE and OBE groups compared to the OCEE group (Tanner 3 breast stage in 75% vs 40% at 12 months).
Conclusions: TDE results in higher serum estradiol concentrations and improved feminization compared to OCEE without a significant difference in inflammatory and other biochemical markers. These preliminary data suggest similar safety profiles among the estrogen forms but more effective feminization with TDE.
Nothing to Disclose: SS, NF, EKN

sort_order

2796

Pub #

P3-727

Session Information

POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)

Title

Elevated Testosterone Concentrations Are Associated with Advanced Bone Age in a Multiethnic Cohort of Girls with Premature Adrenarche (PA)

Author String

RA Nejat, VK Prasad, R David, PC Brar
New York University, New York, NY; New York University School of Medicine, New York, NY

Body

Background: PA, traditionally considered a benign process, is now viewed as a harbinger for future aberration such as polycystic ovary syndrome (PCOS) (1, 2). PA is the presence of pubic hair before age 8 yrs in girls, with DHEAS being the predominantly elevated androgen (3). While the role of androgens in bone growth has been well established *in vitro* (4), correlations between the elevated androgens and advanced bone age (ABA) observed in girls with PA have not been well delineated. The goal of this study was to identify the predominant androgen in a multiethnic cohort of girls with PA and to determine if that androgen was associated with ABA.

Methods: A retrospective chart review was conducted on girls aged 5-7 that presented to our clinic between 2002-2010. The review included anthropometric data, androgen profile, bone age (BA), growth velocity and Tanner stage. Age-matched controls were also identified. Hormone concentrations were determined by radioimmunoassay and chromatography following extraction in our institution's endocrine laboratory. Mann-Whitney U tests and Spearman Correlation tests were used for statistical analyses.

Results: Our cohort of 40 girls with PA were mostly Hispanic (58%) and African-American (25%) with a mean age of 6.89 ± 0.80 yrs, BA of 7.83 ± 1.27 yrs, BMI 19.83 ± 0.75 , BMI Z-score 1.26 ± 0.20 , and growth velocity 7.03 ± 0.45 cm/yr. Testosterone was elevated in 60% of girls with PA (defined as $[ge]10ng/dl$ for pre-pubertal girls) with DHEAS being elevated only in 30% of girls ($[ge]75$ $[mu]g/dl$ for girls aged 6-8; $[ge]55$ $[mu]g/dl$ for girls <5 yr). Girls in the PA group had significantly elevated testosterone (11.55 ± 4.83 ng/dL; $p=0.04$) and DHEAS (65.52 ± 41.84 $[mu]g/dl$; $p=0.04$) levels when compared to age-matched controls ($n=7$). The 17-OHP values in the two groups were not significantly different. 48% girls had an ABA (defined as BA $[ge]1$ yr of chronological age). There was a significant correlation between BA and serum testosterone while controlling for BMI ($r=0.51$, $p=0.05$). There was no significant association between BA and DHEAS, androstenedione, and 17-OHP.

Conclusion: In our cohort of girls, testosterone emerged as the predominant elevated androgen. The adverse long-term effect of hyperandrogenism and consequent PCOS have been well established. Therefore monitoring girls with PA, elevated testosterone and ABA for emergence of aberrations in the hypothalamic gonadal axis may be prudent.

1. Rosenfield RL, J Clin Endocrinol Metab 2007; 92:787
2. Kousta E, Ann N Y Acad Sci 2006; 1092:148
3. Ibanez L, Endocr Rev 2000; 21:671
4. Clarke BL et al., Steroids 2000; 74:296

Nothing to Disclose: RAN, VKP, RD, PCB

sort_order 2797
Pub # P3-728
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)
Title Clinical Presentation of Children with Premature Adrenarche
Author String JE Von Oettingen, Q Sola Pou, LL Levitsky, M Misra
Mass General Hospital for Children and Harvard Medical School, Boston, MA; Massachusetts General Hospital and Harvard Medical School, Boston, MA
Body **Background:** Although premature adrenarche (PA) is a common reason for referral to pediatric endocrinologists, there are only a few reports of the spectrum of clinical presentation of this condition. In addition, while reports suggest associations of high BMI and low birth weight (BW) with PA, this has not been explored in a large population and both genders.
Objectives: To describe the clinical features of a large cohort of PA patients presenting to the Pediatric Endocrine Service of a university hospital, and elucidate factors associated with BMI and BW.
Patients and Methods: Retrospective chart review of 149 patients (107 F, 42 M) with PA.
Results: 81 patients were White, 28 Hispanic, 15 Black, 6 Asian, 5 mixed and 14 had unknown ethnicity. There were two peaks in age at presentation, infancy (0-1y, n=8) and 6-8 y (n=141). Infants were excluded from subsequent analyses. Age at onset of pubic/axillary hair was earlier in girls vs. boys (6.1±1.4 vs. 7.3±2.0y, p<.0001). Mean BW was 3227±864 g and did not differ by gender. BW was low (<2500g) in 16%. BMI standard deviation scores (SDS) were calculated for children >2 y and did not differ in girls vs. boys (1.9± 1.8 vs. 2.0±1.8). Bone age (BA) SDS trended higher in boys vs. girls (1.7±1.4 vs. 1.3±1.2y, p=0.08), which became significant when comparing years of BA advancement (1.5±1.2 vs. 1.0±0.9y, p=0.004). DHEAS was higher in boys vs. girls (110±59 vs. 66±46 mcg/dL, p=0.0004), even after controlling for BA advancement. 17-OHP and testosterone did not differ between genders. When categorized by BMI SDS, girls with BMI SDS [ge]2 had higher BA SDS, greater BA advancement (p<.0001), and higher BW (p=0.01) than girls with BMI SDS <2. This was not observed in boys. When categorized by BW, children with BW <2500 g did not differ from peers with BW >2500 g for BMI SDS, BA SDS, DHEAS, 17-OHP or testosterone. Age at presentation was significantly lower in girls with BW <2500g vs. >2500g (5.4±2.0 vs. 6.2±1.2y, p=0.04), but was not significant in boys. In addition, Black boys and Hispanic girls were more likely to be younger at presentation (p<0.05).
Conclusion: In this large cohort, PA was characterized by earlier onset in girls. Patients tended to be overweight with advanced BA, more marked in boys, who also had higher DHEAS than girls. Higher BMI SDS was associated with more advanced BA and greater BW in girls. Consistent with previous reports, low birth weight was associated with earlier age at presentation in girls.
Nothing to Disclose: JEVO, QS, LLL, MM

sort_order 2798
Pub # P3-729
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)
Title Complete Male to Female Sex Reversal in a Patient with Seizure Disorder and Developmental Delay
Author String HM Tfayli, S Madan-Khetarpal, FX Schneck, SF WitcheI
American University of Beirut, Beirut, Lebanon; University of Pittsburgh, Children's Hospital of Pittsburgh, Pittsburgh, PA; University of Pittsburgh, Children's Hospital of Pittsburgh, Pittsburgh, PA; University of Pittsburgh, Children's Hospital of Pittsburgh, Pittsburgh, PA
Body **Background:** Duplication of the dosage-sensitive gene NR0B1 encoding DAX1 on chromosome Xp21.2 results in male to female sex reversal.
Case: A 14 mo female presented to the neurology service at Children's Hospital of Pittsburgh for evaluation of hypotonia, myoclonic seizures and developmental delay. She was the product of in vitro fertilization to nonconsanguineous parents, born at 41 weeks of gestation with no complications. She was noted to have twitching and startle episodes since few days of age. Hypotonia was noted at around 6 months of age and she was diagnosed with myoclonic seizures at 8 mo of age. In addition, she had global developmental delay. Physical exam was remarkable for weight <3rd%, length at the 10th%, minimal plagiocephaly with wide flattened occiput, bluish sclerae, low-set and slightly posteriorly rotated ears, hypotonia with no clonus, and normal female genitalia with no labial fusion, no palpable gonads and no enlargement of the clitoris.
Evaluation: Karyotype with microarray analysis and FISH was done as part of the work-up for seizure disorder and revealed the following: 46 XY, der(13)t(X;13)(p21.1;p11.2). She was then referred to endocrinology service. Ultrasound of the abdomen revealed a uterus, but no gonads were identified and kidneys were normal. Testosterone concentration was < 0.1 ng/dL, AMH:3.0 ng/mL, Inhibin B: < 30 pg/mL, LH: 0.8 mIU/mL and FSH: 7.2 mIU/ML. Neither parent had a similar translocation.
Conclusion: Our patient had a de novo translocation of the short arm of the X chromosome to the autosomal chromosome 13. This resulted in a derivative chromosome 13 and duplication of the region containing Xp21.1 and Xp11.2. The duplication of the NR0B1 encoding DAX1 resulted in complete male to female sex reversal, while the duplication of the Xp11.2 could explain the noted developmental delay. To our knowledge this is the first report of a complete sex reversal associated with developmental delay and seizure disorder due to translocation between X chromosome and chromosome 13.

Nothing to Disclose: HMT, SM-K, FXS, SFW

sort_order 2799
Pub # P3-730
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)
Title XY Disorders of Sex Development (DSD): A Diagnostic Challenge Linked to Candidate Gene Sequencing
Author String HL Miles, TI Bunch, VM Pilfold-Wilkie, N Lek, IA Hughes
University of Cambridge, Cambridge, UK; KK Women's and Children's Hospital, Singapore
Body
Background: Causes of XY DSD can generally be classified according to defects in testis development, androgen production or action. Diagnostic yield relies on appropriate endocrine investigations and targeted gene analyses, but success is less than optimal. The rate is less than 50% even when normal androgen production has been established and even less with a clinical diagnosis for gonadal dysgenesis.
Aim: To analyse the contribution of candidate gene sequencing when coupled to key phenotypic markers and specific steroid analyses towards making a diagnosis in a large cohort of patients with XY DSD.
Methods: Cases with atypical genital phenotypes and normal XY karyotype were recruited from the Cambridge DSD Database. Detailed clinical, histological, biochemical analyses were available and targeted gene sequencing of AR, HSD17B3, SRD5A2, SRY and SF1 related to the putative diagnosis was performed.
Results: A total of 470 cases was analysed, representing the following diagnoses: CAIS (n=183), PAIS (n=173) 17BHS deficiency (n=29), 5a reductase deficiency (n=33) and gonadal dysgenesis (n=52). AR mutations were present in 92% and 30% of CAIS and PAIS cases analysed, respectively. The PAIS AR mutation -ve group were of lower birth weight than the mutation +ve group (SDS -1.33 vs - SDS 0.33, p=0.002). HSD17B3 mutations were present in 72% and SRD5A2 mutations in 97% of cases analysed. A mutation was identified in 41% of cases in the gonadal dysgenesis group (SRY, 24%; SF1, 17%).
Conclusions: Success in establishing a diagnosis in the 3 main categories of XY DSD exceeded 60% with targeted gene sequencing. The most specific category was CAIS deficiency and yet 8% of the group have no identifiable AR coding gene mutation. The PAIS phenotype is heterogeneous: the acronym should be reserved for AR mutation +ve cases (30%). Birth weight for gestational age accurately predicted the likelihood of identifying a mutation. Urinary steroid analysis was highly specific for SRD5A2 mutations, but less reliable in 17BHS deficiency. The cause of XY gonadal dysgenesis remains unknown in the majority of cases, despite increasing identification of candidate genes. Establishing the cause is more challenging in XY DSD than its less common XX DSD counterpart. Nevertheless, judicious use of targeted gene sequencing coupled with biochemical tests and recognition of phenotypic markers is leading to improved diagnosis. This has significant impact on sex assignment.

Nothing to Disclose: HLM, TIB, VMP-W, NL, IAH

sort_order 2800
Pub # P3-731
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)
Title Snapshot View of a Large Klinefelter Syndrome Cohort from across the United States
Author String MZ Bardsley, M Kruszewski, K Kowal, JL Ross
Thomas Jefferson University, Philadelphia, PA; Nemours, Philadelphia, PA
Body
Objective: To describe the baseline characteristics of a large study population of boys with Klinefelter syndrome (KS)
Background: KS is defined by the karyotype 47,XXY and has a characteristic physical phenotype of tall stature and testicular failure (androgen deficiency).
Methods: The evaluation included history and physical examination and laboratory measurements in 93 boys with KS, ages 4-12.9 years.
Results: The mean age of the cohort was 7.03 ± 2.58 , range 4-12.9 years. Boys had received no previous treatment with androgen in the past year. Karyotype included 88 boys with 47,XXY, 2 mosaic 47,XXY/46,XY, and 3 other KS variants. 73% were Caucasian. Diagnosis was made prenatally or in infancy in 64/93 (69%), and at ages 2-12 years in 29/93 (31%). Participants came from 31 U.S. states, and represented a broad range of socioeconomic status and parental education levels. Mean SD scores (SDS \pm SD) were height: 0.59 ± 1.05 , weight: 0.64 ± 1.11 , head circumference: 0.26 ± 1.2 , body fat: 2.82 ± 2.49 , and body mass index (BMI): 0.49 ± 1.15 . Upper segment/lower segment SDS was -0.76 ± 2.5 , indicating long legs. Mean waist circumference (WC) was above the 75th percentile in 48/93 (52%), suggesting abdominal obesity. Mean testicular volume SDS was -1.1 ± 1.5 and penile length SDS was -1.7 ± 0.8 , suggesting childhood testicular failure. Hypotonia was present in 90/93 (97%), clinodactyly in 83/93 (89%), hypertelorism in 77/93 (83%), decreased muscle mass in 63/93 (68%), flat feet in 68/93 (73%), and mild intention or resting tremor in 33/93 (36%). A total of 72/93 (77%) had received speech therapy, 31/93 (33%) reading assistance and 62/93 (67%) occupational and/or physical therapy (PT/OT). Other psychiatric diagnoses included ADHD in 26/93 (28%) and Pervasive Developmental Disorder (PDD) in 10/93 (11%).
Conclusions: Tall stature, long legs, and abdominal obesity are already evident during childhood in KS, as are small testes and penile length. Notably, mean body fat and waist circumference are significantly above average. Other common but less well described physical findings include hypotonia, flat feet, and decreased muscle mass, as well as clinodactyly, and hypertelorism. Early intervention for speech, reading, and OT/PT is common. Frequent comorbid psychiatric diagnoses include ADHD and PDD. These findings may be used to raise the clinicians' awareness of the diagnosis of KS during childhood.

Sources of Research Support: NIH grant NS 050597.

Nothing to Disclose: MZB, MK, KK, JLR

sort_order 2801
Pub # P3-732
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)
Title A Case of Discordance between Prenatal Genotype and Phenotype
Author String MX Escalante, M Mendiratta, JE Dietrich, NA Sokkary, L McCullough, ME Axelrad, VR Sutton, RY Sonabend, SL French, SK Gunn, LP Karaviti
Baylor College of Medicine, Houston, TX; Baylor College of Medicine, Houston, TX; Baylor College of Medicine, Houston, TX; Baylor College of Medicine, Houston, TX; Baylor College of Medicine, Houston, TX
Body **Background:** 1 in 3000 infants is born with a disorder of sexual differentiation (DSD) and may be cause of high parental distress at the time of sex assignment. With improving techniques in prenatal ultrasounds and the increasing use of genetic amniocentesis, some sexual differentiation disorders (DSD) can now be diagnosed prenatally. While this exposes a need for the development of guidelines for *in utero* evaluation, it also represents an opportunity for early parental counseling.
Clinical Case: A 29 year old G2P1A1 female underwent a routine prenatal ultrasound that raised concern for campomelia and prompted genetic amniocentesis to evaluate for a SOX9 mutation. No mutation was detected but fetus was found to have a 46, XY karyotype which did not correlate with the female phenotype seen by fetal MRI. Upon delivery, a male karyotype was confirmed along with the appearance of external female genitalia (patent external vaginal opening, no clitoromegaly or palpable gonads in both labia majora). A subsequent pelvic ultrasound demonstrated undescended testes in the medial aspect of the inguinal canals bilaterally and a 2.7 x 1.6 x 1 cm utericle within the pelvis.
The combination of 46, XY, genital ambiguity, and absence of a uterus indicated an undervirilized male. Biochemical assessment was performed and both AMH (308 ng/mL, n 0-7.1) and testosterone (149 ng/dL, n 0.05-0.25) were elevated. Because AMH concentrations are known to be elevated in testosterone-insensitive or -deficient patients during the first year of life, the infant was then tested for an androgen receptor gene defect. A novel nonsense mutation (c.2004T>A; p.Y668X) was found and as such, it was predicted to be deleterious and established the diagnosis as complete androgen insensitivity syndrome. A female sex assignment was made.
In cases such as these, an androgen receptor defect could have been tested for at the time of the amniocentesis, and allowed for the diagnosis prenatally.
Conclusion: An anatomic diagnosis of non-specific sexual differentiation disorder can be made upon a prenatal detection of discordance between genotype and phenotype. Presently, there is a discontinuous and uncoordinated approach to the prenatal diagnosis. A multidisciplinary team of experts in DSD under the directions of an ethicist and in conjunction with obstetrical providers is needed to conduct a carefully planned prenatal evaluation and provide informed prenatal counseling.

Nothing to Disclose: MXE, MM, JED, NAS, LM, MEA, VRS, RYS, SLF, SKG, LPK

sort_order 2802
Pub # P3-733
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)
Title SRY- Negative XX Male and XX Ovo-Testicular DSD in a Set of Identical Adolescent Twins
Author String A Choudhary, S Nimkarn
Weill Cornell/New York Presbyterian, New York, NY
Body **BACKGROUND:** Two variations of testicular development, XX males and Ovo-Testicular Disorder of Sex Development (OT-DSD) were reported in a set of monozygotic diamniotic twins who are now in late adolescent years. Typically, XX males have normal male genitalia but small azoospermic testes, whereas OT-DSD individuals have genital ambiguity and various arrangement of ovarian and testicular tissue in their gonads.
CLINICAL CASE: Twin A was evaluated at 7 weeks of age for genital ambiguity and Twin B was evaluated at 16 years of age. The twins were monozygotic diamniotic born vaginally at 37 weeks. Twin A (weight 4 lb 1 oz, length 43 cm) was noted to have ambiguous genitalia at birth. Genitourinary examination showed slightly rugated labia and palpable gonads in the labio- scrotal folds. The phallus was 3.5 cm X 1.4 cm with severe chordee, anterior perineal hypospadias, bifid scrotum with urethral opening at the base of the phallus. Hormonal evaluation at birth showed elevated testosterone (T)(340ng/dl), exaggerated gonadotropin response to LHRH, normal cortisol, ACTH, electrolytes and PRA. A normal ACTH stimulation test excluded CAH. HCG stimulation test showed a normal male T response. Karyotype was XX and the SRY was negative. Pelvis US showed mullerian remnant and no uterus. Cystoscopy identified a urogenital sinus. At 2 months of age, the child underwent orchidectomy, vaginoplasty and clitoroplasty. Histologic examination of gonadal tissues were consistent with ovo-testes. A diagnosis of 46XX OT-DSD was made. The child was raised as a female and estrogen replacement was started at the age of 13. At 16 years, she had pubertal development of Tanner 3 breasts and pubic hair. Lab tests showed an elevated LH, FSH and normal T 18ng/dl. Twin B (Weight 5 lb 9 oz) had normal male genitalia at birth. He was evaluated for the first time at 16 years of age due to parental refusal prior to this time. On evaluation, he was Tanner 3 for pubic hair and had testes of 6 cc bilaterally with normal phallus. Hormonal evaluation showed a pubertal LH, elevated FSH , and androgens consistent with that of a Tanner 2 male. Karyotype was 46 XX with a negative SRY. The boy and his parents have refused further testing at this time.
CONCLUSIONS: We report a rare coexistence of XX male and OT DSD in a set of twins. This is another line of evidence to support that the two conditions are different manifestations of the same disorder of gonadal development.

Disclosures: SN: Speaker Bureau Member, Pfizer, Inc. Nothing to Disclose: AC

sort_order 2803
Pub # P3-734
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)
Title Anti-Müllerian Hormone Levels in a Large Cohort of Healthy Latin-American and Down Syndrome Males
Author String R Grinspon, P Bedecarras, Mdf Borges, L Bussmann, G Iniguez, A Rocha, E Mantovani Rodrigues Resende, V Figueroa Gacitua, A Forrester, C Milani, V Osta, MJ Rial, S Gottlieb, A Chiesa, A Keselman, A Arcari, H Cassinelli, M Gryngarten, P Papendieck, M Troiano, F Clement, M SoledadRodriguez Prieto, R Enacan, I Bergada, MG Ropelato, MG Ballerini, S Recabarren, T Sir-Petermann, E Codner, V Brito, B Mendonca, J-Y Picard, N Josso, V Garzino, R Rey
Hospital de Niños R Gutiérrez, Buenos Aires, Argentina; Universidade Federal do Tri[acirc]ngulo Mineiro, Uberaba, Brazil; Disciplina de Endocrinologia e Metabologia, São Paulo, Brazil; Universidad de Chile, Santiago, Chile; Hospital de Niños Pedro de Elizalde, Buenos Aires, Argentina; [ldquo]Dr Héctor A Milani[rldquo], Junin, Argentina; Hospital de Niños R Gutiérrez, Buenos Aires, Argentina; Hospital de Niños Pedro de Elizalde, Buenos Aires, Argentina; UMR-S782 Université Paris-Sud, Clamart, France; Immunotech SAS, Marseille, France; Universidad de Concepci[ocute]n, Chillán, Chile
Body **Background:** Anti-Müllerian Hormone (AMH), a direct marker of Sertoli cell function, has become a valuable tool to assess testicular tubular function. New ultrasensitive assays have been developed to measure serum AMH, yet reference values are available only for Northern European males. Males with Down syndrome (DS) present a primary hypogonadism but little is known about the chronology of Sertoli cell dysfunction.
Objective: To provide reference levels for AMH in normal Latin-American males and to evaluate Sertoli cell function in boys and adolescents with DS.
Methods: We measured serum AMH by an ultrasensitive assay (AMH/MIS EIA[reg], Immunotech, Beckman Coulter Co.) in 421 healthy Argentine, Brazilian and Chilean males aged 2 days to 52 yr, and AMH and gonadotropins (IFMA) in 101 patients with DS aged 2 months to 20 yr.
Results: In healthy males, median (3rd-97th percentiles) AMH values (pmol/l) were: birth-14 d: 596 (255-1038), 15 d-2.9 yr: 921 (436-2423), 3-8.9 yr: 597 (235-1489), > 9 yr Tanner I: 713 (257-1371), Tanner II: 295 (69-1017), Tanner III: 71 (30-423), Tanner IV: 65 (33-164), Tanner V: 82 (38-195), and > 18 yr: 56 (25-137).
In patients with DS, median (3rd-97th percentiles) AMH levels (pmol/l) were: 15 d-2.9 yr: 379 (68-906), 3-8.9 yr: 470 (163-897), > 9 yr Tanner I: 389 (228-932), Tanner II: 163 (31-464), Tanner III: 60 (29-100), Tanner IV: 26 (9-103), and Tanner V: 57 (6-64). AMH was below the 3rd percentile in 24.4% of the cases before puberty and in 38.5% during puberty. Mean AMH was significantly lower in patients with DS than in controls in all age groups except Tanner II (p<0.05, unpaired t test control vs. DS for each group). LH and FSH were above the normal range respectively in 17.9% and 37.3% of prepubertal patients and in 27% and 75.7% of pubertal ones. Cryptorchidism was present in 34% of patients with DS; when excluded from the analysis, the significant differences in serum AMH were still observed in all groups except prepubertal boys > 9 yr and Tanner II.
Conclusions and Discussion: We report reference AMH values for Latin American males. Serum AMH increases from birth to 3 yr, and decrease to a plateau until pubertal onset when they further decrease until adulthood, similarly to those reported for Northern Europeans. Patients with DS show a primary hypogonadism that involves both tubular and interstitial compartments. Sertoli cell dysfunction is usually present from early infancy, regardless of the existence of cryptorchidism.
Nothing to Disclose: RG, PB, MdfB, LB, GI, AR, EMRR, VFG, AF, CM, VO, MJR, SG, AC, AK, AA, HC, MG, PP, MT, FC, MSP, RE, IB, MGR, MGB, SR, TS-P, EC, VB, BM, J-YP, NJ

sort_order 2804
Pub # P3-735
Session Information POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)
Title Elevated Serum Anti-Müllerian Hormone Levels in Adolescent Girls with Polycystic Ovary Syndrome: Relationship to Ovarian Volume
Author String M Pawelczak, L Kenigsberg, Y-H Liu, S Milla, B Shah
New York University School of Medicine, New York, NY; New York University School of Medicine, New York, NY
Body
Background:
Serum anti-Müllerian hormone (AMH) levels are frequently elevated in patients with Polycystic Ovarian Syndrome (PCOS) due to increased production by granulosa cells in high numbers of preantral and antral follicles. Ovarian volume is often high in PCOS due to increased follicle number and elevated stromal mass. Little is known about the relationship between serum AMH and ovarian ultrasound (US) features in adolescents with PCOS.
Objectives:
To compare serum AMH levels in obese adolescent girls with PCOS and obese controls. To correlate serum AMH levels in the PCOS group with ovarian US features. To correlate serum AMH levels with body mass index (BMI) z-score, severity of hyperandrogenism, and degree of insulin resistance.
Methods:
We performed a cross-sectional retrospective analysis of clinical and biochemical findings in 23 obese adolescent females with PCOS (mean BMI z-score 2, mean age 15.2 yrs) and 12 obese age and sex matched controls (mean BMI z-score 2, mean age 14.1 years). All subjects were post-menarcheal. Serum AMH levels were assessed via ELISA and compared between groups. In the PCOS group, transabdominal ovarian US were reviewed for follicular distribution (peripheral, central, or mixed), number, and ovarian volume. AMH levels were correlated with ovarian US findings, BMI z-score, androgen levels, and fasting insulin levels.
Results:
Mean free testosterone was 9.76 ±5.13 pg/mL in the PCOS group versus 5 ±2.02 pg/mL in controls (p=0.0092). Both groups were comparable in fasting insulin and glucose. Serum AMH was 6.78 ±3.55 ng/mL in the PCOS group versus 3.38 ±1.48 ng/mL in controls (p=0.0004). AMH positively correlated with ovarian volume (left ovary p=0.0007, right ovary p=0.0065) and peripheral follicle distribution (p=0.0027). Ten or more follicles were observed in 83% of US. No significant correlation existed between AMH and BMI z-score, free testosterone, or fasting insulin.
Conclusions:
This study is the first to demonstrate a positive relationship between serum AMH levels and ovarian volume in adolescents with PCOS. Our findings support the use of serum AMH as a reflection of ovarian volume in cases where accurate ultrasounds are not available as well as for follow up. By potentially influencing ovarian volume, AMH may impact stromal mass which is mainly theca cell dependent. These results thereby lend support to the existence of AMH mediated crosstalk between granulosa and theca cells.

Sources of Research Support: In part by grant 1UL1RR029893 from the National Center for Research Resources, National Institutes of Health.

Nothing to Disclose: MP, LK, Y-HL, SM, BS

sort_order

2805

Pub #

P3-736

Session Information

POSTER SESSION: CLINICAL/TRANSLATIONAL - Pediatric Endocrinology: Puberty (1:30 PM-3:30 PM)

Title

Evaluation of Pro-Inflammatory Cytokines in Adolescents with Polycystic Ovary Syndrome

Author String

M Pawelczak, S Milla, Y-H Liu, B Shah
New York University School of Medicine, New York, NY; New York University School of Medicine, New York, NY

Body

Background:

Patients with Polycystic Ovarian Syndrome (PCOS) often suffer from co-morbidities associated with chronic inflammation characterized by elevations in pro-inflammatory cytokines. There is limited data on markers of chronic inflammation in adolescents with PCOS.

Objectives:

To compare serum levels of IL-1 α , IL-6, IL-18, and TNF- α in obese adolescents with PCOS and obese controls. In the PCOS group, to correlate cytokine levels with ovarian ultrasound (US) features. To correlate cytokine levels with body mass index (BMI) z-score, severity of hyperandrogenism, and degree of insulin resistance.

Methods:

We performed a cross-sectional retrospective analysis of clinical and biochemical findings in 23 obese adolescent females with PCOS (mean BMI z-score 2, mean age 15.2 yrs) and 12 obese age and sex matched controls (mean BMI z-score 2, mean age 14.1 years). All subjects were post-menarcheal. Serum IL-1 α , IL-6, IL-18, and TNF- α levels were compared between groups. In the PCOS group, cytokine levels were correlated with ovarian US features, BMI z-score, androgen levels, and fasting insulin and glucose levels.

Results:

Mean free testosterone was 9.76 ± 5.13 pg/mL in the PCOS group versus 5 ± 2.02 pg/mL in the control group ($p=0.0092$). Both groups were comparable in fasting glucose and insulin. TNF α was 7.4 ± 4 pg/mL in the PCOS group versus 4.8 ± 2.8 pg/mL in the control group ($p<0.05$). There was no significant correlation between TNF α and BMI z-score, free testosterone, fasting insulin, or fasting glucose. No correlation existed between TNF α and ovarian follicle number, distribution, or volume. In both groups, the majority of the results were below the lower limit of detectability of the assays for serum IL-1 α and IL-6. There was no significant difference in IL-18 between groups ($p=0.2$).

Conclusions:

Serum TNF α levels are elevated in adolescents with PCOS in patients as young as 12 years. Chronic TNF α elevation is known to contribute to increased acute phase protein release, subendocardial inflammation, atherosclerosis, and insulin resistance. Early identification and treatment of adolescents with PCOS is important to prevent future complications associated with a chronic pro-inflammatory state.

Sources of Research Support: Grant 1UL1RR029893 from the National Center for Research Resources, National Institutes of Health.

Nothing to Disclose: MP, SM, Y-HL, BS

sort_order 2806
Pub # P3-737
Session Information POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)
Title A Novel Mutation in the *KCNK11* Gene Leading to Congenital Hyperinsulinism
Author String P Iyer
University of South Florida/All Children's Hospital, St Petersburg, FL
Body
Introduction: Congenital hyperinsulinism (CHI) results from unregulated insulin secretion. Focal CHI is due to a germline mutation of the paternally inherited *ABCC8/KCNJ11* genes (encode the two subunits of the potassium ATP channel) along with somatic loss of the maternally derived allele in the developing pancreas. We describe the clinical, biochemical, genetic and pathologic data of an infant with a novel mutation in *KCNJ11*.
Clinical Case: A 4.5-month old boy presented with a generalized seizure and serum glucose of 32 mg/dL (<100). Historical data revealed that the infant had other seizure-like activity occurring upon awakening from naps that resolved with breast-feeding. Initial laboratory studies were TSH: 1.8 IU/L (0.8-8.2), Free T4: 1.4 ng/dL (0.89-1.76), cortisol 14 [micro]g/dL (5-20), serum glucose 53 (<100) uric acid 3.5 mg/dL (1.5-6.3), ammonia 25 mmol/L (<33). Insulin ranged from 2.3 to 2.8 mU/mL (0-13) while BG ranged from 31-42 mg/dL. Even with diazoxide therapy at 15 mg/kg for 7 days, the hypoglycemia did not resolve. Thus he was transferred to Children's Hospital of Philadelphia where ¹⁸F-Dopa-PET scan revealed a lesion in the body and tail of the pancreas. A laparotomy revealed a 10 mm lesion in the mid portion of the pancreas on the posterior side and thus a distal pancreatectomy (30%) was performed. Tissue histology revealed abnormal cells that were large and polygonal with eosinophilic cytoplasm and nucleomegaly with clear margins. A genetic analysis showed a mutation of C->T at nucleotide 212 of *KCNK11*, which resulted in a missense mutation of threonine to isoleucine at codon 71. The infant's father had the same mutation; however, the mother did not have any mutations in this gene.
Conclusion: Biochemical and pathologic data suggest that a mutation at nucleotide 212 of the *KCNK11* gene caused by a C->T change results in clinically significant CHI.
Nothing to Disclose: PI

sort_order 2807
Pub # P3-738
Session Information POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)
Title Recurrent Hyperinsulinemic Hypoglycemia after Successful Distal Pancreatectomy for Post Gastric Bypass Nesidioblastosis
Author String H Karanchi, OM Sabek, DW Fraga, M Ordonez, CP Fischer, AO Gaber, DJ Hamilton
The Methodist Hospital, Houston, TX; The Methodist Hospital, Houston, TX; University of South Alabama, Mobile, AL
Body
Introduction:
Noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS) is characterized by postprandial neuroglycopenia, negative prolonged fasts, negative perioperative localization studies for insulinoma, but positive selective arterial calcium stimulation tests and histologic nesidioblastosis in the gradient guided resected pancreas.
Clinical Case:
A 46 year old woman had recurrent episodes of confusion, nausea, fatigue and tremor 2-3 hours after meals with laboratory documented hypoglycemia (plasma glucose < 40 mg/dL). Ingestion of carbohydrates resulted in resolution of symptoms and return of plasma glucose to normal. She underwent Roux-en-Y gastric bypass surgery 31 months prior to onset of these symptoms. CT scan of the abdomen was unremarkable. Glucose ingestion precipitated symptomatic hyperinsulinemic hypoglycemia. Selective arterial calcium stimulation test resulted in a 3-fold increase in insulin in the distribution of the splenic artery (body and tail of pancreas). Nutritional therapy, acarbose and diazoxide failed to control the symptoms. Octreotide was poorly tolerated. A gradient guided laparoscopic distal pancreatectomy was performed. Pathologic examination confirmed the diagnosis of nesidioblastosis and absence of tumor. Islet yield/gram of tissue was 6743 (average in our islet laboratory. 3866). Insulin content per islet equivalent was 83 IU/islet (average. 11.5 IU± 10.6 IU/islet). The patient had complete resolution of all symptoms.
13 months later she presented with recurrent symptoms exactly like before. CT scan of the abdomen was again unremarkable. Glucose ingestion precipitated symptomatic hyperinsulinemic hypoglycemia. Selective arterial calcium stimulation test resulted in 2- and 6.5-fold increases in insulin in the distribution of superior mesenteric and the gastroduodenal artery, respectively. This indicated hyperfunctioning in the previously normal remnant pancreas. Nutritional therapy and acarbose before meals have initially controlled symptoms.
Conclusion:
Several cases of post-gastric bypass NIPHS have been reported but occurrence in the normal remnant pancreas after gradient guided pancreatectomy has not been reported. The mechanisms underlying the disorder remain poorly characterized with some studies referring to [Beta]-cell hyperfunction and others to ductal proliferation and islet neogenesis from undefined pancreatic humoral/paracrine factors both leading to inappropriately increased insulin secretion.
Nothing to Disclose: HK, OMS, DWF, MO, CPF, AOG, DJH

sort_order 2808
Pub # P3-739
Session Information POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)
Title Insulin Autoimmune Syndrome: Not the Usual Suspect for Hypoglycemia
Author String H Zamora, M Agarwal
University of Arkansas for Medical Sciences, Little Rock, AR; Central Arkansas Veterans Health Care System, Little Rock, AR
Body
Background: Insulin autoimmune syndrome (IAS) is a rare cause of hyperinsulinemic hypoglycemia characterized by elevated levels of insulin in the presence of high titers of insulin antibodies to endogenous insulin (1). Although it is a relatively common cause of spontaneous hypoglycemia in Japanese population, there are only a few cases reported in the United States. We report a case of IAS in a Caucasian man who did not achieve spontaneous remission and was treated with prednisone.
Case: A 72 year old white man presented with recurrent hypoglycemia and neuroglycopenic symptoms. He had no prior exposure to exogenous insulin or sulphydryl (SH) group containing medications and no personal or family history of autoimmune diseases. Physical examination was unremarkable. The urine sulfonyleurea screen was negative. Insulin level was 140 uIU/ml (3-19), C-peptide was 6.2 ng/ml (0.8-3.5) with glucose of 55 mg/dl (70-110). Insulin antibodies were greater than 50 U/ml (0-0.4). The cosyntropin test, thyroid function tests, ANA, RF, SPEP and UPEP and chromogranin A were normal. The 72 hour fast protocol was terminated after 26 hours, due to hypoglycemic symptoms with glucose of 47 mg/dl. Insulin level was 42 uIU/ml, C-peptide 5.4 ng/ml and pro-insulin 175.4 pmol/L at that time. The CT scan, MRI of the abdomen and Octreotide scan did not demonstrate any evidence of a malignancy. Continuous glucose monitoring system (CGMS) showed hypoglycemia during different times of the day with no perceivable relation to meals. The diagnosis of insulin autoimmune syndrome was established. Despite dietary interventions, patient continued to have hypoglycemia, persistently elevated insulin and insulin antibody levels. Patient was treated with prednisone with slow taper over eight weeks.
Conclusion: Insulin autoimmune syndrome should be in the differential diagnosis in patients with endogenous hyperinsulinemic hypoglycemia and measurement of insulin antibodies should be part of the evaluation (2). The putative mechanism is the change in the kinetics of the endogenous insulin due to binding with the antibodies. The concentration of insulin, proinsulin and C-peptide is spuriously elevated due to interference of the antibodies in the immunoassays (3). Due to its rarity, there is a paucity of clinical data as to effective management of this condition. Corticosteroids and plasmapheresis have shown benefit in the management of this syndrome.

1. Lupsa, B et al *Medicine* 2009; 88:141-153
2. Cryer, P et al *J Clin Endocrinol Metab*, 2009;94:709-728
3. Basu, A et al *Endocrine Practice* 2005; 11; 97-103

Nothing to Disclose: HZ, MA

sort_order 2809
Pub # P3-740
Session Information POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)
Title Non-Islet Cell Tumor-Induced Hypoglycemia, a Rare Occurrence
Author String SS Zaidi, VT Lakhani
Vanderbilt University Hospital, Nashville, TN
Body Hypoglycemia due to insulin producing tumor (insulinoma) is a rare condition and hypoglycemia due to non-islet cell tumors is even more uncommon. Non islet cell tumor induced hypoglycemia (NICTH) occurs in patients with solid tumors of mesenchymal (fibroma) and epithelial origin (lung, pancreas, stomach) but rarely can occur with tumors of hematopoietic and neuroendocrine origin. Hypoglycemia in NICTH is due to excessive production of IGF-II by the tumor. IGF-II is structurally related to insulin and has insulin like activity by binding to insulin and IGF-II receptor. Subsequently there is reduced gluconeogenesis by liver and accelerated glucose utilization by peripheral tissues causing hypoglycemia. NICTH is biochemically characterized by hypoglycemia, low insulin and C-peptide, low growth hormone, low IGF-I, low IGF binding protein, and increased or normal IGF-II. The pathognomonic feature of NICTH is an IGF-II:IGF-I ratio of 10 or more. Acute hypoglycemia is treated with intravenous glucose or glucagon. Steroids are used for long term control of hypoglycemia which suppresses IGF-II. Diazoxide, a thiazide diuretic is also used but the permanent treatment is surgical removal of tumor.
Here we describe an interesting case of NICTH. An 88 year old male with past history of laryngeal, bladder and testicular cancer, CAD, COPD, hepatitis C was admitted with respiratory failure. On admission patient was hypoglycemic with serum blood glucose of 30 mg/dl. He was started on 5% dextrose which was titrated to 30% at 150 ml/hr. Despite this high intravenous glucose infusion, the patient still had difficulty maintaining blood glucose in the normal range. Adrenal insufficiency and common medications causing hypoglycemia were ruled out. Laboratory tests showed abnormal liver function tests which were normal 6 months ago. CT of the abdomen and pelvis showed multiple hepatic nodules. With his hepatitis C and multiple hepatic nodules, AFP was tested which was 270.925 ng/ml (< 8). Further workup for his hypoglycemia showed C-peptide < 0.2 ng/ml (1.1-4.4), insulin < 0.3 uIU/mL (0-24.9). IGF-I was low < 25 ng/mL (55-166) and IGF-II was normal, 370 (288-736) with IGF-II:IGF-I ratio at 15 (normal <10) consistent with NICTH. Due to his age and co-morbid conditions, his family decided to withdraw care.
NICTH is an uncommon cause of hypoglycemia and should be considered after ruling out common causes of hypoglycemia, as it can be treatable depending on the extent of the disease.

Nothing to Disclose: SSZ, VTL

sort_order 2810
Pub # P3-741
Session Information POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)
Title Insulin Autoimmune Syndrome in a 16-Year-Old African-American Male
Author String MJ Gomez-Cruz, M Jabbar, N Saini, D Eng, B Crawford, D Vazquez, R Menon, C Ming
University of Michigan, Ann Arbor, MI; Hurley Medical Center, Flint, MI
Body Insulin Autoimmune syndrome (IAS) or Hirata's disease is a rare disorder characterized by hypoglycemia associated with serum insulin auto-antibodies (IAb). IAS has been associated with exposure to sulphhydryl group containing medications, e.g. methimazole (MTZ) and penicillamine, for treatment of other underlying autoimmune disease such as Graves' disease and rheumatoid arthritis. Over 200 cases have been reported in Japan and 58 cases have been reported outside the Orient. IAS is more common in patients older than 40 years of age. We describe a rare case of IAS in an African American adolescent.
A 16-year-old healthy African American male was diagnosed with Graves' disease and started on MTZ. Three months later he was found lethargic with a blood sugar of 27 mg/dl and he was given D50 bolus. After arriving in the ER he developed hypoglycemic seizure and was given another D50 bolus. Blood/CSF cultures and drug screen were negative. Abdominal ultrasound, abdominal CT scan and Octreotide Scan were negative. In order to maintain euglycemia he required IV infusion of D7.5%-D12% in addition to regular food intake. A fasting protocol was performed. He had a c-peptide level of 5.65 ng/ml and an insulin level of 177 mU/ml with a blood sugar of 48 ng/dl just 14 minutes into the fast. IAS was the provisional diagnosis and MTZ was eventually discontinued. IAb were significantly elevated (5.7, 5.3, 3.8; reference range 0.00-0.02 nmol/L). Patient underwent a 3-hour oral glucose tolerance test (blood sampled every 30 min). Total / Free insulin ratios were elevated at all time points 1726 [25], 2804 [70], 3248 [85], 3027 [67], 201 [51], 2065 [36], 2080 [31]; total [free] mU/ml.
The patient was managed with prednisone, diazoxide, and propranolol for management of IAS and hyperthyroidism. Prednisone is to provide 1) elevation of blood sugar via insulin resistance; 2) suppression of autoimmunity; and 3) inhibition of conversion of T4 to T3. He underwent thyroid radio-ablation therapy. Three months later, IAB levels decreased to 0.07 nmol/L. Medications are being gradually weaned and he has not had recurrent hypoglycemia.
IAS is a rare cause of hypoglycemia which has been described in the adult population. We describe a rare case of IAS in a 16 year-old adolescent after 3 months of exposure to MTZ. IAS should be considered in the differential diagnosis for hypoglycemia in pediatric patients who have had recent exposure to sulphhydryl group containing medications.

Lupsa BC et al., *Medicine* 2009; 88(3):141

Nothing to Disclose: MJG-C, MJ, NS, DE, BC, DV, RM, CM

sort_order 2811
Pub # P3-742
Session Information POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)
Title Continuous Glucose Monitoring (CGM): An Invaluable Monitoring Tool for Management of Hypoglycemia during Chemotherapy for Acute Lymphoblastic Leukemia (ALL)
Author String N Visavachaiyan, A Aledo, BH Franklin, PC Brar
New York University School of Medicine, New York, NY; Weill Cornell Medical College and The Komansky Center for Children's Health, New York, NY
Body **Background:** ALL maintenance therapy (MT) has been occasionally associated with symptomatic hypoglycemia (SH) [1], attributed to purine analogue (mercaptopurine; 6-MP).[2] 6-MP has been hypothesized to affect substrate utilization of gluconeogenic precursor alanine in the liver.[3] Even though thousands of children in the US are currently on 6-MP, the actual prevalence rate of 6-MP induced hypoglycemia has not been reported.
Case report: 5 year overweight (weight 67th percentile, BMI 90th percentile for his age) male with ALL was evaluated for SH (lethargy and vomiting) which occurred 8-10 hours after fasting while receiving daily 6-MP. Hypoglycemic episodes (capillary blood glucose levels (BGs) were 35-65mg/dL), >20 episodes/ month, occurred predominantly around mid morning, but not during the 5-day dexamethasone pulse. Cortrosyn test yielded a normal cortisol response (0 min: 13 and 60 min: 25.9[micro]g/dL) which ruled out pituitary adrenal suppression. A 12 hour overnight fasting glucose was 49 mg/dL, with suppressed insulin response < 2 [micro]IU/mL, low C-peptide of 0.5ng/mL (0.8-3.5ng/mL), high IGF BPI >160ng/mL (20-105ng/mL), high free fatty acid 2.64mmol/L (0.5-0.9mmol/L) and negative glucagon stimulation test ([Delta] BG <5mg/dL). These results ruled out hyperinsulinism and the diagnosis of ketotic hypoglycemia was made. The patient was placed on cornstarch therapy 5 hours prior to dose of 6-MP. This treatment reduced the SH events to <2 episodes/month. To study the efficacy of cornstarch, patient was placed on iPro professional CGM (Medtronic Diabetes) with a preset low alarm at 70mg/dL, was worn for a period of 5 days while patient was on cornstarch. With 1000 sensor readings the BG range was 65-158mg/dL. Mean absolute difference (MAD%) between sensor and finger stick BG readings (parent monitored patient's BG 4 times/day) was 9.4%. There was only one episode of asymptomatic hypoglycemia down to 65 mg/dl detected in the CGM.
Conclusion: CGM technology helped us devise an effective management plan for our patient. CGM proved useful as an adjunct to characterize the pattern of hypoglycemia and validate the benefit of cornstarch in hypoglycemia associated with 6MP treatment of ALL.
[1] Halonen P et al., J Pediatr 2001;138:428
[2] Ziino O et al., Med Pediatr Oncol 2002;39:32
[3] Halonen P et al., Acta Paediatr 2003;92:37
Sources of Research Support: iPro Professional CGM Medtronic Diabetes.
Nothing to Disclose: NV, AA, BHF, PCB

sort_order 2812
Pub # P3-743
Session Information POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)
Title Factitious Hyperglycemia and Subsequent Iatrogenic Hypoglycemia in a Hospitalized Peritoneal Dialysis Patient Managed with Icodextrin Dialysate
Author String E Rico, M Jakoby
Southern Illinois University School of Medicine, Springfield, IL
Body
Icodextrin is a starch-derived colloid osmotic agent used in some peritoneal dialysates. It is absorbed into the systemic circulation and hydrolyzed to maltose, a disaccharide that causes factitiously elevated capillary blood glucose (CBG) measurements by point-of-care (POC) meters utilizing glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) and glucose-dye-oxidoreductase (GDO) based reactions to detect glucose. Risk for hypoglycemia due to inappropriate administration of insulin is underappreciated in peritoneal dialysis (PD) patients using icodextrin dialysate due to lack of awareness. We report a recent case of icodextrin-related factitious hyperglycemia leading to iatrogenic hypoglycemia, brain injury, and death.
A 57-year-old end-stage renal disease patient managed by PD underwent mitral valve replacement and septal myectomy. Home PD regimen with 7.5 percent icodextrin dialysate was restarted after surgery. The patient had no history of diabetes mellitus, but post-operative CBG measured with GDH-PQQ based Roche glucometers were consistently in the range of 120-180 mg/dL. Supplemental regular insulin was administered per protocol for CBG values over 130 mg/dL. On post-operative day (POD) two, the patient exhibited altered mental status, and laboratory-measured blood glucose was 44 mg/dL. No treatment for hypoglycemia was initiated as POC CBG was 119 mg/dL. Multiple laboratory measured glucose values less than 50 mg/dL were recorded while POC CBG consistently exceeded 100 mg/dL. No treatment for hypoglycemia was provided until late on POD four when the patient became responsive only to painful stimuli. Endocrinology was consulted on POD five; insulin orders were discontinued and blood glucose monitoring was changed to central laboratory testing. MRI of the brain showed changes consistent with metabolic encephalopathy. The patient's family withdrew care on POD ten because she remained unresponsive.
Icodextrin-induced factitious hyperglycemia may lead to inappropriate management, including withholding treatment for true hypoglycemia. Health care providers outside nephrology and endocrinology may not be aware of this risk. Measuring CBG with glucose specific meters (e.g. glucose dehydrogenase flavin adenine nucleotide), recognizing central laboratory measured glucose values as gold standard, and clearly labeling patient charts are keys to avoiding management errors and patient harm.

Nothing to Disclose: ER, MJ

sort_order 2813
Pub # P3-744
Session Information POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)
Title Glucose Monitoring in the Hospital: Beware of Pseudohypoglycemia
Author String K Malhotra, SM Pinkstaff
Sinai Hospital, Baltimore, MD; Sinai Hospital, Baltimore, MD; Johns Hopkins University, Baltimore, MD
Body
INTRODUCTION:
Finger-stick glucose measurement(s) (FSGM) are routinely done in hospitalized patients using point-of-care bedside glucometers. Treatment protocols to correct hypoglycemia (<70 mg/dl) detected by FSGM are an important part of hospital policies. Depending upon the patient's level of consciousness, oral or intravenous glucose is used to correct hypoglycemia, with or without confirmation by laboratory plasma glucose measurement(s) (LPGM). Despite reliance on FSGM, it is underappreciated that readings can be falsely low in patients with digital hypoperfusion. In 2001, the FDA approved the use of alternate site testing (AST) for home glucose monitoring under stable conditions. Although not approved for inpatient use, AST in selected hospitalized patients may suggest a diagnosis of pseudohypoglycemia, thus avoiding unnecessary treatments.
CLINICAL CASE:
A 76 yo woman with ESRD on hemodialysis, without diabetes, was admitted for placement of an arteriovenous graft. Postoperatively, she developed hypotension (BP 68/39 mmHg), and multiple FSGM ranged between 14-64 mg/dl. As per the hypoglycemia protocol, she received 3 ampules of D50 and 950 ml of D5NS. The patient remained awake and alert without any symptoms of hypoglycemia, while she was NPO in the immediate postoperative period. A LPGM equalled 119 mg/dl when the FSGM was 14 mg/dl, suggesting pseudohypoglycemia. Because of recurrent low FSGM, endocrinology was consulted. A detailed assessment confirmed that the patient was asymptomatic and did not fulfill Whipple's triad. BP was 90/37 mmHg, and her fingers were dusky, suggesting digital hypoperfusion. To confirm the clinical impression of pseudohypoglycemia, AST at the inner forearm was ordered. The initial forearm reading was 128 mg/dl when the FSGM was 20 mg/dl. All subsequent glucose monitoring was ordered to be done on the forearm, in the fasting and pre-meal periods. Over the next 48 hours, forearm glucose readings were normal (86-180 mg/dl) and confirmed by daily LPGM.
CONCLUSIONS:
1) Although FSGM are routinely used in the inpatient setting, values may be artifactually low in the presence of digital hypoperfusion.
2) Patients with recurrent low FSGM must be assessed clinically to identify possible pseudohypoglycemia.
3) AST in place of FSGM may be appropriate for selected hospitalized patients in the fasting and pre-meal periods, when accuracy has been validated by LPGM and may avoid unnecessary treatments for pseudohypoglycemia.

1) El Khoury M et al., Pseudohypoglycemia: a cause for unreliable finger-stick glucose measurements. Endocrine Prac. 2008 Apr; 14(3):337-9
2)
<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ClinicalChemistryandClinicalToxicologyDevicesPanel/ucm124658.htm>

Nothing to Disclose: KM, SMP

sort_order 2814
Pub # P3-745
Session Information POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)
Title Insulin Allergy in a Patient with Celiac Disease
Author String N Ungnapatanin, SR Ahmad, CA Koch
University of Mississippi, Jackson, MS
Body Background: Insulin allergy is a rare condition with only a few cases reported. Hypersensitivity reactions to insulin itself and other ingredients in insulin solutions including protamine sulfate and zinc have been identified¹. An allergic reaction to insulin can lead to local symptoms or a generalized reaction ranging from simple urticaria to anaphylaxis². Patients with autoimmune conditions, such as celiac disease (CD), have an increased risk of allergy problems due to an imbalance of their immune system (TH1 and TH2). To our knowledge, an allergic reaction to insulin in a patient with CD has not been reported.
Clinical case: A 43-year woman presented with a generalized urticarial rash secondary to insulin injection. Past medical history included CD (positive anti-tissue transglutaminase antibodies), Hashimoto thyroiditis, and latent autoimmune diabetes in the adult (LADA), suggestive of a form of polyglandular syndrome. The patient had the same generalized pruritic urticaria rash with various types of insulin, including NPH, Glargine, Detemir, Novolog 70/30, Regular, Aspart, and Lispro. She denied a h/o ketoacidosis, took Novolog 70/30 20 u in AM and 10 u in PM and metformin 1 gm bid before being evaluated by us. Her weight was 154 lbs, height 5'4, body mass index 26. Hydroxyzine 25 mg partially relieved her allergic symptoms. Serologic workup was performed: positive anti-thyroglobulin Ab (34.0 IU/mL, nl: 0-4 IU/mL), positive anti-TPO Ab (21 IU/mL, nl: 0-9 IU/mL), positive GAD-65 autoantibody (48.5 U/mL, nl: 0-1.5 U/mL). Elevated total IgE (154 IU/mL, nl: 0-100 IU/mL) while on antihistamine medication. She is currently undergoing evaluation by an allergist for possible insulin desensitization.
Conclusion: CD can be associated with other autoimmune disorders including type 1 DM and autoimmune thyroiditis. Due to a dysregulated immune system in patients with CD or other autoimmune disorders, selected patients may be predisposed to an increased risk for insulin hypersensitivity. We suggest being aware of this potential [ldquo]complication[rldquo] (insulin allergy) in patients with CD, especially when combined with other autoimmune disorders and elevated IgE levels.

(1) Matheu V, et al.: Insulin allergy and resistance successfully treated by desensitisation with aspart insulin. Clin Mol Allergy 2005 , 3:16
(2) Akinci B, Yener S, Bayraktar F, Yesil S (2010) Allergic reactions to human insulin: a review of current knowledge and treatment options. Endocr 37:33-39

Nothing to Disclose: NU, SRA, CAK

sort_order

2815

Pub #

P3-746

Session Information

POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)

Title

Type 1 Diabetes Mellitus, Celiac Disease and NASH-Related Cirrhosis in a 3-Year-Old Boy with Acquired Generalized Lipodystrophy

Author String

M Grover, AE Balazs, CA Bacino, CP Schaaf, SJ Karpen, L Karaviti
Baylor College of Medicine, Houston, TX; Baylor College of Medicine, Houston, TX; Baylor College of Medicine, Houston, TX

Body

Background: Generalized lipodystrophy is a rare condition characterized by widespread loss of adipose tissue in association with extreme insulin resistance, diabetes mellitus (DM), dyslipidemia and non-alcoholic steatohepatitis (NASH). It may be acquired (AGL) or congenital (CGL) in presentation. We present a 3 year old boy with AGL, type 1 DM, celiac disease and NASH-related cirrhosis.
Clinical Case: At age 1 year, the patient developed acute febrile illness, painful facial swelling, profound diarrhea and significant weight loss. He was diagnosed with celiac disease based on intestinal biopsy and started on gluten free diet with marked clinical improvement. However, he experienced progressive loss of subcutaneous fat and developed facial nodules that on biopsy showed lipogranulomas. Subsequently, he presented with hyperglycemia and ketosis. Diagnosis of type 1 diabetes mellitus was based on presence of islet cell antibodies (GAD antibody >30 U/ml, ICA antibody 11.6 U/ml, Insulin Antibody 29.2 U/ml) and metabolic profile (undetectable C peptide, absence of acanthosis nigricans). He was > 95th%ile in height, had no detectable fat stores, severe insulin resistance (insulin requirement of > 8 units/kg/day), hypertriglyceridemia (TG>500mg/dl), marked hepatomegaly and elevated transaminases (ALT>1500 U/L). In addition, he had normal leptin and low adiponectin levels. Given the constellation of lipodystrophy, hepatomegaly, hypertriglyceridemia and insulin resistance, he was diagnosed with generalized lipodystrophy. As he met diagnostic criteria for Berardinelli-Seip syndrome, he underwent genetic testing of AGPAT2 and BSCL2 genes, both of which were negative. Liver biopsy revealed extensive fibrosis, fat deposition and micronodular cirrhosis, initiating a referral for liver transplantation.
Conclusion: Although there isn't a clear autoimmune profile for acquired lipodystrophy, the fact that it is diagnosed in the context of type 1 diabetes and celiac disease supports the idea of a potential associated autoimmunity. NASH has been described in patients with lipodystrophy but the rapid development of cirrhosis in this patient is unusual. To our knowledge, this is the first reported case of NASH-related cirrhosis in a 3-year old associated with AGL. Improvements in insulin resistance, hypertriglyceridemia and NASH have been reported with available therapy for lipodystrophy but whether cirrhosis is reversible remains to be studied.

Nothing to Disclose: MG, AEB, CAB, CPS, SJK, LK

sort_order 2816
Pub # P3-747
Session Information POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)
Title PCOS Causing Increased Virilization in Pregnancy
Author String S Kwun, S Mitta, G Gopalakrishnan
Alpert Medical School of Brown University, Providence, RI
Body **Introduction:** Virilization of PCOS patients during pregnancy happens infrequently and is rarely reported in the literature. The androgen status in PCOS is thought to be elevated secondary to decreased SHBG and elevated androgen production by theca cells. Pregnancy is known to increase adrenal androgen production. We report a case of virilization noted in a pregnant women with PCOS
Clinical Case: A 42 year old female presented at 9 weeks of gestation for worsening of facial hair, frontal hair loss and clitoromegaly. Past medical history was significant for Diabetes, PCOS and Hirsutism. A hormone profile at 10 weeks gestation was notable for a DHEA-S of 46 mcg/dL (nl 35-430mcg/dL), free testosterone level of 7.6 ng/dL (nl 0.3-1.9 ng/dL), total testosterone of 281 ng/dL (nl 8-60 ng/dL) and 17-hydroxyprogesterone of 399 ng/dL (normal < 285 ng/dL). Ultrasonography revealed no evidence of ovarian masses. CT scan of her adrenals prior to the pregnancy was negative for adrenal pathology. She was monitored clinically for the duration of her pregnancy. She delivered a healthy baby girl at 37.5 weeks gestation. Maternal androgen concentrations returned rapidly to normal. Normal DHEA-S 21 mcg/dL (nl 35-430mcg/dL), free testosterone 0.2ng/dL (nl 0.3-1.9 ng/dL), total testosterone 9.7ng/dL (nl 8-60 ng/dL) and 17-hydroxyprogesterone < 40ng/dL (normal < 285 ng/dL) was noted within 4 weeks postpartum. Improvements in hair symptoms was also reported by the patient.
Conclusion: Although virilization should prompt evaluations for adrenal and ovarian tumors, it is important to keep in mind that a normal pregnancy state can lead to virilization in patients with existing PCOS.
Nothing to Disclose: SK, SM, GG

sort_order 2817
Pub # P3-748
Session Information POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)
Title Acromegaloïd Facial Appearance with Hypertrichosis: Report of a New Case and Review of the Literature
Author String A Ghazi, S Khosla, E Nylen, K Becker
Veterans Affairs Medical Center and George Washington University, Washington, DC; Veterans Affairs Medical Center, Washington, DC
Body
Introduction:
Pseudoacromegaly is caused by many congenital and acquired conditions. One such condition is Acromegaloïd Facial Appearance (AFA) syndrome. We present a new case of AFA with hypertrichosis and review the literature regarding this condition.
Case:
57 years old female was evaluated by endocrinology for possible acromegaly. She reports having a peculiar appearance since birth. Examination reveals an intelligent woman of stated age, short stature with a broad bulbous nose, coarse facies with thick facial skin, blepharophimosis, high arched eyebrows, thickened lower lip and increased folds of the palate oral mucosa. She has increased hair growth on upper lip, chin (plucked) and coarse terminal hair of arms and legs (Ferriman Gallwey Score > 12). She had a Tanner 5 development without virilization. She does not have macrocephaly, macroglossia, change in the size of her shoes, gloves or rings, or clubbing of the fingers. Family history: She resembles her son, paternal grandfather and her father's paternal aunt. Her ancestry is Irish, German, and Native American Indian. Laboratory data showed a testosterone level of 11 ng/dl (18-69 ng/dl), Insulin like Growth Factor-1 level (IGF-1) of 98 ng/ml (92-190 ng/ml), negative Growth Hormone (GH) suppression test after a 75grams oral glucose challenge with GH levels of 0.4 ng/ml (<10 ng/ml), 0.1 ng/ml and 0.2 ng/ml at baseline, 60 minutes and 120 minutes respectively. She doesn't have diabetes. High resolution chromosomal analysis showed no abnormalities.
Discussion:
The AFA syndrome, as first described by Hughes, is a condition with characteristic features of thick lips, prominent rugae and frenula inside the mouth, blepharophimosis, high arched eyebrows, bulbous nose, large hands and feet. Our case resembles some previously reported cases on AFA and is only the second case in which chromosomal analysis was performed. Stratakis reported a case/family with a chromosomal anomaly⁵. After literature review, we found 8 other cases/ families described with AFA or its variant AFA with hypertrichosis. These cases and/or families have a variable spectrum of physical findings, variable mode of inheritance (autosomal dominant, autosomal dominant with incomplete penetrance and autosomal recessive) and normal GH and IGF-1 levels¹⁻⁸. More families need to be evaluated for a better understanding of AFA's clinical spectrum, clinical implications and mode of inheritance.
(1) Hughes HE, McAlpine PJ, Cox DW, Philipps S. (1985). An autosomal dominant syndrome with 'acromegaloïd' features and thickened oral mucosa. *J Med Genet* 22:119-125.
(2) Dallapiccola B, Zelante L, Accadia L, Mingarelli R (1992). Acromegaloïd facial appearance (AFA) syndrome: report of a second family. *J Med Genet* 29:419-422.
(3) Irvine AD, Dolan OM, Hadden DR, Stewart FJ, Bingham EA, Nevin NC (1996). An autosomal dominant syndrome of acromegaloïd facial appearance and generalised hypertrichosis terminalis. *J Med Genet* 33:972-974.
(4) da-Silva EO, Duarte AR, Andrade EJ, Furtado GJ (1998). A new case of the acromegaloïd facial appearance syndrome? *Clin Dysmorphol* 7:75-76.
(5) Constantine A Stratakis, Maria L Turner, Antony LaVerdy, Jorge R Toro, Suvimol Hill, Jeanne M Meek, Jan Blancato (2001). A syndrome of overgrowth and acromegaloïdism with normal growth hormone secretion is associated with chromosome 11 pericentric inversion. *J Med Genet* 38:338.
(6) Zelante L, Gasparini P, Savoia A, Lomuto M, Pellicano R (2000). A new case of acromegaloïd facial appearance (AFA) syndrome with an expanded phenotype. *Clin Dysmorphol* 9:221-222.
(7) Paulo R.G. Zen, Ida V.D. Schwartz and Giorgio A. Paskulin (2004). Acromegaloïd facial appearance and hypertrichosis: a case suggesting autosomal recessive inheritance. *Clinical Dysmorphology* 13:49-50.
(8) Usha Kini and Jill Clayton-Smith (2004). Acromegaloïd facial appearance syndrome: a further case report. *Clinical Dysmorphology* 13:251-253.
Nothing to Disclose: AG, SK, EN, KB

sort_order 2818
Pub # P3-749
Session Information POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)
Title Diagnosis and Management of Pseudopheochromocytoma
Author String A Carhill, S Mediwala
Baylor College of Medicine, Houston, TX
Body
Introduction: The presence of severe paroxysmal hypertension should always generate suspicion of a catecholamine-secreting pheochromocytoma¹ but this tumor is uncommon; in most patients the cause is rarely established. This constellation is referred to as [ldquo]pseudopheochromocytoma[rdquo]³. We present a case of pseudopheochromocytoma and review current treatment recommendations.
Case Presentation: A 67-year-old male with a history of hypertension presented to the emergency room with his sixth episode of hypertensive emergency in the past six months. Episodes are characterized by systolic blood pressures greater than 210 and diastolic blood pressures over 110, tachycardia, flash pulmonary edema and acute renal insufficiency. Patient has a history of anxiety disorder, and reports he was reflecting on stressful life events, then began experiencing headache and tachycardia. During prior hospitalization, total plasma metanephrines were elevated at 718pg/mL (0-250) with normetanephrine of 565pg/mL(0-148) and metanephrines of 153 pg/mL(<25). 24-hour urine metanephrines were also elevated at 616ug/24 hr(35-460) and urine normetanephrines of 1851 ug/24 hr(110-1050). Repeat non-acute setting testing showed normal urine metanephrines and plasma normetanephrines were 195pg/mL.; adrenal CT showed normal adrenal glands. At discharge the patient was given a diagnosis of pseudopheochromocytoma, though labile hypertension could not be excluded. Therapy with phenoxybenzamine 20mg twice daily, labetalol 1200mg twice daily and hydroxyzine 50mg PRN with venlafaxine 150mg daily were initiated.
Discussion: Pseudopheochromocytoma is thought to involve the sympathetic system as evidenced by its paroxysmal nature, tachycardia, increased catecholamines and increased baseline plasma metanephrines. Diagnosis should be considered when the hypertensive episodes contain: abrupt elevations in blood pressure, acute onset of physical symptoms (headache, chest pain, shortness of breath), and the attacks are not triggered by fear or panic. The underlying mechanism of sympathetic activation is unclear, but appears to involve emotional factors. Generally patients deny the episodes are related to emotional distress but the largest study to date 14/21 patients acknowledged a history of emotional trauma². Management focuses on adrenergic blockade and psychopharmacologic agents.
Relevant Points: review of clinical features of pseudopheochromocytoma and long term management.
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Nothing to Disclose: AC, SM

sort_order 2819
Pub # P3-750
Session Information POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)
Title Retrocardiac Catecholamine-Producing Paraganglioma: A Diagnostic and Therapeutic Challenge
Author String RM Paragliola, P Locantore, F Gallo, A De Rosa, V Di Donna, L Castellino, A Pontecorvi, F Musumeci, SM Corsello
Catholic University School of Medicine, Rome, Italy; San Camillo - Forlanini Hospital, Rome, Italy
Body Extra-adrenal pheochromocytomas (Pheos), termed paragangliomas (PGs), arise from neuroectodermal tissue and account for about 20% of catecholamine-producing tumors. PGs are located mainly in the abdomen, less commonly in the pelvic sympathetic plexus near the urinary bladder, while only a few cases of mediastinal PGs have been described. Like Pheos these lesions are best treated by surgery. We report the case of a 41 year-old woman who came to our attention because of hypertensive crises associated with headache, sweating and tachycardia. Routine blood exams were normal and ECG showed supraventricular tachycardia (100 bpm). Pheo was suspected on the basis of elevated urinary normetanephrines (3418 mcg/day) and norepinephrines (828.5 mcg/day). MRI showed normal adrenal glands while ¹²³I-MIBG scan revealed a single focal uptake in the mediastinum. CT showed a subcarinal retrocardiac 46 mm mass characterized by inhomogeneous enhancement with hypodense areas, close to left superior pulmonary vein and causing compression to left atrium. The lesion was suspected for retrocardiac paraganglioma and the diagnosis was confirmed by cardiac MRI and by transesophageal echocardiography. Coronary angiography showed a retropericardial lesion with a profuse vascularisation directly arising from the coronary circle. The patient was treated with doxazosine in the aim to control hypertension and to avoid arrhythmia. Cardiac surgery was performed in extracorporeal circulation and an hypertensive crisis occurring during manipulation was treated with i.v. phentolamine. Histology confirmed a paraganglioma (chromogranin A and synaptophysin positive at immunohistochemistry). After surgery, the patient was treated with copious hydration aimed to expand plasma volume and to avoid hypotension: BP was maintained on normal-low values and no hypertensive crises were documented. 3 months after surgery clinical and biochemical evaluation confirmed the remission of the disease: 24-hrs urinary catecholamines and metanephrines were normal and BP was normalized. This case represents a very unusual retropericardial localization of paraganglioma. While the diagnosis of a catecholamine-producing tumor was not difficult on the basis of clinical and biochemical evaluation, the localization required the integration of several imaging techniques. Skilled cardiac surgery and an expert team of endocrinologists and anaesthesiologist are required in the management of such unique cases.

Nothing to Disclose: RMP, PL, FG, ADR, VDD, LC, AP, FM, SMC

sort_order 2820
Pub # P3-751
Session Information POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)
Title Recurrent Hyponatremia Due to Reset Osmostat after Resection of an ADH-Secreting Olfactory Neuroblastoma
Author String KM Perry, A Heyliger, PS Batra, J Truelson, S Milchgrub, R Saxena, AY Chang
UT Southwestern Medical Center, Dallas, TX; UT Southwestern Medical Center, Dallas, TX; UT Southwestern Medical Center, Dallas, TX; UT Southwestern Medical Center, Dallas, TX; UT Southwestern Medical Center, Dallas, TX
Body
Background: Olfactory neuroblastoma (ONB) is a rare neuroectodermal tumor associated with syndrome of inappropriate anti-diuretic hormone (SIADH) secondary to ectopic ADH secretion. Recurrent hyponatremia and SIADH after ONB resection have been proposed as potential markers for persistent disease or tumor recurrence. There is little data about normalization of serum sodium (Na) after resection of an ADH-secreting tumor. In particular, chronic hyponatremia may lead to a reset osmostat, suppression of ADH secretion only at a lower than normal serum Na or osmolar threshold. We evaluated a case of recurrent hyponatremia after ONB resection with the water load test.
Clinical Case: A 56 year old female with a longstanding history of SIADH was evaluated for nasal congestion, right sided headache and lower temporal quadrants. MRI revealed an enhancing mass in the right sphenoid sinus. Before tumor resection, the patient's preoperative Na was 126 mmol/L with an elevated ADH of 7.2 pg/mL. Within 12 hours post-operatively, serum Na rose to 139 and remained 137-139 with an ADH of 0.6. Pathology confirmed grade I-II ONB with immunohistochemical staining positive for ADH. Two months later in the setting of chemotherapy and intravenous fluid, the patient developed asymptomatic hyponatremia with a Na of 125. With fluid restriction, Na rose to 128. ADH was undetectable when Na was less than 125 but detectable at 0.7 with a Na of 128. With this recurrent hyponatremia and sinus mucosal thickening seen on follow-up CT scan, the patient was admitted for a water load test prior to endoscopic biopsies to differentiate reset osmota from unregulated ADH secretion. During the water load, 0.9L of water (15 ml/kg) was given orally over 20 minutes. Serum Na and urine osmolality (UOsm) were checked at baseline and every 30 minutes after completion of the water load. Baseline serum Na was 133 mmol/L, UOsm 405 mOsm/kg and ADH 0.5 pg/mL. One hour after the water load, ADH became undetectable with a Na of 126 with UOsm 344, and Na was stable at 128-129 by the end of the test. Results were consistent with a reset osmostat at a Na of 128. Directed sphenoid biopsies demonstrated fibrosis without evidence of ONB.
Conclusion: This is the first report of reset osmostat after resection of an ADH-secreting ONB. The water load test can differentiate reset osmostat from residual/recurrent tumor in the evaluation of recurrent hyponatremia after resection of an ADH-secreting tumor.
Nothing to Disclose: KMP, AH, PSB, JT, SM, RS, AYC

sort_order 2821
Pub # P3-752
Session Information POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)
Title Porphyria, a Rare Cause of SIADH
Author String A Srinath, V Winstanley, A Lulsegg
Princess Royal University Hospital, Orpington, UK
Body
Background: The syndrome of inappropriate ADH (SIADH) is common cause of hyponatraemia due to excess secretion of vasopressin. We present a rare case of SIADH due to acute intermittent porphyria.
Clinical case: A 22 year old female presented with a one week history of generalized symptoms including low back pain, abdominal pain, vomiting and confusion. On examination she was tachycardic but normotensive and afebrile. She was euvolemic and systemic examination was unremarkable. Shortly after her arrival to hospital however she had a generalised seizure. Biochemistry revealed marked hyponatraemia, sodium 103mmol/L (136-145) but otherwise normal renal function & no evidence of acidosis. She also had a raised Creatinine kinase level at 1243u/l (26-140) and deranged thyroid function, FT4 32.4pmol/l (9.4-22.7), FT3 4.6 pmol/l (3.5-6.5) & TSH 1.4mu/l (0.35-5.50). Urinary sodium was elevated at 64mmol/l (<40), and paired serum and urine osmolality revealed low serum osmolality 218mosmol/kg (275-295) & relatively high urinary osmolality 292mosmol/kg (<100). Random cortisol showed normal stress response at 836nmol/l.
A diagnosis of SIADH was made. She was commenced on hypertonic saline 3% with target sodium correction of 0.5mmol/hr. She had one further seizure during treatment. MRI brain was unremarkable. Once her sodium levels reached 120mmol she was fluid restricted and her sodium levels gradually returned to normal. Medication with Demeclocycline or Vaptans was not required. Her thyroid function normalised with treatment of SIADH representing a sick euthyroid state. She recovered completely and was discharged from hospital. During her admission collateral information revealed a family history of Porphyria in her paternal grandfather, uncle & aunt. Porphyria screen was requested and revealed elevated Amino laevulinic acid, porphobilinogen & urinary total porphyrins. She was referred to tertiary metabolic clinic where a diagnosis of Acute Intermittent Porphyria was made.
Learning points: 1. Porphyria is a rare autosomal dominant disorder that should be considered in patients presenting with atypical medical, psychiatric, or surgical history. Acute attacks are associated with a substantial morbidity and mortality.
2. In this case the patient presented with hyponatraemia. This occurs in approximately 20% of symptomatic AIP and is often due to inappropriate ADH secretion. The association between AIP and SIADH is not clearly established.

Nothing to Disclose: AS, VW, AL

sort_order 2822
Pub # P3-753
Session Information POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)
Title Diabetes Insipidus in a Child after Third Ventriculostomy: A Triphasic Response
Author String KS Tafuri, TA Wilson, A Lane, N Skaria
Stony Brook Children's Hospital, Stony Brook, NY
Body
Background: Endocrinological complications of endoscopic third ventriculostomy (ETV) in children are rare. Diabetes insipidus (DI) accounts for only 0.5% of complications from ETV. To our knowledge, 3 cases of permanent DI have been reported, none with a triphasic response. We present a 6 year old female with DI and the classic triphasic response after ETV.
Clinical Case: A 6 year old girl with cerebellitis and obstructive hydrocephalus underwent emergent ETV with external ventricular drain placement. Shortly after surgery she developed significant polyuria and polydipsia. By post-op day 1 her urine output was 9.8cc/kg/hr with a 389 ml negative balance. Initial tests showed Na 148 mEq (135-145), serum osmolality 298 (280-295 mOsm/kg), urine osmolality 95 (500-800 mOsm/kg) and a vasopressin level <0.5 (0-4.7pg/ml). DDAVP was administered with improvement in urine output to 3.1cc/kg/h. Post-op CT scan revealed the catheter tip in the floor of the third ventricle. The catheter tip was retracted but DDAVP requirement persisted until late postop day 2. The last dose of DDAVP was administered in the evening of post-op day 2. Repeat testing on post-op day 3 showed Na 141 with improvement of urine output to 1.9cc/kg/h without DDAVP. Testing of anterior pituitary function was normal. By post-op day 6, the urine output remained stable with improvement of urine osmolality to 622. Eventually the hydrocephalus improved. The ventricular drain was removed and the child was discharged home without DDAVP. No etiology for the cerebellitis was identified. On post-op day 10 the child re-presented to the ED with symptoms of polyuria and polydipsia. Laboratory evaluation showed Na 144, serum osmolality 302 urine osmolality 72, and a vasopressin <0.5. She was restarted on DDAVP for recurrence of DI and remains clinically stable.
Conclusions: Diabetes insipidus after endoscopic third ventriculostomy in children is rare but can occur. The anatomical location of the hypothalamus during perforation of the ventricular floor makes the hypothalamus particularly vulnerable to injury. In the few cases of DI reported, most are transient. To our knowledge we present the only case of a child with permanent DI demonstrating the classic triphasic response. We present this case to emphasize the importance of considering endocrinological complications after ventriculostomy.
Nothing to Disclose: KST, TAW, AL, NS

sort_order 2823
Pub # P3-754
Session Information POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)
Title 19-Year-Old Female with Hypodipsia-Hypermnatremia-Syndrome Due to Alobar Holoprosencephaly
Author String C Domm, P-M Holterhus, H Moenig
Medizin; Universit[au]tsklinikum Schleswig-Holstein, Campus Kiel, Kiel, Germany; Allgemeine P[au]diatrie, Universit[au]tsklinikum Schleswig-Holstein, Campus Kiel, Kiel, Germany
Body
Background: Hypodipsia is characterized by reduced thirst even in the face of dehydration and/or salt-excess.
Alobar holoprosencephaly is a cephalic disorder which is characterized by a malformation of the prosencephalon, which fails to divide into two hemispheres during embryonal development.
Clinical case: We report the case of a 19-year old female patient which was referred to our clinic due to progressive confusion. According to the mother the patient had a low daily fluid intake since birth. At age 2[frac12] she was diagnosed with autism due to behavioral anomalies.
Laboratory results showed a hypernatremia of 179 mmol/l (normal range: 136-145 mmol/l). Physical examination revealed dehydration with dry mucous membranes and a prolonged reaction time. An MRI of the brain showed a mild alobar holoprosencephaly.
The patient was treated with isotonic chloride solution for adequate volume expansion, followed by 5 % dextrose infusion. Serum sodium levels were frequently reassessed and hyponatremia was normalized over a 4-day period.
Diabetes insipidus was ruled out using a water deprivation test. However, vasopressin secretion was found to be slightly delayed and blunted. Quantitative measurement of serum ADH-levels during the water deprivation test showed low concentrations within the standard value range.
So far, no new episodes of hypernatremia have occurred. The patient and her family were advised to strictly ensure frequent and scheduled fluid intake.
Conclusion: Control of fluid intake, hydration status and animation to drink fluids is essential for the health of this patient. There is no indication for a therapy using medication.

Nothing to Disclose: CD, P-MH, HM

sort_order 2824
Pub # P3-755
Session Information POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)
Title Endocrinopathy in POEMS Syndrome: Adrenal Insufficiency, Hypogonadism and Hypothyroidism of Autoimmune Etiology
Author String AV Marino, LR Reynolds
University of Kentucky, Lexington, KY
Body Introduction: POEMS is a rare multisystem syndrome, characterized by polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes. POEMS syndrome is more prevalent in Japanese and White males with a median age of 51 years at presentation.
Clinical case: We report a case of a 49-year-old African American male, who presented with the acute onset of bilateral upper and lower extremity weakness. He was found to have a progressive peripheral neuropathy. Further work-up revealed an iliac bone lesion, suggestive of plasma cell dyscrasia on biopsy and pathologic evaluation, monoclonal gammopathy, splenomegaly and skin hyperpigmentation.
Endocrine evaluation revealed a history of primary hypothyroidism and secondary hypogonadism. During the current hospitalization he was found to have primary adrenal insufficiency with a subnormal response to cosyntropin and elevated ACTH of 177 pg/mL (7-69). Patient had positive antithyroid peroxidase antibodies with titer of 50 IU/ml (0-9). Vascular endothelial growth factor (VEGF) level was elevated at 992 pg/mL (9-86).
Conclusion: 2 Major and 1 minor criteria are required for diagnosis of POEMS. Major criteria include polyneuropathy and monoclonal plasma proliferative disorder. Minor criteria include sclerotic bone lesions, Castleman disease, organomegaly, edema, endocrinopathy and skin changes. Only a few reported cases and 2 large studies describe [rdquo]portion of the syndrome (1-3) The prevalence of endocrinopathy is 84%, with hypogonadism being the most common feature, followed by hypothyroidism, glucose intolerance and hyperprolactinemia.(1) Elevation of VEGF is believed to play a main pathogenic role in this disease.(4)
Our patient had all 5 classical features of POEMS syndrome with multiple endocrinopathies. The demographic characteristics and possible autoimmune etiology of the endocrine disorders makes it a unique case. Review of the literature reveals only one other reported case of an African American patient having this condition.(1) Adrenal insufficiency was described in a single case report.(5) A Mayo clinic review described abnormal ACTH stimulation response and elevated ACTH in some patients. Additionally, circulating autoantibodies against the endocrine system are not reported in the literature, and our patient has elevated antithyroid peroxidase antibodies level.
To our knowledge, this is the first published case that supports an autoimmune hypothesis in etiology of endocrine disorders in POEMS.

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Nothing to Disclose: AVM, LRR

sort_order 2825
Pub # P3-756
Session Information POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)
Title Autoimmune Thyroiditis, Autoimmune Hepatitis, Rheumatoid Arthritis and Foregut Carcinoid -- A Case Report
Author String Y Feng, A Busta
Beth Israel Medical Center, New York, NY

Body

Background

Autoimmune polyglandular syndrome (APS) is characterized by multiple autoimmune endocrine gland dysfunction, and can be associated with non endocrine disorders.(1,2)APS is divided into three types, Type I is characterized by the classic triad of Addison's disease, hypoparathyroidism, and chronic mucocutaneous candidiasis; Type II is characterized by the triad of Addison's disease, autoimmune thyroid disorder and type 1 diabetes mellitus.(3) Type III has also been reported which includes patients with an autoimmune thyroid disorder in addition to a second autoimmune disorder but not Addison's disease. It is not uncommon to see the presence of immune markers for endocrine glands in APS, often without overt disease.

Case Presentation

After a long standing history of abdominal pain, the patient was diagnosed with gastric carcinoid tumor and underwent a total gastrectomy in April 2009, at age 39. She was diagnosed with autoimmune hepatitis and rheumatoid arthritis 12 and 10 years ago respectively. She was prescribed steroids for several years, and developed steroids induced diabetes and adrenal insufficiency. She also has a history of secondary amenorrhea, diagnosed in 2009. She was recently diagnosed with Vitamin D deficiency. Her family medical history was unremarkable. Her thyroid function test (TFT) was normal. In November 2010, the thyroglobulin levels were increased to 63 ng/mL. Celiac disease and type 1 diabetes immune markers were negative.

Discussion

This is an APS III composed of autoimmune thyroiditis (likely early stage), and non-endocrine autoimmune disease such as hepatitis, and rheumatoid arthritis. The association of foregut carcinoid tumor with APS III, makes it a unique clinical case.

Autoimmunity is believed to be a major factor contributing to the pathophysiology of PAS III,(4,5) which is supported by the presence of organ-specific autoantibodies and the lymphocytic infiltration of affected organs.(6) In addition the overlap of carcinoid and APS III in this case also raised the mutual correlation of carcinogenesis and autoimmunity in APS III. It is postulated that carcinogenesis directly interferes with the function of B-,T-lymphocytes and nature killer cells, which cause autoimmune reactions in both endocrine and non-endocrine organs.(7) Reversely, autoreactive immune cells may contribute to the growth of tumor.

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Nothing to Disclose: YF, AB

sort_order 2826
Pub # P3-757
Session Information POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)
Title A Case of Autoimmune Polyglandular Syndrome Type 1 (APS-1) Presenting as Recurrent Esophageal Candidiasis
Author String DW Yi, YH Kang, SM Son
Pusan National University School of Medicine, Yangsan, Korea; Pusan National University Yangsan Hospital, Yangsan, Korea
Body Background: Autoimmune polyglandular syndrome type 1 (APS-1) is a very rare autosomal recessive disorder characterized by chronic mucocutaneous candidiasis (CMC), primary hypoparathyroidism, and primary adrenal insufficiency. We present a case characterized by recurrent esophageal candidiasis, primary adrenal insufficiency, and autoimmune thyroiditis and review of the literature.
Clinical case: A 21-year-old female patient presented with general weakness, nausea and odynophagia. Her past medical history demonstrated esophageal candidiasis treated 2 months earlier. The blood pressure was 90/62 mmHg, and the pulse rate was 68 beats per minute. Initial laboratory tests revealed no abnormality except hyponatremia (sodium 115 mmol/L, reference 138-148) and hypokalemia (potassium 3.2 mmol/L, reference 3.5-5.3). Basal hormone levels were as follows: T3 0.78 ng/mL (0.58-1.59), free T4 1.22 ng/dL (0.70-1.48), TSH 1.55 uIU/mL (0.27-4.2), ACTH 214.9 pg/mL (10-60), cortisol 2.2 u/dL (5-25), renin 0.4 ng/mL/hr (0.2-2.8), aldosterone 16.3 pg/mL (40-310), LH 3.39 mIU/mL (2.4-12.6), FSH 7.04 mIU/mL (1.6-19.0), estradiol 31.9 pg/mL (12.5-166), and intact PTH 14.9 pg/mL (10-60). In rapid ACTH stimulation test, levels of basal cortisol, 30 minutes, and 60 minutes were 2.40, 10.1, and 10.7 ug/dL, respectively. Autoantibody tests were positive for anti-microsome antibody (153 IU/mL, reference <60), anti-thyroglobulin antibody (285 IU/mL, reference <60), and negative for 21-hydroxylase autoantibody. Gastrointestinal endoscopy revealed esophageal candidiasis, which improved under systemic treatment with fluconazole. An abdominal CT scan showed no abnormality and thyroid scan revealed mild diffuse enlargement of bilateral thyroid glands. On the basis of these results, she was diagnosed as having APS-1. She was successfully treated with glucocorticoid/mineralocorticoid replacement and has remained asymptomatic.
Conclusion: CMC is usually the first and the most frequent feature of APS-1. Clinicians should suspect APS-1 in any patient who presents with CMC. And the patient should be evaluated carefully by clinical, biochemical and immunological tests to recognize symptoms and signs of imminent endocrine glandular failure.
Nothing to Disclose: DWY, YHK, SMS

sort_order 2827
Pub # P3-758
Session Information POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)
Title Clinical Manifestations of a Novel *SOX2* Mutation May Result from Failure to Repress β -Catenin-Mediated Target Activation: Suggestion for a New Mechanism for the Interaction between *SOX2* and β -Catenin
Author String KS Alatzoglou, CL Andoniadou, D Kelberman, H-G Kim, E Botse-Baidoo, JR Pedersen-White, LC Layman, JP Martinez-Barbera, MT Dattani
UCL Institute of Child Health and Great Ormond Street Hospital for Children, London, UK; UCL Institute of Child Health, London, UK; UCL Institute of Child Health, London, UK; Institute of Molecular Medicine & Genetics, Medical College of Georgia, Augusta, GA; The Medical College of Georgia, Augusta, GA
Body
Background: *SOX2* is an early developmental transcription factor and marker of stem cells and is implicated in pituitary gland development. Heterozygous *SOX2* mutations have been described in patients with severe ocular abnormalities and hypogonadotropic hypogonadism (HH) with or without associated abnormalities (esophageal atresia, developmental delay, sensorineural deafness, hippocampal malformation, hypoplasia of the corpus callosum and hypothalamic hamartoma). Murine and human *SOX2* interact with β -catenin and can repress its activity in vitro. Experimental data have suggested that this action is mediated via the carboxyl-terminal domain of the protein. We report a novel missense *SOX2* mutation in the high-mobility group (HMG) domain that results in failure to repress β -catenin mediated target activation in-vitro, whilst DNA-binding and transactivation are intact.
Case Presentation: A 21-year old woman presented with bilateral congenital anophthalmia, primary amenorrhea (Breast stage 2) with HH (FSH 1 IU/L, LH 0.6 IU/L, estradiol <15pg/mL), developmental delay and thinning of the posterior aspect of the corpus callosum on MRI. Genetic analysis revealed heterozygosity for a novel *SOX2* mutation (c.G261T, p.K87N) in the HMG DNA binding domain.
Results: Functional studies of the mutant protein using a reporter containing the *Hesx1* promoter upstream of luciferase showed comparable transactivation to the wild-type *SOX2* protein ($p > 0.5$). Electrophoretic mobility shift assay (EMSA) confirmed that the mutant protein retained its ability to bind to a consensus probe. However co-transfection of the TOPFLASH reporter with a constitutively active form of human β -catenin (S33Y) and the p.K87N *SOX2* mutant, failed to repress β -catenin mediated activation. In contrast, co-transfection with wild-type *SOX2* resulted in a significant repression of β -catenin mediated activation ($p < 0.001$). We hypothesize that this result may be mediated by altered direct interaction with β -catenin, rather than binding to TCF/LEF sites, as we demonstrated on EMSA that neither wild-type nor p.K87N *SOX2* bound to a TCF/LEF consensus probe.
Conclusion: We report a novel *SOX2* mutation, p.K87N, that is located in the HMG domain. Unexpectedly, it did not impair transactivation or DNA-binding, but failed to repress β -catenin mediated target activation. This suggests that, in addition to the carboxyl-terminal domain, the HMG domain of *SOX2* may be important for the interaction with β -catenin.

Nothing to Disclose: KSA, CLA, DK, H-GK, EB-B, JRP-W, LCL, JPM-B, MTD

sort_order 2828
Pub # P3-759
Session Information POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)
Title Rare Presentation of McCune-Albright Syndrome: Case Report
Author String DY Eimori, LA Caetano, ACW Xavier, APT Liberati, WRG Brida, SR Correa-Silva, SMP Vecchiatti, RA Guerra
Hospital do Servidor P[uaacute]blico Municipal, São Paulo, Brazil
Body **BACKGROUND:** The McCune-Albright syndrome is a rare disease that takes place due to activating somatic mutations in the alpha subunit gene (*GNAS*) of the G protein, leading to a constitutively stimulated adenylate cyclase activity. It is classically characterized by *cafe-au-lait* spots, polyostotic fibrous dysplasia and hyperfunctioning endocrinopathies, such as precocious puberty (the most frequent), hyperthyroidism, Cushing's syndrome, among others. The disease is twice as frequent in females.
CLINICAL CASE: A 25-year-old male patient had the syndrome diagnosed 10 years ago. At diagnosis, he presented complaints of knee pain for 1 year and hip pain for 3 months. During the initial clinical and laboratorial investigation it was verified: facial asymmetry, *cafe-au-lait* spots located on the abdomen and left side of the back; lytic lesions in radiograph of femur (diaphysis, trochanter), cranium, hands. The biopsy of the femoral lesion was compatible with fibrous dysplasia. His condition evolved with a history of multiple fractures (long bones and hand) during the clinical assessment. Cranial CT scan showed thickening of the skullcap with expansive and sclerotic aspect, involving the skull base including the mastoid and orbits. He used alendronate for 6 years, and has been using pamidronate for 2 years; a significant improvement of his serum alkaline phosphatase levels was obtained (AP=3143 to 755U/L; Range: 40-150U/L). There was also an alteration of thyroid function (TSH=0.3mU/L; Range: 0.4-4.0mU/L). In 2002, he started propylthiouracil (PTU), as he presented palpitations, agitation, tremor of extremities and diarrhea; at that time he had TSH of 0.01mU/L and Free T4 of 1.7ng/dl (Range: 0.89-1.76ng/dl). Currently, his thyroid function is normal in use of PTU.
CONCLUSION: The case reported highlights a rare presentation of this syndrome, in a male, with association of fibrous dysplasia and hyperthyroidism, without precocious puberty. It's important to emphasize the excellent response of the metabolic bone disease (bone pain reduction and lower incidence of new fractures) with pamidronate treatment.
Nothing to Disclose: DYE, LAC, ACWX, APTL, WRGB, SRC-S, SMPV, RAG

sort_order 2829
Pub # P3-760
Session Information POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)
Title Elevated Prolactin in Geroderma Osteodysplastica (Wrinkly Skin Syndrome) Associated with Chromosomal 15 Duplication
Author String P Santhanam, A Elkadry, S Bendre
Joan C Edwards School of Medicine, Huntington, WV; WVU Charleston Area, Charleston, WV
Body
Introduction
Geroderma Osteodysplastica (Wrinkly Skin Syndrome) is a rare condition characterized by loose skin, growth deficiency, hip dislocation and dysmorphic facial features, mental retardation, and osteoporosis diagnosed by radiological tests. We present a case of Wrinkly Skin Syndrome and evaluate the endocrine abnormalities associated with the condition.
Case report
A 6 year old female was referred to the pediatric endocrinology clinic for wrinkly hands and dysmorphic features. The child also had delayed overall development. A few months ago, she was evaluated by the neurology for unwitnessed seizure episodes and the EEG had been normal. Her mother complained of her increased appetite, easy bruisability, constipation and appearance of wrinkly hands and skin.
In the past, she had experienced two episodes of traumatic fractures in the arm and elbows. Her father had a chromosome 15 duplication disorder and some of her first cousins had Attention Deficit Hyperactivity Disorder (ADHD).
The physical examination showed delayed development, wrinkled skin in the hands and feet, large head with frontal bossing, pear shaped pointing chin, thin lips and alae nasae, large fan shaped ears, beakish nose and thinning of hair in the anterolateral part of the head. She also had poor dentition and caries. Other clinical findings included systolic murmur in the left sternal border, periumbilical lipohypertrophy, poor labial fat and gaped vaginal orifice, hyperflexible small joints, sacroiliac dimples and overall poor subcutaneous fat deposition.
The initial differential diagnosis included progeria associated conditions, one of the presenility or Cockayne syndrome. The final diagnosis was Geroderma Osteodysplastica or Wrinkly Skin Syndrome. Initial laboratory evaluation obtained were a urine analysis, comprehensive metabolic panel, complete blood count, fasting lipid profile, serum prolactin, serum TSH and free thyroxine. All the tests were within normal reference range except the prolactin which was elevated.
Conclusion
Geroderma Osteodysplastica (Wrinkly Skin Syndrome) in our patient was associated with elevated prolactin with no other major abnormalities. The cause for the elevated prolactin was not known.
Nothing to Disclose: PS, AE, SB

sort_order

2830

Pub #

P3-761

Session Information

POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)

Title

Short Stature by Extreme Shortfall in Production of IGF-I and Delayed Puberty in a Patient with Glycogen Storage Disease Type 1A: A Case Report

Author String

CG Pereira, JB Daltrozo, MF Ronsoni, MHB Canalli, G Colombo, ME Kowalski, ET Pereira, MH Coral, A Hohl
University Hospital - Federal University of Santa Catarina, Florianopolis, Brazil

Body

Background: Glycogen storage disease type 1A or Von Gierke disease (DVG) is a rare inborn errors of metabolism, autosomal dominant, characterized by deficiency of the enzyme glucose-6-phosphatase (G6Pase), responsible for 80 % of cases and usually present with hepatomegaly and hypoglycemia (1). Short stature and delayed puberty are also described.
Case presentation: A 19 y.o. white, male, with DVG diagnosed at 12 months for recurrent respiratory infections, pre-puberty, height 123.5 cm (171.5 target), diffuse muscle atrophy, yellowish skin, thin voice, hepatomegaly and clinical signs of chronic liver disease. Hypertriglyceridemia and hyperuricemia in treatment. Anemia from iron deficiency. Normal levels of ALT, AST, albumin, prothrombin time and bilirubin. Alkaline phosphatase 1030 U/L (nl 98 to 317 U/L) at the expense of the fraction of liver and GGT 668 U/L (nl 15 to 85 U/L). Conventional X-ray of left hand with skeletal maturation of 10 y.o. and with osteoporosis just articulate. Uric acid 9.1 mg/dL (nl 3.5 to 7.2 mg/dL) and triglycerides 690 mg/dL (nl < 190 mg/dL). Testosterone < 20.0 ng/dL (nl 245 to 1,600 ng/dL), FSH 0.68 mU/mL (nl 0.7 to 11.1 mU/mL), GH 1.95 ng/mL (nl < 1.0 ng/mL), IGF-1 < 25 ng/dL (nl 141 to 483 ng/dL) and IGFBP-3 1.05 mcg/mL (nl 2.9 to 7.3 mcg/mL). Stimulant test with insulin-induced hypoglycemia show normal increase in serum growth hormone. Sellar MRI normal. Abdominal ultrasound with numerous hepatic nodules, the largest of 10 x 9 cm, consistent with adenomas. Abdomen CT with the same features without criteria of malignancy and kidney stones.
Clinical lessons/Conclusion: DVG commonly presents with hyperuricemia and hypertriglyceridemia, which is part of the etiology of liver adenomas and renal lithiasis. Malignant transformation of liver nodules is described in 10% of cases. This clinical case is consistent with the literature except for the extrem short stature (studies show generally height above 140 cm) and low levels of IGF-1, which tends to be normal although there are values of GH changed. In this case, hepatic dysfunction resulting from multiple adenomas prevents adequate production of IGF-1. The patient was referred for liver transplantation and not starting hormone replacement due to increase risk of adenomas and malignant transformation of them. Prescribed use calcium, vitamin D, iron, fibrate and allopurinol.

(1) Chou JY, Jun HS, Mansfield BC: Glycogen storage disease type I and G6Pase- β deficiency: etiology and therapy. Nat Rev Endocrinol. 2010 Dec;6(12):676-88.

Nothing to Disclose: CGP, JBD, MFR, MHBC, GC, MEK, ETP, MHC, AH

sort_order 2831
Pub # P3-762
Session Information POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)
Title Hypokalemic Paralysis after Single Steroid Dose in Native American Man
Author String W Almuti, A Nuristani, MH Horani
Banner Good Samaritan Hospital, Phoenix, AZ; SIP Hospitalist Company, Phoenix, AZ; Alsham Endocrinology, Chandler, AZ
Body
This is a 39-year-old Native American male with no significant past medical history who presented to emergency department with allergic reaction to Hydrocodone containing cough syrup for which he was given Solu-Medrol 60 mg Intravenously in addition to Benadryl and Pepcid. few hours later patient collapsed to the ground without loss of consciousness and was unable to stand up. At ED patient was found to have profound hypokalemia with a potassium of 1.5 and noted to have blood glucose level of 463, also noted to have a bicarbonate serum level of 13, B- hydroxy Butyrate was normal chloride of 106 and had a slightly elevated troponin of 0.24 with a normal CK of 48. The patient had an EKG, findings which revealed QT prolongation mimicking RBBB and U waves. The patient was treated with PO and IV potassium chloride in intensive care unit and his paralysis resolved with normalization of his serum potassium
Tyrotoxicosis as etiology of hypokalemia was ruled out with normal TSH at level 0.87 with a free T4 of 1.1. also Renal tubular acidosis was ruled out by the lack of anion gap in the urine lytes. Pt was not on any diuretic. No licorice intake or Herbal Medicine. Patient has HB1C of 7.7 consistent with new diagnosis of type 2 diabetes
Normal Renal arterial duplex ruled out renal artery stenosis as a possible etiology of hypokalemia. patient was normotensive with aldosterone to rennin ratio less than 20. The etiology of hypokalemia was thought to intracellular shift of potassium secondary to steroids, which was confirmed by calculation of transtubular potassium gradient (TTKG)
Glucocorticoids can cause hypokalemia due to their stimulation of the sodium-potassium ATPase mediated by insulin and amylin and due to their side effect of insulin resistance resulting in hyperglycemia(1). Glucocorticoids have been shown to increase the number of Na⁺/K⁺ATPase molecules in skeletal muscle. They also increase insulin secretion in the basal state and the first-phase insulin release after a glucose load(2).
Conclusion : Glucocorticoids should be administered with caution in patients with periodic paralysis.

1. Neuromuscul Disord. 2009 Mar;19(3):217-9. Epub 2009 Feb 7.
2. Intern Med. 2007;46(17):1431-3. Epub 2007 Sep 3

Nothing to Disclose: WA, AN, MHH

sort_order 2832
Pub # P3-763
Session Information POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)
Title A Rare Case of Squamous Cell Esophageal Cancer Causing Malignant Hypercalcemia and Cardiac Dysrhythmia
Author String MF Assal, G Petersen
UCLA at Kern Medical Center, Bakersfield, CA
Body
Objective: To present a case of Acute Hypercalcemia secondary to Esophageal Cancer causing Right Bundle Branch Block.
Case Presentation: A 58 year old Hispanic male was recently diagnosed with Squamous Cell Esophageal Cancer, who presented to our emergency room with severe confusion, and mental status changes. His past medical history includes hypertension but no previous history of cardiac disease.
Patient found to be in severe hypercalcemia with total serum calcium level of 16.3 mg/dl (Normal reference: 8.5-10.1 mg/dl) and ionized calcium 2.21mmol/l (1.12-1.32mmol/l), serum phosphorus: 2.3 mg/dl (2.5-4.9 mg/dl), Parathyroid hormone Intact less than 3 (10-65 pg/ml) and PTH-related peptide: 84 (14-27pg/ml)
EKG initially showed Normal Sinus Rhythm with a heart rate of 96 beat per minute and non specific anterior T wave abnormalities with corrected QT interval 378 msec.
Few hours later repeat EKG showed newly found right bundle branch block, lateral ST elevation, with heart rate 105 and corrected QT interval 435 msec.
The patient was started on aggressive hydration, and was given one dose of intravenous pamidronate 90 mg. Cardiac enzymes were negative and pulmonary embolism was ruled out with CT Angiogram of the chest.
Cardiac workup ruled out other causes of dysrhythmia. Echocardiogram showed normal left ventricular ejection fraction and myocardial perfusion test was negative.
Further workup of esophageal cancer was suspicious for both pleural and liver metastases without bone involvement.
Malignant hypercalcemia was the cause of mental status changes and new diagnosis of right bundle branch block as with correction of hypercalcemia, mental status of the patient started to improve gradually with the resolution of his right bundle branch block on EKG.
Conclusion:
Hypercalcemia is a frequent complication of malignant disease but it is not well known in Esophageal Cancer. Also Hypercalcemia is well known to cause neurologic, electrolyte and renal signs but cardiac effects are less often evident which usually includes prolongation of the P-R interval and the QRS complex and shortening of the Q-T interval. However, Right Bundle Branch Block appears to be an unusual manifestation of hypercalcemia, so early diagnosis of Malignant Hypercalcemia is essential for treatment of life threatening cardiac complication at an early stage and humoral hypercalcemia should be suspected as the cause of hypercalcemia in any patient with a solid tumor in the absence of bony metastases.
Nothing to Disclose: MFA, GP

sort_order 2833
Pub # P3-764
Session Information POSTER SESSION: CLINICAL - Case Reports: Clues To Prompt Future Investigation (1:30 PM-3:30 PM)
Title Infant Gynecomastia Due to Omeprazole Use
Author String AC Gelb, M Gottschalk
UCSD School of Medicine and Rady Children's Hospital, San Diego, CA
Body Background: Gynecomastia has been associated with the use of many drugs. We report an infant with gynecomastia and elevated estrogen levels with a history of Omeprazole use and reduced estrogen levels after discontinuation of the medication.
Case Presentation: A 29 day old infant male was found to have increasing bilateral gynecomastia since 4 days old. There was no history of nipple discharge or other clinical signs of puberty. The infant began Omeprazole at 8 days old. Three weeks later, he had firm, Tanner 3 breasts with the right breast measuring 3 cm in diameter and the left breast measuring 3.5 cm in diameter. He had normal male genitalia. Initial hormone studies were collected 2 days after the discontinuation of Omeprazole (at 31 days old). He had an Estradiol of 20 pg/mL (3-10 pg/mL), Estrone of 12 pg/mL (5-15 pg/mL), Estriol of 0.24 ng/dL ([le]0.2 ng/dL), LH of 2.6 IU/L (0.3-2.8 IU/L), FSH of 1.0 IU/L (<2.5 IU/L), and total testosterone of 77 ng/dL (75-400 ng/dL). Repeat testing 12 days after the discontinuation of Omeprazole showed improvement in all estrogen levels with an Estradiol of 11 pg/mL, Estrone of <10 pg/mL, and Estriol of <0.1 ng/dL. Although there was no long term follow up, the patient's gynecomastia was improving prior to his hospital discharge.
Conclusion: It has been reported that Omeprazole interferes with the metabolism of estradiol by the inhibition of hepatic enzymes, including recombinant P450 CYP3A4. As a result of this interference, estradiol levels can become elevated and lead to gynecomastia. Estrogen levels were not tested prior to Omeprazole discontinuation and the overall decrease in these levels may reflect normal infant physiology. However, the patient's estrogen levels at 31 days were elevated for age, all estrogen levels improved and clinical improvement was seen after Omeprazole discontinuation. Physicians who prescribe Omeprazole for infants need to be aware of this potential side effect. Patients who experience gynecomastia with Omeprazole may also be predisposed to developing gynecomastia with the use of other drugs known to interfere with metabolism through the same hepatic enzymes. This predisposition may be associated with genetic polymorphisms of cytochrome P450 enzymes. This knowledge will be useful for physicians when providing counseling on drug interactions and adverse reactions in such patients.

Nothing to Disclose: ACG, MG

sort_order 2834
Pub # CMF9-1
Session Information CASE MANAGEMENT FORUM: CLINICAL - Endocrine Management of the Bariatric Patient (2:45 PM - 3:30 PM)
Title Endocrine Management of the Bariatric Patient
Author String CM Apovian
Boston Medical Center, Boston, MA
Body Session supported by: Allergan, Inc.

Disclosures: CMA: Advisory Group Member, Amylin Pharmaceuticals, Johnson & Johnson, Pfizer, Inc., Abbott Laboratories, Allergan, Orexigen; Principal Investigator, Atkins Foundation, Metaproteomics, Amylin Pharmaceuticals.

sort_order 2835
Pub # CMF9-2
Session Information CASE MANAGEMENT FORUM: CLINICAL - Endocrine Management of the Bariatric Patient (2:45 PM - 3:30 PM)
Title Endocrine Management of the Bariatric Patient
Author String LM Kaplan
Massachusetts General Hospital, Boston, MA
Body Session supported by: Allergan, Inc.

Disclosures: LMK: Consultant, Amylin Pharmaceuticals, Medtronic Minimed, Allergan; Principal Investigator, Johnson & Johnson, Merck & Co.; Scientific Board Member, Rhythm Pharmaceuticals, GI Dynamics, Gelesis.

sort_order	2836
Pub #	CMF10-1
Session Information	CASE MANAGEMENT FORUM: CLINICAL - Management of Opiate-Induced Neuroendocrine Dysfunction (2:45 PM - 3:30 PM)
Title	Management of Opiate-Induced Neuroendocrine Dysfunction
Author String	JA Wass Churchill Hospital, Oxon, UK
Body	Nothing to Disclose: JAW

sort_order	2837
Pub #	CMF10-2
Session Information	CASE MANAGEMENT FORUM: CLINICAL - Management of Opiate-Induced Neuroendocrine Dysfunction (2:45 PM - 3:30 PM)
Title	Management of Opiate-Induced Neuroendocrine Dysfunction
Author String	K Ho Princess Alexandra Hospital, Queensland, Australia
Body	Nothing to Disclose: KH

sort_order	2838
Pub #	CMF11-1
Session Information	CASE MANAGEMENT FORUM: CLINICAL - Management of Thyroid Disease during Pregnancy (2:45 PM - 3:30 PM)
Title	Management of Thyroid Disease during Pregnancy
Author String	EK Alexander Brigham & Women's Hospital, Boston, MA
Body	Nothing to Disclose: EKA

sort_order	2839
Pub #	CMF11-2
Session Information	CASE MANAGEMENT FORUM: CLINICAL - Management of Thyroid Disease during Pregnancy (2:45 PM - 3:30 PM)
Title	Management of Thyroid Disease during Pregnancy
Author String	EN Pearce Boston University Medical Center, Boston, MA
Body	Nothing to Disclose: ENP

sort_order	2840
Pub #	CMF12-1
Session Information	CASE MANAGEMENT FORUM: CLINICAL - Primary Hyperaldosteronism (2:45 PM - 3:30 PM)
Title	Primary Hyperaldosteronism
Author String	RJ Auchus University of Texas Southwestern Medical Center, Dallas, TX
Body	Nothing to Disclose: RJA

sort_order	2841
Pub #	CMF12-2
Session Information	CASE MANAGEMENT FORUM: CLINICAL - Primary Hyperaldosteronism (2:45 PM - 3:30 PM)
Title	Primary Hyperaldosteronism
Author String	JW Findling Medical College of Wisconsin, Milwaukee, WI
Body	Nothing to Disclose: JWF

sort_order	2842
Pub #	M35
Session Information	MEET-THE-PROFESSOR: CLINICAL - Controversies in the Diagnosis of Diabetes Mellitus (2:45 PM - 3:30 PM)
Title	Controversies in the Diagnosis of Diabetes Mellitus
Author String	K Osei Ohio State University Medical Center, Columbus, OH
Body	Session supported by: Merck & Co., Inc. Nothing to Disclose: KO

sort_order	2843
Pub #	M36
Session Information	MEET-THE-PROFESSOR: CLINICAL - Diagnosis & Management of Male Hypogonadism in the Older Man (2:45 PM - 3:30 PM)
Title	Diagnosis & Management of Male Hypogonadism in the Older Man
Author String	FJ Hayes Saint Vincent's University Hospital, Dublin, Ireland
Body	Nothing to Disclose: FJH

sort_order	2844
Pub #	M37
Session Information	MEET-THE-PROFESSOR: CLINICAL - Investigation & Management of Hypocalcemia (2:45 PM - 3:30 PM)
Title	Investigation & Management of Hypocalcemia
Author String	MA Levine Children's Hospital of Philadelphia, Philadelphia, PA
Body	Nothing to Disclose: MAL

sort_order	2845
Pub #	M38
Session Information	MEET-THE-PROFESSOR: CLINICAL - Management of Gender-Variant Youth (2:45 PM - 3:30 PM)
Title	Management of Gender-Variant Youth
Author String	NP Spack Children's Hospital Boston, Boston, MA
Body	Nothing to Disclose: NPS

sort_order	2846
Pub #	M39
Session Information	MEET-THE-PROFESSOR: CLINICAL - Pediatric Thyroid Nodules & Cancer (2:45 PM - 3:30 PM)
Title	Pediatric Thyroid Nodules & Cancer
Author String	AJ Bauer Walter Reed Army Medical Center, Rockville, MD
Body	Nothing to Disclose: AJB

sort_order	2847
Pub #	
Session Information	CONFERENCE EVENT: International Endocrine Scholars Oral Presentation Session (3:30 PM - 5:30 PM)
Title	International Endocrine Scholars Oral Presentation Session
Author String	
Body	

sort_order	2848
Pub #	S52-1
Session Information	SYMPOSIUM SESSION: BASIC - Dynamic Regulation of Metabolic Processes by Nuclear Receptors (3:45 PM - 5:15 PM)
Title	Nuclear Receptor NHR-49 as Chief Supply-Side Energy Economist in <i>C. elegans</i>
Author String	M Van Gilst Fred Hutchinson Cancer Research Center, Seattle, WA
Body	Disclosure Incomplete: MVG

sort_order 2849
Pub # S52-2
Session Information SYMPOSIUM SESSION: BASIC - Dynamic Regulation of Metabolic Processes by Nuclear Receptors (3:45 PM - 5:15 PM)
Title Coordinated Regulation of Hepatic Lipid Metabolism by Nuclear Receptors, Protein Acetylation & microRNAs in Health & Disease
Author String JK Kemper
University of Illinois at Urbana-Champaign, Urbana, IL
Body Obesity is a major medical problem worldwide. In obese individuals, the liver is characterized by fatty liver and subsequently chronic inflammation and insulin resistance. The nuclear bile acid receptor FXR is critical in maintaining metabolite levels by activating or repressing its target genes but little is known about how FXR activity is regulated and how it is dysregulated in metabolic disease states. Recently we have shown that aberrantly elevated acetylation of FXR and elevated microRNAs due to altered FXR's transcriptional pathways contribute to abnormal transcriptional responses and detrimental metabolic outcomes in metabolic disease states. FXR acetylation was dynamically regulated by opposing actions of p300 acetylase and SIRT1 deacetylase in response to fasting and feeding under normal conditions but in fatty livers of obese mice, FXR acetylation at Lys-217 was dramatically elevated. FXR acetylation dampened its transactivation ability by inhibiting binding of FXR/RXR α to DNA. Consistent with the idea that hyperacetylation can alter FXR transcriptional pathways and may contribute to the disrupted metabolic homeostasis, subsets of hepatic FXR binding sites unique for either normal or obese mice were observed by genome-wide chromatin immunoprecipitation-sequencing (ChIP-seq) and potential target genes near FXR binding sites were involved in novel biological processes including cellular kinase signaling, G protein/TLR signaling, inflammation, apoptosis, autophagy, energy metabolism, as well as lipid metabolism. Furthermore, in recent microRNA (miR) studies, miR34a and miR199a downregulated SIRT1, a key metabolic regulator and life longevity protein, and interestingly these miRs were highly elevated in obese mice. Activation of FXR by GW4064 restored miRs and SIRT1 levels toward normal with improved metabolic outcomes. Our data demonstrate that aberrant acetylation of FXR and elevated miRs contribute to abnormal transcriptional regulation of FXR target genes with deleterious metabolic effects. These studies may provide novel therapeutic strategies by targeting aberrant FXR acetylation to treat FXR-related human diseases, such as metabolic syndrome and cancer.

Sources of Research Support: NIH (DK080032, DK06277) and the ADA.

Nothing to Disclose: JKK

sort_order	2850
Pub #	S52-3
Session Information	SYMPOSIUM SESSION: BASIC - Dynamic Regulation of Metabolic Processes by Nuclear Receptors (3:45 PM - 5:15 PM)
Title	Epigenetic Regulation of PPARgamma and Adipogenesis
Author String	K Ge NIDDK/ NIH, Bethesda, MD
Body	

sort_order	2851
Pub #	S53-1
Session Information	SYMPOSIUM SESSION: BASIC - New Aspects of Signaling & Secretion in the Gonadotrope (3:45 PM - 5:15 PM)
Title	Gonadotrope Decoding of Gonadotropin-Releasing Hormone Pulsatility
Author String	SC Sealfon Mount Sinai School of Medicine, New York, NY
Body	Disclosure Incomplete: SCS

sort_order 2852
Pub # S53-2
Session Information SYMPOSIUM SESSION: BASIC - New Aspects of Signaling & Secretion in the Gonadotrope (3:45 PM - 5:15 PM)
Title Integration of Activin, Gonadotropin-Releasing Hormone & Steroid Hormone Action in the Pituitary Gonadotrope
Author String PL Mellon
University of California, San Diego, La Jolla, CA
Body Reproduction is controlled by three major classes of hormones acting at the level of the pituitary to regulate transcription and secretion of LH and FSH from gonadotrope cells. Feedback loops of gonadal steroids, autocrine and endocrine actions of the activin/inhibin/follistatin system, and differential hypothalamic GnRH pulse frequencies are integrated to modulate the function of the gonadotrope cell of the anterior pituitary. Our immortalized pituitary gonadotrope model cell line, L β T2, expresses GnRH receptor, activin, follistatin, inhibin, ER, AR, PR, and GR, as well as FSH and LH. Studies in these cells have allowed identification of regulatory mechanisms responsible for transcriptional regulation of the α GSU, LH β , FSH β and GnRH receptor genes by each of these classes of hormones. However, the fundamental basis of reproductive control depends upon differential secretion of LH versus FSH from this single cell type. The current goal is to understand how integration of these hormonal stimuli creates the oscillating balance of LH and FSH that controls the estrous cycle and modulates reproductive function. We have recently shown that activin induction of the FSH β gene is reliant on the Forkhead transcription factor FoxL2. Activin synergizes with GnRH and progesterone on the FSH β gene and these interactions also rely on FoxL2. Though the LH β gene is also induced by activin and GnRH, in contrast to FSH β , these hormones are not synergistic. In further contrast to FSH β , LH β is repressed by steroid hormones, indicating that quite different molecular mechanisms are acting at each of the gonadotropin β -subunit genes. Thus, activin and FoxL2 are required for the full actions of steroids and GnRH on the FSH β gene, while these hormones act more independently to regulate the LH β gene. Such synergistic mechanisms are fundamental to differential secretion of LH versus FSH from the anterior pituitary gonadotrope in response to gonadal steroids, the activin/inhibin/follistatin system, and pulsatile GnRH.

Varykina G. Thackray and Djurdjica Coss (Department of Reproductive Medicine, Center for Reproductive Science and Medicine, University of California, San Diego, CA 92093-0674) are also authors on this abstract.

Sources of Research Support: NICHD/NIH through a cooperative agreement (U54 HD012303) as part of the Specialized Cooperative Centers Program in Reproduction Research (P.L.M.), R01 HD020377 and DK044838 (P.L.M.), R01 HD57549 (D.C.), and K01 DK080467 (V.G.T.).

Nothing to Disclose: PLM

sort_order	2853
Pub #	S53-3
Session Information	SYMPOSIUM SESSION: BASIC - New Aspects of Signaling & Secretion in the Gonadotrope (3:45 PM - 5:15 PM)
Title	Signals Controlling Secretary Trafficking of Gonadotropins
Author String	I Boime Washington University Medical School, St Louis, MO
Body	Nothing to Disclose: IB

sort_order 2854
Pub # S54-1
Session Information SYMPOSIUM SESSION: TRANSLATIONAL - Adrenal Disorders in Children & Adolescents (3:45 PM - 5:15 PM)
Title Clinical Effects of Cushing Syndrome in Children
Author String MB Lodish
National Institute of Child Health & Human Development/National Institutes of Health, Bethesda, MD
Body Cushing's syndrome is rare in the pediatric age group, yet presents unique diagnostic and management challenges. This clinical session will present an overview of the work-up and management of pediatric Cushing's syndrome, providing a brief overview of the field and highlighting recent progress. The classification and epidemiology of Cushing's syndrome in children will be discussed, along with diagnostic guidelines (1-3). Common clinical features in the presentation of Cushing's syndrome in children will be outlined. An algorithm to guide the clinician investigating Cushing's syndrome will be examined. An up-to-date review of treatment strategies of pediatric Cushing's syndrome will be presented. Particular issues related to post-treatment management in pediatric patients will focus on growth, bone health, metabolic syndrome, cardiovascular health, and puberty as they affect the developing child with Cushing's syndrome (4-6). Recommendations for the care of patients during the post-surgical period with regard to recovery of the HPA axis and tapering glucocorticoid therapy will be addressed. Finally, recent advances in the field will be introduced.

(1)Magiakou, M.A., et al., N Engl J Med 1994; 331:629-36
(2)Batista, D.L., et al., Pediatrics 2007; 120:e575-86
(3)Savage, M.O., et al., Curr Opin Endocrinol Diabetes Obes 2008; 15:346-51
(4)Batista, D.L., et al., J Clin Endocrinol Metab 2009; 94:2757-65
(5)Lodish, M.B., et al., J Clin Endocrinol Metab 2009; 94:2002-8
(6)Lodish, M.B., et al., J Pediatr 2010; 156:1001-5

Sources of Research Support: The Eunice Kennedy Shriver National Institute of Child Health and Human Development Division of Intramural Research.

Nothing to Disclose: MBL

sort_order 2855
Pub # S54-2
Session Information SYMPOSIUM SESSION: TRANSLATIONAL - Adrenal Disorders in Children & Adolescents (3:45 PM - 5:15 PM)
Title Novel Genetic Causes of Familial Glucocorticoid Deficiency
Author String AJL Clark
William Harvey Research Institute/Queen Mary University of London, London, UK
Body Familial Glucocorticoid Deficiency (FGD) is a rare autosomal recessive disorder characterized by resistance to the action of ACTH and consequently glucocorticoid deficiency with preserved mineralocorticoid and gonadal function. We identified mutations in the ACTH receptor (melanocortin 2 receptor; MC2R) in 1993, although these only explained around 25% of cases. More recently a genetic approach identified mutations in a novel gene which we named melanocortin 2 receptor accessory protein (MRAP). The product of this gene is a small protein essential for trafficking of the MC2R to the cell membrane and for binding of ACTH. A similar clinical phenotype may also be produced by less severe mutations in STAR. Nevertheless approximately 50% of all cases of FGD have no genetic explanation. Use of homozygosity mapping, targeted exon capture and high throughput sequencing has recently identified two new FGD genes. These are (1) a gene essential for DNA replication, which is mutated in a phenotypic variant of FGD found exclusively in the Irish traveler population, and (2) a gene that is essential for maintenance of the mitochondrial redox state. In view of the function of this latter gene other components of the mitochondrial redox pathway were screened and an inactivating mutation in a further gene in this class was identified in FGD. In summary, new technological approaches have identified three new genes associated with FGD which reveal a range of mechanisms leading to failure of the zona fasciculata cell and development of ACTH insensitivity.
Nothing to Disclose: AJLC

sort_order 2856
Pub # S54-3
Session Information SYMPOSIUM SESSION: TRANSLATIONAL - Adrenal Disorders in Children & Adolescents (3:45 PM - 5:15 PM)
Title Why Pediatric Adrenocortical Tumors Differ from Adult Tumors
Author String MQ Almeida
University of Sao Paulo, Sao Paulo, Brazil

Body Adrenocortical carcinomas account for only 0.05-0.2% of all cancers, with an estimated incidence of 0.5-2 per million per year in adults (1, 2). However, the incidence of adrenocortical tumors is remarkably high in Southern Brazil, where it is estimated to be 10-15 times greater than the worldwide incidence (2-4). Differently from adults, pediatric adrenocortical neoplasms with apparently poor prognosis based on histopathological features have often a good clinical outcome (5, 6). To date, few molecular markers are helpful to predict poor prognosis in children with adrenocortical carcinomas (1, 7-10). In the last decade, considerable advances toward understanding the molecular mechanisms of adrenocortical tumorigenesis have mainly been made in adrenocortical tumors of adults from distinct ethnicities (8, 11-15). Some of these studies have recently inspired the molecular analysis of adrenocortical tumors of children and adolescents, most of them from Brazilian origin (7, 16-20). A high incidence of a P53 germline mutation (p.R337H) was demonstrated in 35 of 36 children with adrenocortical tumors originated from Southern Brazil (16). This mutation was located outside the highly conserved DNA binding domain, resulting in the substitution of arginine for histidine at codon 337 of the tetramerization domain of P53 protein. This missense mutation was also present in 76% of children with benign and malignant sporadic adrenocortical tumors in another Brazilian series from our Institution (17). Additionally, the p.R337H mutation was identified in 14% of adult patients with adrenocortical tumors (17). We and others demonstrated that IGF-II is over-expressed in both adult and pediatric adrenocortical tumors (7, 12-14). The mitogenic effects of IGF-II are mediated by the IGF receptor type 1 (IGF-IR) (21). Interestingly, a strong increase in IGF-IR expression was found in pediatric adrenocortical carcinomas, but not in adult carcinomas (7). Furthermore, a selective IGF-IR kinase inhibitor had anti-tumor effects in adult and pediatric adrenocortical tumor cell lines (7). Recent studies revealed an important role for the steroidogenic factor-1 (SF-1) in adrenocortical tumorigenesis (19). More recently, we demonstrated a higher frequency of SF-1 over-expression and gene amplification in pediatric than in adult adrenocortical tumors (20). Therefore, we conclude that adrenocortical tumors in children and adults have different mechanisms of tumorigenesis.

1. Allolio B, Fassnacht M. *J Clin Endocrinol Metab* 2006; 91(6):2027-37
2. Latronico AC, Chrousos GP. *J Clin Endocrinol Metab* 1997; 82(5):1317-24
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Sources of Research Support: In part by Funda[ccedil]o de Amparo [agrave] Pesquisa do Estado de São Paulo (FAPESP) and by Conselho Nacional de Desenvolvimento Científico e Tecnol[ocute]gico (CNPq).

Nothing to Disclose: MQA

sort_order 2857
Pub # S55-1
Session Information SYMPOSIUM SESSION: TRANSLATIONAL - Novel Therapeutic Targets for Thyroid Disease (3:45 PM - 5:15 PM)
Title Clinically-Relevant Targeting of the Membrane Thyroid Hormone Receptor
Author String PJ Davis
Ordway Research Institute Inc, Albany, NY

Body Integrin $\alpha\beta3$ is a heterodimeric structural protein of the plasma membrane that is expressed primarily by cancer cells, by dividing endothelial and vascular smooth muscle cells and by osteoclasts. The integrin generates local membrane signals and discrete intracellular signals in response to the binding of extracellular matrix proteins and of small molecule ligands when these ligands occupy specific receptors on the integrin. Integrin $\alpha\beta3$ also engages in crosstalk with growth factor receptors, e.g., vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF) receptors, that are clustered with the integrin. $\alpha\beta3$ bears a high affinity cell surface receptor for thyroid hormone that enables L-thyroxine (T_4) and 3, 5, 3'-triiodo-L-thyronine (T_3) to stimulate cancer cell proliferation and angiogenesis (1) and to modulate or set the basal activity of, certain membrane ion pumps, such as the Na/H antiporter. Tetraiodothyroacetic acid (tetrac) blocks binding and actions of T_4 and T_3 at the receptor on $\alpha\beta3$; tetrac also has anti-proliferative actions at the integrin thyroid hormone receptor beyond inhibiting the effects of agonist thyroid hormone analogues at this site. We have reformulated tetrac as a nanoparticle (nanotetrac) that acts exclusively at the $\alpha\beta3$ receptor and does not enter cells. Nanotetrac disorders expression of genes in multiple cancer cell survival pathways. Nanotetrac and tetrac also inhibit pro-angiogenic actions *in vitro* of VEGF, basic fibroblast growth factor, EGF and platelet-derived growth factor in neovascularization assays. Nanotetrac and tetrac block human cancer cell proliferation *in vitro* and in xenografts (human pancreas, lung, renal cell and breast carcinomas, follicular thyroid [2] and medullary thyroid carcinomas [3]). Xenograft tumor mass and tumor-relevant blood supply are reduced by 50%-80% with systemic administration of nanotetrac or tetrac. Tetrac also radiosensitizes glioma cells *in vitro* by interfering with basal and post-irradiation repair of DNA double-strand breaks (4). Thus, the receptor described on integrin $\alpha\beta3$ for T_4 and T_3 -the function of which is materially affected by tetrac and nanoparticulate tetrac--provides insights into tumor cell biology and into vascular biology and is proposed to have therapeutic implications.

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Nothing to Disclose: PJD

sort_order	2858
Pub #	S55-2
Session Information	SYMPOSIUM SESSION: TRANSLATIONAL - Novel Therapeutic Targets for Thyroid Disease (3:45 PM - 5:15 PM)
Title	Thyroid Hormone Analogs: New Lipid-Lowering Drugs
Author String	E Ridgway University of Colorado, Denver, Aurora, CO
Body	Nothing to Disclose: ECR

sort_order

2859

Pub #

S55-3

Session Information

SYMPOSIUM SESSION: TRANSLATIONAL - Novel Therapeutic Targets for Thyroid Disease (3:45 PM - 5:15 PM)

Title

Potassium Channels as Novel Targets in Thyroid Disease

Author String

GW Abbott
Weill Cornell Medical College, New York, NY

Body

Thyroid dysfunction causes defects including cretinism, dwarfism, alopecia, cardiac structural abnormalities and cardiac arrhythmia. After observing several of these traits in a transgenic mouse line lacking the *Kcne2* potassium ion channel beta subunit gene, we discovered that KCNE2 and the KCNQ1 alpha subunit form a thyroid-stimulating hormone-stimulated, thyrocyte-expressed potassium channel that is required for normal thyroid hormone biosynthesis (1). KCNQ1 and KCNE2 also each contribute to generation of repolarizing currents in cardiac myocytes. Hence, inherited mutations in the KCNQ1 and KCNE2 genes are linked to the inherited ventricular arrhythmia Long QT Syndrome (LQTS), and the more common arrhythmia atrial fibrillation (AF), which affects 2-3 million people in the United States. Both these cardiac arrhythmias are also linked to altered thyroid function, suggesting the possibility of an endocrine component to KCNQ1- and KCNE2-linked cardiac arrhythmias. Our current work in this area focuses on determining the mechanistic role of KCNQ1-KCNE2 in the thyroid, and its potential as a therapeutic target. Using micro positron emission tomography (microPET), we showed that *Kcne2*^{-/-} mice have a thyroid iodide accumulation defect. Combining microPET with perchlorate discharge assays, we next found that *Kcne2* deletion has little effect on iodide organification in the thyroid, *in vivo*. In contrast, we discovered that a KCNQ1-specific antagonist inhibits iodide uptake in the thyroid of methimazole-treated wild-type mice, *in vivo*. These findings suggest that the KCNQ1-KCNE2 potassium channel facilitates thyrocyte basolateral iodide uptake, which occurs *via* the sodium iodide symporter (NIS). Furthermore, they suggest the possibility of therapeutic pharmacological targeting of the KCNQ1-KCNE2 potassium channel to manipulate thyroid function. Future studies will include investigation of why iodide uptake by NIS is impaired by KCNQ1-KCNE2 channel disruption.

(1)Roepke, T.K., et al., *Kcne2* deletion uncovers its crucial role in thyroid hormone biosynthesis. *Nat Med*, 2009. 15(10): p. 1186-94.

Sources of Research Support: NIH Grant HL079275 and an Irma T. Hirschl Career Scientist Award to GWA.

Nothing to Disclose: GWA

sort_order 2860
Pub # S56-1
Session Information SYMPOSIUM SESSION: TRANSLATIONAL - The Rewards of Sex: It's All Plastic (3:45 PM - 5:15 PM)
Title Estrogen Modulation of Hypothalamic Neuroplasticity
Author String TL Horvath
Yale University School of Medicine, New Haven, CT
Body We uncovered that leptin rapidly re-arranges the synaptic input of hypothalamic arcuate nucleus feeding circuits resulting in increased pro-opiomelanocortin (POMC) tone followed by decreased food intake and adiposity. The gonadal steroid, estradiol, can also reduce appetite and adiposity and influences synaptic plasticity. We found that estradiol (E2) triggers a robust increase in the number of excitatory inputs on arcuate nucleus POMC neurons in wild type animals. This re-arrangement of synapses in the arcuate nucleus is leptin-independent because it also occurred in leptin- (*ob/ob*) and leptin receptor deficient (*db/db*) mice, and was paralleled by decreased food intake and body weight gain as well as increased energy expenditure. However the action of estradiol did converge intracellularly with leptin signaling as it triggered Stat3 activation. These observations support the notion that synaptic plasticity of arcuate nucleus feeding circuits is a critical element in body weight regulation and offer alternative approaches to reduce adiposity under conditions of failed leptin signaling.
Nothing to Disclose: TLH

sort_order 2861
Pub # S56-2
Session Information SYMPOSIUM SESSION: TRANSLATIONAL - The Rewards of Sex: It's All Plastic (3:45 PM - 5:15 PM)
Title Estrogen Modulation of Addiction Behaviors
Author String JB Becker
University of Michigan, Ann Arbor, MI
Body Drug taking patterns are sexually dimorphic. Women tend to increase their rate of consumption of alcohol, marijuana, opioids and cocaine more rapidly than do men. Once addicted to a drug, women can find it more difficult to quit than men do, and women tend to have greater lifetime use and greater current use of cocaine than their male counterparts. Furthermore, estradiol enhances the subjective effects of cocaine in women. In animal models there are also sex differences in acquisition of drug taking and in the motivation to take drugs of abuse, such as cocaine. In female rats, we have shown that there are rapid effects of estradiol on the ascending dopamine system. These effects of estradiol enhance the female's motivation to engage in drug taking behaviors. We have found that estradiol rapidly enhances amphetamine or cocaine induced increases in dopamine in dialysate from the nucleus accumbens and striatum. Additionally, female rats exhibit greater behavioral sensitization to cocaine, acquire cocaine self-administration more rapidly, and work harder to receive cocaine than males. Estradiol enhances these sex differences in females. Recent experiments have investigated the role of hormones during development on expression of sex differences in drug taking behavior in the adult. We find that the enhanced acquisition of drug taking induced by estradiol is dependent on a developmental event that occurs in females before puberty, but the effect of estradiol to enhance motivation to take cocaine in females also requires prior hormone exposure at puberty in the female rat. Thus, sex differences in addiction behaviors are mediated at least in part by organizational effects of hormones during development that determine whether estradiol enhances drug taking behaviors.

Sources of Research Support: National Institute on Drug Abuse. R01 DA 12677 Gender differences in drug abuse.

Disclosures: JBB: Advisory Group Member, Arborwind, LLC.

sort_order 2862
Pub # S56-3
Session Information SYMPOSIUM SESSION: TRANSLATIONAL - The Rewards of Sex: It's All Plastic (3:45 PM - 5:15 PM)
Title The Role of Estrogen & Melanocortin Signaling in Ventral Striatum Dysfunction
Author String M Lutter
University of Texas Southwestern Medical Center, Dallas, TX
Body Anorexia nervosa (AN) is a severe, debilitating mental illness characterized by preoccupation with body weight, intense fear of weight gain, and failure to maintain normal body weight even in the face of emaciation. Recently, human neuroimaging studies in patients with AN have identified decreased activity in brain reward regions, particularly the ventral striatum. Rodent models are a good system for understanding the anatomy and function of specific neural circuits and may shed light onto the pathophysiology of eating disorders such as AN. The ventral striatum has been implicated in the regulation numerous cognitive processes relevant to motivated behaviors including habit learning, set-shifting, and reward-incentive learning. Deficits in ventral striatal function have been suggested as an underlying mechanism for many of the features of AN including difficulty processing positive and negative emotional stimuli, social isolation, and inflexible behavioral strategies. Neuropsychological testing has demonstrated that deficits in both state-dependent factors, such as starvation, and trait-dependent factors, such as genetic vulnerability, contribute to the impairment in striatal function. The goal of this research proposal is to utilize mouse models to identify the signaling pathways that mediate state-dependent affects on striatal function. Two candidates for mediating for the state-dependent effects of starvation are estrogen signaling and the central melanocortin system, both of which are known be reduced in starvation and are expressed in the ventral striatum. We present evidence that both estrogen and melanocortin signaling converge on a sub-set of neurons within the ventral striatum to regulate reward-related behaviors relevant to AN.

Sources of Research Support: NIH Grant MH084058-01A1 awarded to ML.

Nothing to Disclose: ML.

sort_order	2863
Pub #	S57-1
Session Information	SYMPOSIUM SESSION: TRANSLATIONAL - Uterine Biology: Cell-Specific Actions of Steroid Hormones (3:45 PM-5:15 PM)
Title	Control of Endometrial Cell Fate by Steroid Hormones & FOXO Transcription Factors
Author String	JJ Brosens Imperial College London, London, UK
Body	Nothing to Disclose: JJB

sort_order	2864
Pub #	S57-2
Session Information	SYMPOSIUM SESSION: TRANSLATIONAL - Uterine Biology: Cell-Specific Actions of Steroid Hormones (3:45 PM-5:15 PM)
Title	Steroidal Regulation of Embryo Implantation: Insights from New Mouse Models
Author String	IC Bagchi University of Illinois at Urbana-Champaign, Urbana, IL
Body	Nothing to Disclose: ICB

sort_order 2865
Pub # S57-3
Session Information SYMPOSIUM SESSION: TRANSLATIONAL - Uterine Biology: Cell-Specific Actions of Steroid Hormones (3:45 PM-5:15 PM)
Title Progesterone Resistance in Endometriosis
Author String J Kim
Northwestern University, Chicago, IL

Body Endometriosis is a common gynecologic disorder characterized by the presence and growth of the endometrial glands and stroma outside of the uterus. While there is evidence that endometriosis is a disease that is estrogen-dependent, the role of progesterone remains somewhat ambiguous. Direct effects of progestins on endometriotic lesions have not been well characterized. We have begun to elucidate the role of progestins on ovarian endometriomas, which largely consist of endometriotic stromal cells. One of the hallmarks of progesterone response in the normal eutopic endometrium is the decidualization of the stroma, which is initiated during the luteal phase of the menstrual cycle. We found that in vitro decidualization of endometriotic stromal cells from ovarian endometriomas was significantly attenuated compared to normal stromal cells, demonstrating an impaired response to the progestin, medroxyprogesterone acetate (MPA) and the cAMP analog, dibutyryl. Further analysis revealed significantly lower levels of the progesterone receptor (PR) as well as the forkhead transcription factor (FOXO1), which we have demonstrated to play an important role during decidualization of normal endometrial stromal cells. In addition, we observed consistently high basal levels of phospho(Ser473)-AKT in endometriotic stroma cells compared to normal cells, and upon treatment with MPA+cAMP. The increased phospho(Ser473)-AKT and decreased FOXO1 levels were observed in endometriosis tissues as well. Inhibition of both PI3K and AKT using pharmacologic inhibitors, LY294002 and MK-2206 potentiated endometriotic stromal cells to MPA+cAMP treatment, significantly increasing expression of the decidual genes, IGFBP1 and PRL, as well as levels of nuclear FOXO1. Furthermore, we observed an increase in total PR at the protein but not mRNA levels when endometriotic stromal cells were treated with the AKT inhibitor inferring that active AKT promote PR protein degradation. Whether this increase in PR protein has any functional consequences is currently under investigation. With the use of in vitro and in vivo systems, we are testing our overall hypothesis that there is a close crosstalk between PR and the AKT pathway in endometriosis which contributes to altered PR expression as well as its transcriptional function, involving FOXO1. These novel mechanisms will help clarify the issue of progesterone resistance in endometriosis.

Sources of Research Support: NIH HD044715.

Nothing to Disclose: JK

sort_order	2866
Pub #	S58-1
Session Information	SYMPOSIUM SESSION: CLINICAL - Consequences of XX-cess in Men (3:45 PM - 5:15 PM)
Title	Pathogenesis of Klinefelter
Author String	RS Swerdloff Los Angeles Biomedical Research Institute at Harbor-University of California, Los Angeles Medical Center, Torrance, CA
Body	Disclosures: RSS: Principal Investigator, Clarus, Abbott Laboratories.

sort_order 2867
Pub # S58-2
Session Information SYMPOSIUM SESSION: CLINICAL - Consequences of XX-cess in Men (3:45 PM - 5:15 PM)
Title Social & Behavioral Issues in Klinefelter Syndrome
Author String AB Bojesen
Vejle Hospital, Sygehus Lillebaelt, Vejle, Denmark
Body Klinefelter syndrome (KS) is the most common sex-chromosome disorder in man with a prevalence of approximately 1:600 males and is defined as a male having a karyotype containing an extra X-chromosome (47,XXY) and variants hereof, including mosaics. The key findings in KS; small testes; azoospermia and increased LH/FSH, are found in practically all KS patients but other features like hypogonadism; gynecomastia; increased height; sparse beard and body hair; abdominal obesity; increased risk of diabetes and metabolic syndrome; autoimmune diseases and many other signs and symptoms have been found with varying incidence. Learning disability is a major problem and many patients also suffer from psychiatric disturbances and social withdrawal. The accumulated clinical consequence of these problems was not described until recently where epidemiological studies showed increased morbidity and mortality, resulting in a loss in lifespan of approximately 2 years. Another study showed decreased measures of quality of life, especially in those with low educational levels. In our Danish cohort of KS persons we investigated the social and economic consequences and found a dramatic inferior outcome compared to normal men; KS men had significantly fewer partnerships at a later age, less fatherhoods at a later age, lower educational level, lower income, and were retired at an earlier age. The KS men were also convicted more often compared to the background population. In addition, it remains a problem that less than 10% of males with KS are diagnosed during childhood and adolescence, and that only 25% of all expected KS are diagnosed at all. Conclusion: Apart from various physical problems, many men with Klinefelter syndrome struggle with learning disability, psychosocial and psychiatric problems that can lead to a life without partner and children; low education, low income and early retirement; increased risk of criminality and consequently, low quality of life and excess mortality. In order to improve outcome we believe that proper clinical care should focus on early diagnosis, improved intervention measures during school, proper testosterone supplementation and adult follow-up, according to guidelines set forth in recent reviews. Continued research is needed in all areas of interest in KS.

Nothing to Disclose: ABB

sort_order	2868
Pub #	S58-3
Session Information	SYMPOSIUM SESSION: CLINICAL - Consequences of XX-cess in Men (3:45 PM - 5:15 PM)
Title	Management of Klinefelter Syndrome: Cradle to Grave
Author String	A Juul National University Hospital, Copenhagen, Denmark
Body	Nothing to Disclose: AJ

sort_order	2869
Pub #	S59-1
Session Information	SYMPOSIUM SESSION: CLINICAL - Controversies in Lipid Management (3:45 PM - 5:15 PM)
Title	Sophisticated Lipid Tests: Are They Useful?
Author String	EJ Schaefer Tufts University, Boston, MA
Body	Session supported by: Kowa Pharmaceuticals America, Inc. and Lilly USA, LLC Disclosure Incomplete: EJS

sort_order

2870

Pub #

S59-2

Session Information

SYMPOSIUM SESSION: CLINICAL - Controversies in Lipid Management (3:45 PM - 5:15 PM)

Title

Should We Focus on Increasing High-Density Lipoprotein Levels?

Author String

FL Dunn

University of Texas Southwestern Medical Center, Dallas, TX

Body

Epidemiologic studies have consistently shown that high-density lipoprotein cholesterol (HDL-C) levels are inversely associated with risk of developing coronary heart disease (CHD). This observation has led to the inclusion of low HDL-C levels as a major cardiovascular risk factor in most risk prediction models. However, therapies directed at increasing HDL-C have failed to consistently show a benefit in terms of reducing cardiovascular events, and appears to be dependent on the mechanism of raising HDL-C. Fibrates modestly raise HDL-C, and post-hoc analysis of several clinical trials indicate that they reduce CHD risk in patients with high triglycerides and low HDL-C. Several clinical trials also suggest that nicotinic acid reduces cardiovascular risk. The benefits of adding nicotinic acid to optimal statin therapy is currently being tested in two large cardiovascular outcome trials (AIM-HIGH and HPS2-THRIVE). A novel class of drugs known as cholesterol ester transfer protein inhibitors (CETP inhibitors) markedly increase HDL-C levels. However, clinical trials of one such compound, torcetrapib, showed increased risk of death and no improvement in progression of carotid and coronary atherosclerosis. These results suggest that the mechanism of raising HDL-C is important in preventing CHD events, and support current NCEP ATP III guidelines that do not set a specific goal for raising HDL-C pending the results of cardiovascular outcome studies.

Session supported by: Kowa Pharmaceuticals America, Inc. and Lilly USA, LLC

Nothing to Disclose: FLD

sort_order 2871
Pub # S59-3
Session Information SYMPOSIUM SESSION: CLINICAL - Controversies in Lipid Management (3:45 PM - 5:15 PM)
Title Should We Lower Triglycerides?
Author String LR Tannock
University of Kentucky, Lexington, KY

Body Extreme hypertriglyceridemia (> 1000 mg/dl) is clearly associated with risk of acute pancreatitis, and should be treated. However, whether or not to treat modest elevations in triglycerides (200-1000 mg/dl) is controversial, in part due to lingering controversy regarding triglycerides as an independent cardiovascular risk factor. In addition, the use of fasting vs non-fasting triglycerides is debated, with some authors even proposing an [ldquo]oral triglyceride tolerance test[rdquo]. The recent findings of the ACCORD lipid trial, with a lack of cardiovascular benefit seen with the addition of fenofibrate to statin, has cast further doubt on the potential for reducing cardiovascular risk by targeting triglycerides. However, both primary and secondary prevention monotherapy studies using fibrates have reported significant reductions in cardiovascular disease, especially in subjects with high triglycerides and low HDL. Similarly, a subgroup analysis of ACCORD suggests a benefit for the addition of fibrate in subjects with the combination of high triglycerides and low HDL. Niacin and pioglitazone are two other agents that lower triglycerides, and although controversial, outcome studies suggest cardiovascular benefit for each in monotherapy. Furthermore, imaging studies demonstrate that the addition of either niacin or pioglitazone to statin-treated patients reduces progression of atherosclerosis. However, due to the close inverse relationship between triglycerides and HDL it is not possible to separate whether the benefits observed in these clinical trials are due to the lowering of triglycerides, raising of HDL, or both. In conclusion, patients with moderate elevations in triglycerides (and low levels of HDL) are likely at increased cardiovascular risk and probably benefit from treatment directed at lowering triglycerides, although LDL lowering therapies should remain the first goal of treatment.

Session supported by: Kowa Pharmaceuticals America, Inc. and Lilly USA, LLC

Nothing to Disclose: LRT

sort_order 2872
Pub # S60-1
Session Information SYMPOSIUM SESSION: CLINICAL - Endocrine Clinical Trials in the Elderly (3:45 PM - 5:15 PM)
Title Vitamin D Dose Response Study: Effect on Serum 25-Hydroxyvitamin D and Parathyroid Hormone
Author String JC Gallagher, A Sai, TJ Templin, LM Smith
Creighton University School of Medicine, Omaha, NE; University of Nebraska Medical Center, Omaha, NE
Body Abstract Embargoed.

Sources of Research Support: NIH Grant AG28168 awarded to JCG.

Nothing to Disclose: JCG, AS, TJT, LMS

sort_order 2873
Pub # S60-2
Session Information SYMPOSIUM SESSION: CLINICAL - Endocrine Clinical Trials in the Elderly (3:45 PM - 5:15 PM)
Title Transitioning to Denosumab Further Improves BMD in Postmenopausal Women Who Received 5 or More Years of Continuous Alendronate Therapy
Author String HG Bone, DL Kendler, MA Bolognese, ML Brandi, A Hodsman, P Orcel, M Austin, A Grauer, C Libanati
Michigan Bone and Mineral Clinic, Detroit, MI; University of British Columbia, Vancouver, Canada; Bethesda Health Research Center, Bethesda, MD; University of Florence, Florence, Italy; St Joseph's Health Care London, London, Canada; Groupe Hospitalier Lariboisiere Universite, Paris, France; Amgen Inc, Thousand Oaks, CA
Body Denosumab (DMAb) treatment led to significantly greater BMD gains throughout the skeleton in women who transitioned from alendronate (ALN) to DMAB compared with those who remained on ALN, as reported in STAND (Study of Transitioning from Alendronate to Denosumab).¹ To participate in STAND, women had to have received ALN for [ge] 6 months. The primary endpoints have been previously reported.¹ We now report on the efficacy and safety from a subset of women from STAND who transitioned to DMAB after 5 or more years of continuous ALN therapy. STAND was a randomized, double-blind, double-dummy study in 504 postmenopausal women aged 67.6 ± 7.8 years with low BMD and a median ALN exposure of 3 years (range: 0.5 to 16). Women were transitioned to DMAB (60 mg every 6 months subcutaneously) or were continued on branded ALN therapy (70 mg weekly) for 12 months. In STAND, 149 women aged 70.0 ± 7.6 years had received ALN for [ge] 5 years. These women were slightly older and had worse hip but not spine BMD than those treated with ALN for < 5 years. A total of 70 women transitioned to DMAB and 79 women remained on ALN. Transitioning to DMAB for 12 months led to further significant increases in BMD of 2.95% (lumbar spine), 1.66% (total hip), and 1.02% (femoral neck). In contrast, those who remained on ALN had smaller changes in BMD of 1.55% (lumbar spine), 0.97% (total hip), and 0.25% (femoral neck). An interaction-by-subgroup analysis showed that the greater gains in BMD at all measured skeletal sites observed with transition to DMAB in the subgroup exposed to ALN for [ge] 5 years were consistent with the overall population results. Of the women who received ALN for [ge] 5 years, a similar number of adverse events were reported by those who transitioned to DMAB and those who continued to receive ALN (81.4% and 84.8%, respectively). The most frequently reported adverse events for both groups combined were nasopharyngitis (16.1%), back pain (11.4%), nausea (7.4%), bronchitis (7.4%), pain in extremity (7.4%), and arthralgia (7.4%). There were no cases of osteonecrosis of the jaw, delayed fracture healing or atypical femoral fractures. In conclusion, consistent with the results from the overall STAND study,¹ transitioning to DMAB after [ge] 5 years of continuous ALN treatment led to further significant gains in BMD at the lumbar spine, total hip, and femoral neck, and demonstrated a similar safety profile compared with those who continued on ALN.
1) Kendler DL et al., JBM 2010;25:72
Sources of Research Support: Amgen Inc.
Disclosures: HGB: Investigator, Amgen, Merck & Co., Nordic Bioscience; Advisory Group Member, Amgen, Merck & Co., Novartis Pharmaceuticals; Honoraria, Amgen, Merck & Co.; Speaker Bureau Member, Amgen. DLK: Investigator, Eli Lilly & Company, GlaxoSmithKline; Medical Advisory Board Member, Merck & Co.; Advisory Group Member, Novartis Pharmaceuticals, Amgen, Pfizer Global R&D; Coinvestigator, Roche Pharmaceuticals; Speaker, Aventis Pharmaceuticals. MAB: Speaker, Amgen, Astra Zeneca, Eli Lilly & Company, GlaxoSmithKline, Novartis Pharmaceuticals; Investigator, Amgen, Eli Lilly & Company, Merck & Co., Roche Pharmaceuticals, Proctor & Gamble, Takeda. MLB: Speaker, Amgen, Merck & Co., Servier, Warner Chilcott, GlaxoSmithKline, Eli Lilly & Company. MA: Employee, Amgen. AG: Employee, Amgen. CL: Employee, Amgen. Nothing to Disclose: AH, PO

sort_order 2874
Pub # S60-3
Session Information SYMPOSIUM SESSION: CLINICAL - Endocrine Clinical Trials in the Elderly (3:45 PM - 5:15 PM)
Title The Effects of Testosterone on Muscle Performance and Physical Function in Older Men with Mobility Limitation
Author String TG Travison, S Basaria, TW Storer, AM Jette, R Miciek, WR Farwell, NA Mazer, AD Coviello, PE Knapp, A-H Nguyen, L Collins, S Bhasin
Boston University School of Medicine, Boston, MA; VA Boston Healthcare System, Boston, MA; Boston University School of Public Health, Boston, MA; Hoffman LaRoche, Ltd, Basel, Switzerland
Body **Background.** Testosterone supplementation increases skeletal muscle mass, but its effects on muscle strength and physical function have been inconsistent across trials. Most testosterone trials have been conducted in healthy older men without functional limitations; the safety and efficacy of testosterone in improving muscle performance and physical function has not been demonstrated in older individuals with mobility limitation.
The Testosterone in Older Men with Mobility Limitations Trial determined the effects of testosterone on muscle performance and physical function in older men with mobility limitation. The trial's Data and Safety Monitoring Board recommended early trial cessation due to increased frequency of adverse events in the testosterone arm (1). The trial's efficacy data are reported here.
Methods. Men > 65 years, with mobility limitation, total testosterone 100-350ng/dL or free testosterone<50pg/mL, were randomized to placebo or 10-g testosterone gel daily for 6-months. Primary outcome was leg-press strength. Secondary outcomes included chest-press strength, stair-climb and 40-m walk, muscle mass, physical activity, self-reported function, and fatigue. Outcomes and proportions of subjects exceeding Minimal Clinically Important Difference (MCID) in study arms were compared.
Results. Of 209 randomized subjects, 165 had follow-up efficacy measures. Mean age was 74-years and mean short physical performance battery score 7.7. Leg-press strength improved significantly more in testosterone than in placebo arm (difference=132.7-Newtons(95% confidence interval 46.7,218.8) (p<0.004). Testosterone arm exhibited greater improvements in chest-press strength and power, and loaded stair-climb than placebo. Compared to placebo, significantly greater proportion of men receiving testosterone improved their leg-press strength (43%-vs-18%,P=0.01) and stair-climbing power (28-vs-10%,P=0.03) more than MCID. Increases in leg-press strength and stair-climbing power were associated with changes in testosterone levels and muscle mass. Physical activity, self-reported function, and fatigue did not change.
Conclusion. Testosterone administration in older men with mobility limitation was associated with clinically meaningful improvements in muscle strength and stair-climbing power. Improvements in muscle strength and only some physical function measures should be weighed against the risk of adverse events in this population.
Basaria et al., N Engl J Med 2010; 363:109.
Sources of Research Support: NIH Grant 1U01AG14369.
Nothing to Disclose: TGT, SB, TWS, AMJ, RM, WRF, NAM, ADC, PEK, A-HN, LC, SB

sort_order	2875
Pub #	S61-1
Session Information	SYMPOSIUM SESSION: CLINICAL - Hunting for Genes & Wild Goose Chases (3:45 PM - 5:15 PM)
Title	Whole Genome Sequencing for Endocrine Diseases: Promise & Pitfalls
Author String	DM Altshuler Massachusetts General Hospital, Boston, MA
Body	Nothing to Disclose: DMA

sort_order 2876
Pub # S61-2
Session Information SYMPOSIUM SESSION: CLINICAL - Hunting for Genes & Wild Goose Chases (3:45 PM - 5:15 PM)
Title From Genome-Wide Association Studies for Adiposity to New Insights in Biology
Author String RJF Loos
Institute of Metabolic Science, Cambridge, UK
Body Since 2007, genome-wide association studies (GWAS) have dramatically increased the pace of gene discovery for common obesity. So far, more than 50 genetic loci have been found to be robustly associated with obesity-related traits, including BMI and WHR. While these are easily-obtained obesity susceptibility measures, they do not allow distinguishing lean from fat mass. Therefore, using body fat percentage, a more accurate measure of body composition, may identify new loci more directly associated with adiposity.
In a recent large-scale genome-wide association meta-analysis of body fat percentage, including 36,626 individuals in the discovery stage and up to 39,576 individuals in the replication stage, association for three loci reached $P < 5 \times 10^{-8}$. One locus being the previously established *FTO* locus, and two new loci, i.e. one near *IRS1* and one near *SPRY2*. Both new loci harbour genes with a potential link to adipocyte physiology. *SPRY2* is a homolog of *SPRY1*, known to be a regulator of adipose tissue differentiation in mice. However, more intriguing is the locus near *IRS1*. This locus was previously found to be associated with type 2 diabetes and CVD, but opposite to what would be expected, the body-fat-lowering allele was associated with increased risk. Interestingly, the association with body fat percentage was significantly more pronounced in men than in women and this sexual dimorphism was also observed in follow-up analyses. More specifically, the body-fat-lowering allele was associated with an impaired metabolic profile, including increased insulin resistance, increased triglyceride levels and decreased HDL-cholesterol and adiponectin levels. Furthermore, carriers of the body-fat-lowering allele had less subcutaneous fat, but not visceral fat, at least in men. This observation suggests that the near-*IRS1* locus might affect the ability of subcutaneous adipose tissue to expand, leading to ectopic lipid deposition. The mechanistic basis for the sexual dimorphism remains elusive, but might be due to the fact that men have on average less fat mass and a lower *IRS1* expression than women, which may make them more vulnerable for the effects of the near-*IRS1* locus. Although the locus maps 500kb upstream of *IRS1*, the body-fat-lowering allele shows decreased *IRS1* expression.
Taken together, this GWAS of body fat percentage identified loci that were not discovered in previous GWAS of BMI, WHR or obesity and provide new insights into adiposity and insulin resistance.
Nothing to Disclose: RJFL

sort_order 2877
Pub # S61-3
Session Information SYMPOSIUM SESSION: CLINICAL - Hunting for Genes & Wild Goose Chases (3:45 PM - 5:15 PM)
Title Expanding the Phenotypes of Genetic Endocrine Diseases
Author String BB Mendonca
University Sao Paulo Faculdade de Medicina, Sao Paulo, Brazil
Body
Advances in molecular biology techniques have allowed the etiological clarification of several genetic endocrine diseases. 21-hydroxylase deficiency is a common genetic disorder caused by mutations in *CYP21A2* encoding the adrenal 21-hydroxylase, microsomal P450c21, which correlate well with impaired P450c21 enzymatic activity and clinical presentation, but genotype and phenotype discrepancies can occur. Indeed, children with severe *CYP21A2* mutations and residual 21-hydroxylase activity have been reported, and the mineralocorticoid deficiency in some salt-wasting patients can be ameliorated by hepatic P450 21-hydroxylation of progesterone. The discovery of mutations in P450 oxidoreductase (POR), the protein that transfers electrons from reduced NADPH to all microsomal P450s, elucidated the molecular basis of some CAH cases with biochemical changes similar to those determined by *CYP21A2* mutations. The phenotypic spectrum of POR mutations is broad, ranging from ambiguous genitalia in both sexes, associated or not to skeletal malformations, to primary amenorrhea. Lipoid CAH has been associated with defects in two different genes: *STAR*, encoding the steroidogenic acute regulatory protein, and *CYP11A1*, encoding the cholesterol side-chain cleavage enzyme (P450scc). Severe loss-of-function mutations in both genes are associated with prematurity, complete underandrogenization, and early-onset adrenal failure (complete form). Partial lipoid CAH is a recently recognized disorder caused by mutations that result in partially functioning proteins, conferring a phenotype of mild undervirilization in boys and later-onset adrenal failure. More recently, genome-wide linkage analysis identified mutations in *STAR* in association with a phenotype resembling familial glucocorticoid deficiency (FGD). Therefore, it now seems that certain *STAR* mutations may masquerade as familial glucocorticoid deficiency and be responsible for a subset of unexplained FGD cases. Steroidogenic factor-1 (SF1, encoded by *NR5A1*) is an important mediator of adrenal and reproductive function in humans. Mutations in *NR5A1* have now been reported in association with a wide range of human disorders - from adrenal insufficiency associated to disorder of sex development in 46,XY patients to male infertility or primary ovarian insufficiency. In conclusion, the variety of phenotypes associated with mutations in genes involved in endocrine development and function has increasingly expanded in recent years.

Bachega TA et al 1998; J Clin Endocrinol Metab.
Gomes LG et al, 2009; J Clin Endocrinol Metab 94(1):89-95
Miller W et al.,2011; Endocrine Rev 32.
Ferraz-de-Souza B et al., 2010; Mol Cell Endocrinol

Nothing to Disclose: BBM

sort_order 2878
Pub # L6-1
Session Information PLENARY: TRANSLATIONAL - Genetic Variation of the Androgen Receptor: From Gene Regulation to Prostate Cancer (5:30 PM - 6:30 PM)
Title Genetic Variation of the Androgen Receptor: From Gene Regulation to Prostate Cancer
Author String DM Robins
University of Michigan Medical School, Ann Arbor, MI
Body The androgen receptor (AR) regulates gene expression programs central to male differentiation and androgen-dependent disease. Particularly in the prostate, AR orchestrates normal development as well as cancer ontogeny and progression. Because of AR's key role in prostate cancer, the AR gene has been scrutinized for germline polymorphisms and somatic mutations associated with disease. While genetic variations are found, their impact is controversial. To assess the functional significance of AR genetic variation, we converted the mouse gene to the human sequence by germline recombination and engineered an allelic series to probe the role of an AR polymorphic glutamine (Q) tract implicated in cancer risk. In these humanized AR mice, Q tract length subtly influences systemic strength of the androgen axis. Compounded with a prostate-targeted oncogene, AR Q tract length affects tumor progression and response to castration. Mutation profiling of these tumors offers experimental evidence that somatic AR variants are selected by treatment. This finding is validated in metastases from patients stratified by therapy. In both mouse and human tumors, numerous diverse mutations occur at low frequency. Cell-based assays reveal that mutant ARs exploit multiple mechanisms to resist androgen deprivation, including alterations in ligand specificity, target gene selectivity, and chaperone interaction. Thus certain AR mutations may be ["drivers"] that provide a growth advantage to subpopulations of cells in a continually evolving tumor environment. Notably, many of the mutations occur in AR's N-terminal domain and thereby influence ligand-independent as well as -dependent actions. Mechanisms utilized by these genetic variants permute normal AR functions and suggest novel approaches to target pathological activity of wild type AR, and its interacting partners, to avoid treatment resistance.

Session supported by: Lilly USA, LLC

Sources of Research Support: NIH (RO1-DK56356, P50-CA69568, RO1-CA144032); DOD (DAMD17-02-1-0099, W81XWH-08-1-0034); Core Services of UM Cancer Center (P30-CA46592) and Michigan Diabetes Research and Training Center (P60-DK20572).

Nothing to Disclose: DMR

sort_order 2879
Pub # L6-2
Session Information PLENARY: TRANSLATIONAL - Recent Findings from the Women's Health Initiative Hormone Therapy Trials: Do They Inform Clinical Decision Making? (5:30 PM - 6:30 PM)
Title Recent Findings from the Women's Health Initiative Hormone Therapy Trials: Do They Inform Clinical Decision Making?
Author String JE Manson
Brigham & Women's Hospital/Harvard Medical School, Boston, MA
Body Recent findings from the Women's Health Initiative (WHI) Hormone Therapy (HT) Trials highlight striking differences between the effects of estrogen plus progestin (E+P) and estrogen-alone (E-alone) on cancer and other chronic disease outcomes. Based on continued follow-up post-intervention, adverse effects of E+P on breast cancer incidence and mortality, as well as lung cancer mortality, heart disease and total mortality, have emerged for E-alone but are less apparent for E+P. These findings, together with other research, support the need to consider whether separate clinical practice guidelines should be developed for the two HT regimens. In addition, emerging evidence suggests that lower doses of hormones and the transdermal route of delivery may be associated with lower risks of venous thromboembolism and stroke, than conventional regimens. Recent studies also provide further support for the [critical window] hypothesis for coronary heart disease, with a benefit of estrogen in relation to atherosclerosis when started in proximity to the menopause transition but increasing risk of plaque rupture once advanced plaques are present. Given the large volume of new data on HT in recent years, a critical reappraisal of the evidence is needed to address pressing clinical questions including: (a) should HT ever be initiated in asymptomatic women or for any purpose other than management of menopausal symptoms?, and (b) should HT ever be continued for reasons other than symptom management and, if so, when should it be stopped? Recent evidence suggests that the answers to these questions may differ for the two HT regimens. The increase in CVD events seen during the first 1-2 years of the E+P trial, together with the increase in incidence or mortality of several forms of cancer (breast, lung, ovary) with E+P would argue for a [no] answer to both questions for E+P. However, the more favorable coronary outcomes with E-alone than with E+P, especially in younger women, absence of an increased risk of breast or lung cancer with E-alone, comparable bone health benefits, and emerging evidence for reduction in all-cause mortality among younger women, may support a reappraisal of clinical practice and duration-of-use guidelines for E-alone among women with hysterectomy.

Nothing to Disclose: JEM

sort_order	2880
Pub #	CMF9-1
Session Information	CASE MANAGEMENT FORUM: CLINICAL - Endocrine Management of the Bariatric Patient (5:30 PM - 6:15 PM)
Title	Endocrine Management of the Bariatric Patient
Author String	CM Apovian Boston Medical Center, Boston, MA
Body	Session supported by: Allergan, Inc. Disclosures: CMA: Advisory Group Member, Amylin Pharmaceuticals, Johnson & Johnson, Pfizer, Inc., Abbott Laboratories, Allergan, Orexigen; Principal Investigator, Atkins Foundation, Metaproteomics, Amylin Pharmaceuticals.

sort_order 2881
Pub # CMF9-2
Session Information CASE MANAGEMENT FORUM: CLINICAL - Endocrine Management of the Bariatric Patient (5:30 PM - 6:15 PM)
Title Endocrine Management of the Bariatric Patient
Author String LM Kaplan
Massachusetts General Hospital, Boston, MA
Body Session supported by: Allergan, Inc.

Disclosures: LMK: Consultant, Amylin Pharmaceuticals, Medtronic Minimed, Allergan; Principal Investigator, Johnson & Johnson, Merck & Co.; Scientific Board Member, Rhythm Pharmaceuticals, GI Dynamics, Gelesis.

sort_order	2882
Pub #	CMF10-1
Session Information	CASE MANAGEMENT FORUM: CLINICAL - Management of Opiate-Induced Neuroendocrine Dysfunction (5:30 PM - 6:15 PM)
Title	Management of Opiate-Induced Neuroendocrine Dysfunction
Author String	JA Wass Churchill Hospital, Oxon, UK
Body	Nothing to Disclose: JAW

sort_order	2883
Pub #	CMF10-2
Session Information	CASE MANAGEMENT FORUM: CLINICAL - Management of Opiate-Induced Neuroendocrine Dysfunction (5:30 PM - 6:15 PM)
Title	Management of Opiate-Induced Neuroendocrine Dysfunction
Author String	K Ho Princess Alexandra Hospital, Queensland, Australia
Body	Nothing to Disclose: KH

sort_order	2884
Pub #	CMF11-1
Session Information	CASE MANAGEMENT FORUM: CLINICAL - Management of Thyroid Disease during Pregnancy (5:30 PM - 6:15 PM)
Title	Management of Thyroid Disease during Pregnancy
Author String	EK Alexander Brigham & Women's Hospital, Boston, MA
Body	Nothing to Disclose: EKA

sort_order	2885
Pub #	CMF11-2
Session Information	CASE MANAGEMENT FORUM: CLINICAL - Management of Thyroid Disease during Pregnancy (5:30 PM - 6:15 PM)
Title	Management of Thyroid Disease during Pregnancy
Author String	EN Pearce Boston University Medical Center, Boston, MA
Body	Nothing to Disclose: ENP

sort_order	2886
Pub #	CMF12-1
Session Information	CASE MANAGEMENT FORUM: CLINICAL - Primary Hyperaldosteronism (5:30 PM - 6:15 PM)
Title	Primary Hyperaldosteronism
Author String	RJ Auchus University of Texas Southwestern Medical Center, Dallas, TX
Body	Nothing to Disclose: RJA

sort_order	2887
Pub #	CMF12-2
Session Information	CASE MANAGEMENT FORUM: CLINICAL - Primary Hyperaldosteronism (5:30 PM - 6:15 PM)
Title	Primary Hyperaldosteronism
Author String	JW Findling Medical College of Wisconsin, Milwaukee, WI
Body	Nothing to Disclose: JWF

sort_order	2888
Pub #	M35
Session Information	MEET-THE-PROFESSOR: CLINICAL - Controversies in the Diagnosis of Diabetes Mellitus (5:30 PM - 6:15 PM)
Title	Controversies in the Diagnosis of Diabetes Mellitus
Author String	K Osei Ohio State University Medical Center, Columbus, OH
Body	Session supported by: Merck & Co., Inc. Nothing to Disclose: KO

sort_order	2889
Pub #	M36
Session Information	MEET-THE-PROFESSOR: CLINICAL - Diagnosis & Management of Male Hypogonadism in the Older Man (5:30 PM - 6:15 PM)
Title	Diagnosis & Management of Male Hypogonadism in the Older Man
Author String	FJ Hayes Saint Vincent's University Hospital, Dublin, Ireland
Body	Nothing to Disclose: FJH

sort_order	2890
Pub #	M37
Session Information	MEET-THE-PROFESSOR: CLINICAL - Investigation & Management of Hypocalcemia (5:30 PM - 6:15 PM)
Title	Investigation & Management of Hypocalcemia
Author String	MA Levine Children's Hospital of Philadelphia, Philadelphia, PA
Body	Nothing to Disclose: MAL

sort_order	2891
Pub #	M38
Session Information	MEET-THE-PROFESSOR: CLINICAL - Management of Gender-Variant Youth (5:30 PM - 6:15 PM)
Title	Management of Gender-Variant Youth
Author String	NP Spack Children's Hospital Boston, Boston, MA
Body	Nothing to Disclose: NPS

sort_order	2892
Pub #	M39
Session Information	MEET-THE-PROFESSOR: CLINICAL - Pediatric Thyroid Nodules & Cancer (5:30 PM - 6:15 PM)
Title	Pediatric Thyroid Nodules & Cancer
Author String	AJ Bauer Walter Reed Army Medical Center, Rockville, MD
Body	Nothing to Disclose: AJB

sort_order	2893
Pub #	
Session Information	CMES SYMPOSIA: Cushing's Syndrome: Case-Based Discussions (6:30 PM - 9:30 PM)
Title	Cushing's Syndrome: Case-Based Discussions
Author String	
Body	Corcept Therapeutics

sort_order	2894
Pub #	
Session Information	CONFERENCE EVENT: Career Development Workshop: How To Write a Successful Career Development Award Application (7:00 PM - 9:00 PM)
Title	Career Development Workshop: How To Write a Successful Career Development Award Application
Author String	
Body	Registration and fee required. Co-Sponsored by the Association for Patient-Oriented Research and The Endocrine Society

sort_order	2895
Pub #	CDW7-1
Session Information	CAREER DEVELOPMENT WORKSHOP: Career Development Workshop: How To Write a Successful Career Development Award Application (7:00 PM - 9:00 PM)
Title	How To Write a Successful Career Development Award Application
Author String	DM Shoback University of California San Francisco/Veterans Affairs Medical Center, San Francisco, CA
Body	Disclosure Incomplete: DMS

sort_order	2896
Pub #	CDW7-2
Session Information	CAREER DEVELOPMENT WORKSHOP: Career Development Workshop: How To Write a Successful Career Development Award Application (7:00 PM - 9:00 PM)
Title	How To Write a Successful Career Development Award Application
Author String	JY Wu Massachusetts General Hospital, Boston, MA
Body	Disclosure Incomplete: JYW

sort_order	2897
Pub #	CDW7-3
Session Information	CAREER DEVELOPMENT WORKSHOP: Career Development Workshop: How To Write a Successful Career Development Award Application (7:00 PM - 9:00 PM)
Title	How to Write A Successful Career Development Award Application
Author String	Williams BRIGHAM & WOMEN'S HOSP, Boston, MA
Body	

sort_order	2898
Pub #	CDW7-4
Session Information	CAREER DEVELOPMENT WORKSHOP: Career Development Workshop: How To Write a Successful Career Development Award Application (7:00 PM - 9:00 PM)
Title	How To Write a Successful Career Development Award Application
Author String	MC Gelato State University of New York Health Science Center, Stony Brook, Stony Brook, NY
Body	Disclosure Incomplete: MCG

sort_order	2899
Pub #	L7-1
Session Information	PLENARY: TRANSLATIONAL - Roy O Greep Award Lecture: Epigenetics & Metabolism: The Circadian Link (8:00 AM - 9:15 AM)
Title	Roy O Greep Award Lecture: Epigenetics & Metabolism: The Circadian Link
Author String	P Sassone-Corsi University of California, Irvine, CA
Body	Nothing to Disclose: PS-C

sort_order	2900
Pub #	L7-2
Session Information	PLENARY: TRANSLATIONAL - Developmental Critical Periods & Hormonal Specification of Hypothalamic Neural Circuits (8:00 AM - 9:15 AM)
Title	Developmental Critical Periods & Hormonal Specification of Hypothalamic Neural Circuits
Author String	RB Simerly University of Southern California, Los Angeles, CA
Body	Disclosure Incomplete: RBS

sort_order	2901
Pub #	CMF13-1
Session Information	CASE MANAGEMENT FORUM: CLINICAL - Management of Subclinical Hyperthyroidism (8:30 AM - 9:15 AM)
Title	Management of Subclinical Hyperthyroidism
Author String	KD Burman Washington Hospital Center, Kensington, MD
Body	Disclosures: KDB: Consultant, Up To Date; Investigator, Exelixis, Inc., Amgen, Pfizer, Inc.

sort_order	2902
Pub #	CMF13-2
Session Information	CASE MANAGEMENT FORUM: CLINICAL - Management of Subclinical Hyperthyroidism (8:30 AM - 9:15 AM)
Title	Management of Subclinical Hyperthyroidism
Author String	GA Brent Veterans Affairs Greater Los Angeles Healthcare, Los Angeles, CA
Body	Nothing to Disclose: GAB

sort_order	2903
Pub #	CMF14-1
Session Information	CASE MANAGEMENT FORUM: CLINICAL - Medical Therapy of Cushing Disease: Safety & Efficacy (8:30 AM - 9:15 AM)
Title	Medical Therapy of Cushing Disease: Safety & Efficacy
Author String	XY Bertagna Hospital Cochin, Paris, France
Body	Session supported by: Corcept Therapeutics Nothing to Disclose: XYB

sort_order 2904
Pub # CMF14-2
Session Information CASE MANAGEMENT FORUM: CLINICAL - Medical Therapy of Cushing Disease: Safety & Efficacy (8:30 AM - 9:15 AM)
Title Medical Therapy of Cushing Disease: Safety & Efficacy
Author String LK Nieman
National Institute of Child Health and Human Development/National Institutes of Health, Bethesda, MD
Body Session supported by: Corcept Therapeutics
Disclosure Incomplete: LKN

sort_order	2905
Pub #	M40
Session Information	MEET-THE-PROFESSOR: CLINICAL - Clinical Management of Adrenocortical Carcinoma (8:30 AM - 9:15 AM)
Title	Clinical Management of Adrenocortical Carcinoma
Author String	MA Habra University of Texas MD Anderson Cancer Center, Houston, TX
Body	Session supported by: Corcept Therapeutics Nothing to Disclose: MAH

sort_order 2906
Pub # M41
Session Information MEET-THE-PROFESSOR: CLINICAL - Continuous Glucose Monitoring & Its Role in Diabetes Management (8:30 AM - 9:15 AM)
Title Continuous Glucose Monitoring & Its Role in Diabetes Management
Author String DL Trence
University of Washington Medical Center, Seattle, WA
Body Session supported by: Medtronic Diabetes

Disclosures: DLT: Stock Owner, Medtronic Minimed; Principal Investigator, Novo Nordisk.

sort_order	2907
Pub #	M42
Session Information	MEET-THE-PROFESSOR: CLINICAL - Key Issues in Managing the Perimenopause (8:30 AM - 9:15 AM)
Title	Key Issues in Managing the Perimenopause
Author String	MI Cedars University of California, San Francisco, CA
Body	Nothing to Disclose: MIC

sort_order	2908
Pub #	M43
Session Information	MEET-THE-PROFESSOR: CLINICAL - Klinefelter Syndrome from Cradle through Adolescence (8:30 AM - 9:15 AM)
Title	Klinefelter Syndrome from Cradle through Adolescence
Author String	I Fennoy Columbia University College of Physicians & Surgeons, New York, NY
Body	Nothing to Disclose: IF

sort_order	2909
Pub #	M45
Session Information	MEET-THE-PROFESSOR: CLINICAL - Renal Bone Disease for the Endocrinologist (8:30 AM - 9:15 AM)
Title	Renal Bone Disease for the Endocrinologist
Author String	MS Cooper University of Birmingham, Birmingham, UK
Body	Nothing to Disclose: MSC

sort_order	2910
Pub #	M46
Session Information	MEET-THE-PROFESSOR: CLINICAL - Who Needs MODY Screening? (8:30 AM - 9:15 AM)
Title	Who Needs MODY Screening?
Author String	L Philipson University of Chicago, Chicago, IL
Body	Disclosure Incomplete: LP

sort_order	2911
Pub #	M44
Session Information	MEET-THE-PROFESSOR: CLINICAL - Management of the Abnormal C's: Coronary Calcium Scores, CIMT, CRP & Other Cryptic Markers of Coronary Artery Disease (8:30 AM - 9:15 AM)
Title	Management of the Abnormal C's: Coronary Calcium Scores, CIMT, CRP & Other Cryptic Markers of Coronary Artery Disease
Author String	A Chait University of Washington, Seattle, WA
Body	Disclosure Incomplete: AC

sort_order 2912
Pub # S66-1
Session Information SYMPOSIUM SESSION: TRANSLATIONAL - How Does Growth Hormone Signal? (9:30 AM - 11:00 AM)
Title Genomic & Epigenetic Approaches to Unraveling the Complexity of Growth Hormone-Regulated Liver Sex Differences
Author String DJ Waxman
Boston University, Boston, MA

Body Global expression profiles have identified >1,000 genes that are sex-differentially expressed in mouse and rat liver and impact numerous physiological and pathophysiological processes. These genes are regulated by sex-dependent plasma GH patterns, with male-specific genes suppressed and female-specific genes induced in livers of male mice given GH by continuous infusion (female-like GH profile) (1). Mouse knockout studies have identified the GH-activated transcription factor STAT5b and the liver-enriched transcription factor HNF4A as essential for liver sex differences, however, the precise mechanisms through which these factors regulate liver sexual dimorphism have remained elusive. Our recent findings evidence dynamic, sex-dependent STAT5 binding to liver chromatin in vivo in direct response to each plasma GH pulse, while GH time course studies reveal an unanticipated complexity in the sex-dependent responses to GH. Major advances have been made with our development and analysis of detailed, high quality global DNase hypersensitivity (DHS) maps for mouse liver (2). The ~71,000 DHS sites identified encompass a large fraction (up to 93%) of binding sites identified by ChIP-seq for nine liver-expressed transcription factors, consistent with their being functionally important for liver gene expression. 1,284 of the liver DHS sites show significant sex differences; moreover, continuous GH infusion suppressed ~98% of the male-specific DHS sites while inducing a subset (44%) of female-specific DHS sites in male liver. There was a strong association of sex-specific DHS sites with sex-specific transcription; however, a majority of sex-specific DHS sites were distant (>100 kb) from sex-specific genes. By analyzing the enrichment of sequence motifs within sex-dependent and GH-regulated DHS sites, we identified STAT5 and HNF4A, both known to be required for liver sexual dimorphism, in addition to several novel candidates for investigation. Further details about one of these candidates, CUX2, will be presented along with related findings. The liver DHS maps obtained are expected to serve as a valuable resource for elucidation of transcriptional networks controlling a wide range of biological processes. This approach can readily be applied to mapping condition-specific regulatory sites in mammalian cells and tissues under a wide variety of physiological and pathophysiological conditions.

Session supported by: Novo Nordisk Inc. & Pfizer, Inc.

(1) Sex differences in the expression of hepatic drug metabolizing enzymes. Waxman DJ, Holloway MG. *Mol Pharmacol*. 2009 Aug;76(2):215-228.

(2) Unbiased, genome-wide in vivo mapping of transcriptional regulatory elements reveals sex differences in chromatin structure associated with sex-specific liver gene expression. Ling G, Sugathan A, Mazor T, Fraenkel E, Waxman DJ. *Mol Cell Biol*. 2010 Dec;30(23):5531-5544.

Sources of Research Support: NIH grant DK33765.

Nothing to Disclose: DJW

sort_order 2913
Pub # S66-2
Session Information SYMPOSIUM SESSION: TRANSLATIONAL - How Does Growth Hormone Signal? (9:30 AM - 11:00 AM)
Title Growth Hormone Signaling to the Nucleus: Multiple Players in the Transcriptional Repertoire
Author String J Schwartz
University of Michigan Medical School, Ann Arbor, MI
Body Physiological responses to Growth Hormone (GH) are often mediated by changes in the expression of genes in target cells. In adipocytes, GH target cells which are central in metabolic regulation, a gene profile identified over 500 GH-responsive genes regulated in distinct temporal patterns following GH treatment. The transcription factor C/EBP beta, which mediates c-Fos activation by GH, also mediates the induction of multiple other early response genes by GH, by mechanisms involving phosphorylated C/EBP beta and coactivator recruitment. These findings suggest that C/EBP beta, like Stat5, is a transcription factor mediating the activation of multiple genes in response to GH. Computational analysis of the GH-regulated gene profile also identified the gene encoding a transcriptional repressor, B-cell lymphoma 6 (Bcl6), as the most highly repressed gene. Not only was Bcl6 inhibited by GH in vitro and in vivo, but Bcl6 was found to repress Socs2-luciferase and to interfere with its activation by GH. On the GH-regulated sequence of Socs2, endogenous Bcl6 was found by chromatin immunoprecipitation (ChIP) to occupy Socs2 in the absence of GH, and Bcl6 occupancy decreased upon GH treatment. Conversely, occupancy of Stat5, an activator of Socs2, increased in response to GH as Bcl6 decreased. Bcl6 and Stat5 may thus play reciprocal roles in regulating Socs2 in response to GH. Genome-wide analysis by ChIP-Sequencing suggests that a mechanism involving reciprocal occupancy by Bcl6 and Stat5 contributes to regulating multiple GH target genes. Dissection of GH-regulated transcriptional regulatory mechanisms expands our understanding of GH signaling to the nucleus, and the repertoire of positive and negative factors that regulate genes mediating the diverse responses to GH.

Session supported by: Novo Nordisk Inc. & Pfizer, Inc.

Coauthors:
Grace Lin, Christopher R. LaPensee, Tracy X. Cui, Jeffrey S. Huo, Teresa I. Cesena, Graciela Piwien-Pilipuk. Dept of Molecular & Integrative Physiology, Program in Cellular & Molecular Biology, University of Michigan, Ann Arbor MI.

Nothing to Disclose: JS

sort_order 2914
Pub # S66-3
Session Information SYMPOSIUM SESSION: TRANSLATIONAL - How Does Growth Hormone Signal? (9:30 AM - 11:00 AM)
Title Growth Hormone Receptor Activation
Author String MJ Waters
University of Queensland, Brisbane, Australia
Body Growth hormone regulates a multitude of processes through its single pass transmembrane (TM) receptor. The receptor exists as a constitutive dimer, held together largely by its TM helices, so that receptor activation results from hormone-induced rearrangement of the two receptor subunits. Constitutive dimerisation is supported by FRET, BRET and CoIP data, as well as ToxR studies in bacterial membranes and cysteine crosslinking data. Because GH possesses two asymmetrically placed receptor binding sites, its binding rotates the extracellular domain and lifts the first receptor to facilitate locking together of the two receptors through the lower fibronectin domain, bringing the two receptors close together at the upper membrane boundary. FRET reporters placed below the TM domain where the JAK2 kinase binds (Box1) surprisingly reveal an opening/separation movement upon receptor activation by a variety of constitutively activating mutations. This could lead to activation of receptor-bound JAK2 if the opening movement slides the pseudokinase inhibitory domain of one JAK2 away from the catalytic domain of the other JAK2. Mutations to Box1 prevent JAK2 activation in vitro and in vivo, and while in vivo mutation results in inability of JAK2 to activate STAT5a/b and dwarfism, it is still possible to activate hepatic ERK and Src with GH administration (1). This is associated with a set of Src-regulated hepatic transcripts different from JAK2 regulated hepatic transcripts in mouse receptor mutants (2). In FDCP1 cells, mutation of Box1 also allows ERK activation while preventing JAK2/STAT5 activation, and siRNA knockdown of Src family kinase Lyn blocked ERK activation by GH, so we can conclude that the GH receptor can use a Src family kinase independently of JAK2. Src/ERK activation requires an intact FG' loop in the lower extracellular fibronectin domain, and this loop differs in its disposition between agonist and antagonist bound forms of the crystal structure of the extracellular domain. It appears that movement of this loop is part of the Src activation process independently of JAK2 activation.
In conclusion, it is now clear that the GH receptor is not activated by hormone-dependent dimerisation, and that there are subtleties in its activation process. How signalling from cell surface coordinates with the function of nuclear-localised GH receptor is an interesting question which remains to be elucidated.

Session supported by: Novo Nordisk Inc. & Pfizer, Inc.
(1) Rowlinson SW et al., Nature Cell Biol 2008; 10:740-47
(2) Barclay JL et al., Mol Endocrinol 2009;24:204-17

Sources of Research Support: NHMRC (Australia) Grants to MJW.

Nothing to Disclose: MJW

sort_order

2915

Pub #

S71-1

Session Information

SYMPOSIUM SESSION: CLINICAL - Management of Congenital Adrenal Hyperplasia: Beyond Childhood (9:30 AM - 11:00 AM)

Title

Management of Congenital Adrenal Hyperplasia in Adulthood

Author String

DP Merke

National Institute of Child Health & Human Development/National Institutes of Health, Bethesda, MD

Body

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is characterized by impairment of cortisol biosynthesis and androgen excess, with or without aldosterone deficiency. CAH shows a wide range of clinical severity with various treatment approaches. Treatment of the classic form is aimed at replacing cortisol and aldosterone and effectively controlling excess androgen by using the lowest possible glucocorticoid dose. Treatment of the nonclassic form is targeted at controlling excess androgen symptoms and may or may not involve glucocorticoid therapy. Hydrocortisone is the treatment of choice for children, but there is no consensus on how patients should be treated as adults. Current glucocorticoid therapy is suboptimal because it is often difficult to reduce excess androgen without giving excess glucocorticoid, and patients may experience hypercortisolism, androgen excess, or a combination of these states. Treatment of CAH, especially in the adult patient, remains controversial given the lack of prospective randomized controlled trials comparing treatment regimens. Moreover, CAH is a chronic disease and health priorities change throughout the lifecycle. Management of CAH in adulthood will be discussed prioritizing avoidance of Cushingoid side effects and optimization of reproductive, sexual, and bone health.

Nothing to Disclose: DPM

sort_order	2916
Pub #	S71-2
Session Information	SYMPOSIUM SESSION: CLINICAL - Management of Congenital Adrenal Hyperplasia: Beyond Childhood (9:30 AM - 11:00 AM)
Title	The 17-alpha & 11-beta Hydroxylase Deficiency Forms of Congenital Adrenal Hyperplasia
Author String	CE Kater Federal University of Sao Paulo, Sao Paulo, Brazil
Body	Nothing to Disclose: CEK

sort_order

2917

Pub #

S71-3

Session Information

SYMPOSIUM SESSION: CLINICAL - Management of Congenital Adrenal Hyperplasia: Beyond Childhood (9:30 AM - 11:00 AM)

Title

Management of Congenital Adrenal Hyperplasia during Pregnancy: Optimizing Outcomes

Author String

SF Witchel
Children's Hospital of Pittsburgh/University of Pittsburgh, Pittsburgh, PA

Body

Fertility in women with congenital adrenal hyperplasia (CAH) and, especially women with classical salt-losing CAH, is deemed to be reduced. Ovulatory dysfunction, local endometrial consequences of excessive progestin exposure, dyspareunia, genital anomalies, poor self-esteem, limited relationships, and/or other psychosocial factors contribute to this situation. Yet, a recent report indicated a near normal conception rate in women with classic CAH who actively tried to conceive and highlighted the importance of adequate control of androgen and progestin levels to increase fertility (1). Prior to conception, optimization of hormone replacement therapy, attention to anatomic concerns, and genetic counseling including *CYP21* genotype analyses for both parents should be addressed (2). For the couple at risk for conceiving a child with classical CAH, a pre-conception conversation to review: a) the reported potential efficacy of prenatal dexamethasone treatment to decrease virilization of affected female infants and b) the available data regarding the safety and experimental nature of this treatment is appropriate (3). This conversation can include discussion of studies demonstrating deleterious long term consequences of prenatal dexamethasone on the infant (4). Next, ovulation induction agents, enhanced glucocorticoid suppression, and in vitro fertilization can be reviewed. Assessment of the male partner and other anatomic or reproductive factors can be undertaken. Once conception has been achieved, individualized optimization of glucocorticoid and mineralocorticoid replacement regimens is critical. Glucocorticoids that cross the placenta should be avoided in women with CAH (3). These patients may also have a higher risk for gestational diabetes, pregnancy-induced hypertension, intra-uterine fetal demise, and other antepartum complications. Anticipatory guidance should be offered regarding need for stress glucocorticoid doses during delivery and likely need for delivery by Caesarian section for women who have undergone feminizing genitoplasty. Overall, the management of conception, pregnancy, and delivery of women with CAH or at risk for a child with CAH involves an interdisciplinary team approach involving endocrinologists, obstetricians, and geneticists focusing on preconception counseling and optimal management during pregnancy labor, and delivery. With appropriate, careful, and individualized management, a positive outcome can be expected.

1. Caster[agrave]s A, et al., Clin Endocrinol(Oxf)2009;70:833
2. Moran et al., J Clin Endocrinol Metab 2006;91:3451
3. Speiser PW, et al., J Clin Endocrinol Metab 2010;95:4133
4. Fukumoto K, et al., Mol Psychiatry 2009;14:1119

Nothing to Disclose: SFW

sort_order 2918
Pub # S62-1
Session Information SYMPOSIUM SESSION: BASIC - New Dimensions in Oocyte & Sperm Maturation (9:30 AM-11:00 AM)
Title The Molecular Control of Oocyte Maturation: A 2011 Perspective
Author String M Conti
University of California, San Francisco, CA
Body Mammalian oocytes remain in a suspended state of the meiotic cell cycle that, in women, can last more than forty years. The transition from meiotic prophase to metaphase is induced by the LH surge and thus depends on signals originating from the somatic cells that surround the oocyte. Although some of the basic concepts on the mechanisms maintaining the meiotic arrest and induction of maturation were proposed several decades ago, only recently have we gained an understanding of the process at the molecular level. High levels of cAMP are required to maintain meiotic arrest in mammalian oocytes. Contrary to common belief, recent data have shown that the oocyte itself produces cAMP sufficient to maintain this arrest. The components of cyclic nucleotide signaling expressed in the oocyte have been identified and their function defined genetically in the mouse. Critical for the control of cAMP levels in the oocyte is a cyclic nucleotide phosphodiesterase termed PDE3A. The same enzyme is functioning in frog, rodents, and primates including human oocytes. Oocytes defective in this enzymatic function are unable to reenter meiosis. These data have led to the hypothesis that resumption of meiosis is mediated by signals that activate PDE3A. In spite of early observations implicating other cyclic nucleotides, only very recent data show that this signal is likely cGMP. Cyclic GMP is a competitive inhibitor of PDE3A, accumulates at high levels in oocytes arrested in prophase, and decreases prior to maturation. The current hypothesis is that cGMP is generated by granulosa cells and diffuses to the oocyte through gap junctions. The generation of cGMP in granulosa cells depends on an autocrine/paracrine loop involving a natriuretic peptide and the cognate receptor NPR2. The LH surge produces a dramatic decrease in cGMP and at the same time closure of the gap junctions between granulosa cells. Complex intracellular pathways and extracellular paracrine loops involving EGF-like growth factors are required for LH to induce a decrease of both cGMP and the permeability of gap junctions. Although the above data account for most mechanisms leading to oocyte maturation, it remains to be determined if identical circuits are active in other species including humans. Understanding this physiological process at a molecular level opens new opportunities for treatment of infertility and for contraception.

Sources of Research Support: NIH RO1GM080527 and NIHRO1HD052909.

Nothing to Disclose: MC

sort_order 2919
Pub # S62-2
Session Information SYMPOSIUM SESSION: BASIC - New Dimensions in Oocyte & Sperm Maturation (9:30 AM-11:00 AM)
Title From Ovulation to Ovarian Cancer
Author String JS Richards
Baylor College of Medicine, Houston, TX
Body Ovulation is initiated by the surge of luteinizing hormone (LH) that activates multiple signaling cascades. Activation of protein kinase A rapidly induces expression of the EGF-like factors amphiregulin (AREG), epiregulin (EREG) and betacellulin (BTC). These factors activate the EGF receptor, RAS, MEK1 ERK1/2 cascade in a rapid but transient manner. These events induce marked changes in the gene expression profiles in granulosa cells and cumulus cell-oocyte complexes (COCs) that mediate ovulation. In addition, granulosa cells become terminally differentiated, non-dividing luteal cells. To determine if activation of RAS at an earlier stage of follicular development would alter granulosa cell fate or the expression of specific genes, a dominant stable form of KRAS (KRASG12D) was introduced using specific mouse Cre-lox strains. In the KrasG12D mutant mice, follicular development was derailed at an early stage. Granulosa cells ceased dividing, were non-apoptotic and failed to differentiate. As a consequence, abnormal follicle-like structures devoid of oocytes accumulated in the ovary. Because the abnormal granulosa cells expressed high levels of the tumor suppressor PTEN, we sought to disrupt the Pten gene in mice expressing KrasG12D to restore normal follicle development. When the Kras/Pten double mutant mice were generated with Amhr2-Cre mice, abnormal follicles persisted but ovarian surface epithelial (OSE) cells in the same ovaries transformed and became low grade, invasive serous adenocarcinomas at an early age and with 100% penetrance. No OSE transformation occurred when the double mutant mice were generated with the Cyp19-Cre mice where Cre recombinase is expressed exclusively to granulosa cells. Gene expression profiles indicate that the transformed OSE cells express an altered genetic program. The Kras/Pten/Amhr2Cre mice provide the first in vivo model of this ovarian cancer subtype in women. Collectively, these results indicate that granulosa cells and OSE cells respond to the same oncogenic factors in markedly different ways. Whereas activated Kras causes granulosa cells to exit the cell cycle, it predisposes OSE cells to transformation by loss of Pten.

Sources of Research Support: In part by NIH-HD-16229 and the Eunice Kenney Shriver NICHD/NIH through cooperative agreement [HD-07495] as part of the Specialized Cooperative Centers Program in Reproduction and Infertility Research.

Nothing to Disclose: JSR

sort_order 2920
Pub # S62-3
Session Information SYMPOSIUM SESSION: BASIC - New Dimensions in Oocyte & Sperm Maturation (9:30 AM-11:00 AM)
Title A Mysterious Non-Coding RNA at the X-Inactivation Center
Author String J Lee
Massachusetts General Hospital, Boston, MA
Body The X-inactivation center is known for an abundance of long noncoding transcripts with specific function during dosage compensation of the mammalian female. The Tsx gene resides at the X-inactivation center and is thought to encode a protein expressed in testis (1), but its function has remained mysterious. Here, we find that Tsx is actually noncoding and the long transcript is expressed robustly in meiotic germ cells, embryonic stem cells, and brain. We characterize Tsx by creating knockout mice and determine its function in vivo (2).

(1) Chureau et al., 2002, Comparative sequence analysis of the X-inactivation center region in mouse, human, and bovine. *Genome Research* 12:894-908.
(2) Anguera et al., unpublished observations.

Sources of Research Support: HHMI.

Nothing to Disclose: JL

sort_order	2921
Pub #	S63-1
Session Information	SYMPOSIUM SESSION: BASIC - Novel Models Identify Novel Mechanisms of Metabolic Regulation (9:30 AM - 11:00 AM)
Title	Zebra Fish: A Novel Model To Explore the Regulation of Energy Balance
Author String	RD Cone Vanderbilt University Medical School, Nashville, TN
Body	Nothing to Disclose: RDC

sort_order 2922
Pub # S63-2
Session Information SYMPOSIUM SESSION: BASIC - Novel Models Identify Novel Mechanisms of Metabolic Regulation (9:30 AM - 11:00 AM)
Title Nuclear Receptors, Metabolism & the Conqueror Worm
Author String Z.Wang
University of Texas Southwestern Medical Center, Dallas, TX

Body The nuclear receptor DAF-12 plays a central role in controlling the larval development of *C. elegans*. Activation of DAF-12 by its ligands called dafachronic acids (DAs) commits the nematode to development into reproductive adult, which will otherwise arrest at a diapause stage called dauer. But the molecular mechanisms remain unclear. Furthermore, whether the DAF-12 signaling pathway is conserved in other nematode species, especially parasitic ones, is also unknown. One aspect of my studies is to investigate the molecular mechanisms by which this DA-DAF-12 signaling pathway regulates the *C. elegans* development. By measuring a series of metabolic parameters, we demonstrated that DAF-12 activation markedly elevated aerobic utilization of fatty acids. In accordance with this, expression of a network of metabolic genes responsible for energetic catabolism of fatty acids was up-regulated as well. Importantly, inhibition of these metabolic genes abolished the reproductive growth stimulated by DAF-12. These results revealed a DAF-12-controlled metabolic network that coordinates energy metabolism and larval development in *C. elegans*. The other emphasis of my work is on the role of DAF-12 in parasitic nematodes. Our results showed that, as seen in *C. elegans*, DAF-12 activation also induced recovery from the infective L3 (IL3), which is the dauer larva of the parasites. Moreover, the metabolic genes controlled by *C. elegans* DAF-12 were identified in parasitic nematodes. These facts indicate that the DAF-12 signaling pathway is conserved in parasitic nematodes. Importantly, administration of DA dramatically reduced the formation of the pathogenic larvae that are mostly resistant to current anthelmintic drugs, indicating the unique therapeutic potential of DAF-12 ligands to treat nematode parasitic diseases. To understand the pharmacology of targeting DAF-12, we solved the 3-dimensional structure of DAF-12 in a parasitic nematode called *Strongyloides stercoralis* that infects human. These results reveal the molecular basis for DAF-12 ligand binding and identify DAF-12 and its downstream metabolic genes as unique therapeutic targets in parasitic nematodes. Based on this, we have discovered several small molecules that activate *Strongyloides stercoralis* DAF-12 and these molecules may provide lead compounds for developing novel anthelmintic drugs.

Nothing to Disclose: ZW

sort_order	2923
Pub #	S63-3
Session Information	SYMPOSIUM SESSION: BASIC - Novel Models Identify Novel Mechanisms of Metabolic Regulation (9:30 AM - 11:00 AM)
Title	microRNA Regulation of Metabolism
Author String	G Ruvkun Harvard Medical School/Massachusetts General Hospital, Boston, MA
Body	Nothing to Disclose: GR

sort_order 2924
Pub # S64-1
Session Information SYMPOSIUM SESSION: BASIC - Thyroid Hormone Receptor Signaling in Development & Disease (9:30 AM - 11:00 AM)
Title Role of Thyroid Hormone Receptors in Tumorigenesis & Metastasis
Author String A Aranda
Consejo Superior de Investigaciones Cientificas, Madrid, Spain
Body
In addition to the well-known role of the thyroid hormone receptors (TRs) in growth, development and metabolism, there is increasing evidence that they can act as tumor suppressors. We have observed that TRs repress transcriptional induction of cyclin D1 by the *ras* oncogene and block transformation and tumor formation by *Ras*-transformed fibroblasts in nude mice. The domains and mechanisms responsible for the anti-transforming actions of the receptor are divergent from those operating in classical T3-dependent transcriptional regulation. Mutant receptors that cannot bind classical coactivators are able to display these actions, whereas receptors defective in corepressors binding are unable to antagonize transcription, transformation and tumor development by *ras*. Depletion of corepressors, particularly NCoR, reverses significantly the anti-transforming actions of TR β , further demonstrating an important functional role of endogenous corepressors in suppression of *ras*-mediated transformation by the receptor. In mouse embryonic fibroblasts TR β can also induce cellular senescence, a tumour suppressor mechanism considered as a first barrier against carcinogenesis. Furthermore, expression of TR β in hepatocarcinoma and breast cancer cells reduces tumor growth, causes partial mesenchymal-to-epithelial cell transition, and has a striking inhibitory effect on invasiveness, extravasation, and metastasis formation in nude mice. On the other hand, when cells are inoculated into hypothyroid animals, tumor growth is retarded, but tumors are more invasive and metastatic growth is enhanced. In cultured cells, TR β abolishes anchorage-independent growth and migration, blocks responses to growth factors, and regulates expression of genes that play a key role in tumorigenicity and metastatic growth. Finally, in a model of chemically induced skin carcinogenesis, TR β expression is lost during tumor progression and increased aggressiveness of the tumors in found in genetically modified mice lacking TRs, illustrating the role of these receptors as inhibitors of tumor malignancy. These results show the role of TRs as tumor and metastasis suppressors and suggest that these receptors represent a potential therapeutic target in cancer.

Sources of Research Support: BFU2007-62402 from MCINN, RD06/0020/0036 from FIS and FP6-018652 (CRESCENDO) from the EU.

Nothing to Disclose: AA

sort_order

2925

Pub #

S64-2

Session Information

SYMPOSIUM SESSION: BASIC - Thyroid Hormone Receptor Signaling in Development & Disease (9:30 AM - 11:00 AM)

Title

Thyroid Hormone Receptors & Coregulators in Adult Stem Cell Development

Author String

Y-B Shi

National Institute of Child Health & Human Development/National Institutes of Health, Bethesda, MD

Body

Organ-specific adult stem cells are critical for the homeostasis of adult organs and organ repair and regeneration. Unfortunately, it is difficult to investigate the origins of these stem cells and the mechanisms of their development, especially in mammals. Intestinal remodeling during frog metamorphosis offers a unique opportunity for such studies. During the transition from a herbivorous tadpole to a carnivorous frog, the intestine is completely remodeled with the larval epithelial cells undergo apoptotic degeneration and are replaced by adult epithelial cells developed de novo. The entire metamorphic process is under the control of thyroid hormone, which offers a unique opportunity to study the development and regulation of adult intestinal stem cells. We will present evidence to show that adult epithelial stem cells are induced by thyroid hormone through dedifferentiation of the larval epithelial cells. While thyroid hormone action in larval epithelial cells can induce the formation of putative progenitors of the adult stem cells, the formation of such stem cells and their eventual differentiation into the adult epithelium require thyroid hormone action in the non-epithelial tissues as well, like through the connective tissue, leading to the formation of proper stem cell niche. Furthermore, we will show that thyroid hormone receptor recruits the coactivator protein arginine methyltransferase 1 (PRMT1) to regulate gene expression during this period. More importantly, PRMT1 is upregulated in the larval epithelial cells destined to become adult stem cells and knocking down or overexpression of PRMT1 leads to reduced or increased proliferating adult cells, respectively, during intestinal metamorphosis. These results thus support a critical role of PRMT1 in the development and/or proliferation of adult intestinal stem cells during vertebrate development.

Sources of Research Support: Intramural Research Program of NICHD, NIH.

Nothing to Disclose: Y-BS

sort_order

2926

Pub #

S64-3

Session Information

SYMPOSIUM SESSION: BASIC - Thyroid Hormone Receptor Signaling in Development & Disease (9:30 AM - 11:00 AM)

Title

Making Sense: Thyroid Hormone & the Development of Retinal Photoreceptors

Author String

D Forrest

National Institute of Diabetes & Digestive & Kidney Diseases/National Institutes of Health, Bethesda, MD

Body

Thyroid hormone is critically required for development of the nervous system both in model species and humans. In human infants with untreated congenital hypothyroidism, the principal concern has been the risk of mental retardation related to defects in central functions in the brain. Studies in rodent species have identified a variety of activities for thyroid hormone in different brain regions. However, more recent genetic studies of thyroid hormone receptors in model species has revealed that one of the most important functions of thyroid hormone is in the development of the senses. An unexpectedly critical function of thyroid hormone receptors is in the development of the color visual system. Color vision is mediated by cone photoreceptor populations with sensitivities to different regions of the visible light spectrum. Most mammalian species have dichromatic color vision whereas humans have trichromatic color vision mediated by cone types that respond to short, medium or long wavelengths of light. A specific isoform of thyroid hormone receptor b, TRb2, is one of the earliest markers of immature cones and was first identified in the chick embryonic retina. Targeted mutagenesis in mice has demonstrated that TRb2 serves a key role in generating cone diversity. Further studies show that the activity of TRb2 in immature cones is under the control of type 3 deiodinase, a thyroid hormone-inactivating enzyme. These findings reveal that controls that constrain thyroid hormone action are as important as those that stimulate thyroid hormone action at different stages of neurodevelopment.

Sources of Research Support: Intramural research program at NIDDK.

Nothing to Disclose: DF

sort_order 2927
Pub # S65-1
Session Information SYMPOSIUM SESSION: BASIC - Vitamin D Receptor & Cancer (9:30 AM - 11:00 AM)
Title Vitamin D Receptors & Colon Cancer
Author String JW Pike
University of Wisconsin, Madison, WI
Body 1,25-Dihydroxyvitamin D3 (1,25(OH)2D3) exerts biological activity in target tissues by regulating the expression of genes involved in cellular proliferation, differentiation and mature cell function. These activities are mediated by the vitamin D receptor (VDR) which binds to DNA sequences at target genes as an RXR heterodimer and functions to nucleate coregulatory complexes essential for gene modulation. We have used both gene expression studies and chromatin immunoprecipitation (ChIP) linked to deep sequencing techniques (ChIP-seq) to explore the sites of action of VDR/RXR and TCF4/b-catenin in human LS180 colorectal cancer cells. We have also used these techniques to examine colocalization with other DNA binding proteins, lineage-specific factors and coregulators as well. VDR and RXR co-localize to a set of several thousand response element-containing binding sites on the human genome in LS180 cells upon activation by 1,25(OH)2D3. While both C/EBP β and CDX2 pre-mark many of these sites, suggesting their potential role as lineage factors, VDR/RXR binding is accompanied by the recruitment of numerous coregulators that likely mediate the actions of the hormone on gene expression. ChIP-seq analysis of TCF4/b-catenin binding also revealed numerous sites of action on genes that are involved in colorectal cancer cell proliferation. Interestingly, significant co-localization of both VDR/RXR and TCF4/b-catenin occurred at a small number of sites that were comprised of growth regulating genes that included c-FOS, RUNX1, SOX9 and c-MYC. Closer examination of these genes revealed both independent as well as overlapping sites of VDR/RXR and TCF4/b-catenin binding located many kilobases distal to the promoters they regulate. The expression of the c-FOS gene was upregulated and the c-MYC gene was downregulated in the presence of 1,25(OH)2D3. Further exploration of the functional activity of the enhancers within the c-FOS and c-MYC genes using isolated reporter analyses revealed striking TCF4/b-catenin mediated basal activity and 1,25(OH)2D3 modulated up- and down-regulation. These studies demonstrate that both c-FOS and c-MYC are direct targets of vitamin D action and that the hormone may modulate proliferation via actions at these and other genes. Our results have also revealed an important set of overarching principles regarding the actions of 1,25(OH)2D3 in cells and demonstrated the utility of this approach in identifying unique gene targets of hormone action.

Nothing to Disclose: JWP

sort_order 2928
Pub # S65-2
Session Information SYMPOSIUM SESSION: BASIC - Vitamin D Receptor & Cancer (9:30 AM - 11:00 AM)
Title Vitamin D Receptor in Breast Cancer: Genes, Proteins & Pathways
Author String J Welsh
State University of New York-Albany, Rensselaer, NY
Body To gain insight into pathways regulated by vitamin D3 and the vitamin D receptor (VDR) that impact on development or progression of breast cancer, we conducted genomic profiling in several distinct human and mouse model systems. In mouse experiments, we assessed the effects of dietary vitamin D3 on gene expression in mammary tumors driven by the neu oncogene (MMTV-neu model). Of 45K genes on the Affymetrix arrays, 592 genes were identified as differentially expressed (fold change >2) in MMTV-neu tumors from mice chronically fed adequate (250 IU/kg) vs high (5,000 IU/kg) vitamin D3. Twenty-eight genes were altered more than 5-fold in tumors of mice fed high dietary vitamin D3, including ATP1A2, CLCA2, EMB, CPE, and CST10 ([darr]) and SLC6A2, CHIA, LY6D and AMY1 ([uarr]). Additional genes previously identified as putative VDR targets that were altered by high dietary vitamin D3 in mouse mammary tumors included TXNIP ([uarr]) and SHH ([darr]). In complementary studies, we characterized genomic profiles in VDR positive non-transformed human mammary epithelial (HME) cells treated with 100nM 1,25D for 24h. Genes regulated by 1,25D in HME cells included CD14, TLR2/4, ITGB3, BMP2/6, ID2/4, SLC1A1 and IL1RL1 ([uarr]) and KDR, BIRC3, GLUL and FOSB ([darr]). The putative tumor suppressor Dipeptidyl peptidase-4 (DPP4), also known as CD26, was identified as a common VDR target gene as it was induced 2-fold in tumors of mice fed high dietary vitamin D3 and 5-fold in HME cells treated with 1,25D. DPP4 was also consistently induced in human breast cancer organotypic slices incubated with 1,25D ex vivo. Comparison of 1,25D modulated genomic profiles in normal and transformed cells in human and murine model systems indicated that a subset of VDR target genes is significantly and selectively altered by transformation. Collectively, these in vivo and in vitro data demonstrate that vitamin D3 signaling impacts on common pathways that drive differentiation, alter metabolic flux, remodel the extracellular matrix and trigger innate immunity in mammary tissue. Furthermore, these data support the concept that the process of carcinogenesis disrupts the regulation of multiple VDR target genes in mammary cells.

Sources of Research Support: NIH CA69700, A Sister's Hope and the NIH Bio-Active Nutrient Gene Expression Omnibus Project (BANGE0).

Nothing to Disclose: JW

sort_order 2929
Pub # S65-3
Session Information SYMPOSIUM SESSION: BASIC - Vitamin D Receptor & Cancer (9:30 AM - 11:00 AM)
Title Vitamin D Receptor (VDR) Methylation & VDR Insensitivity in Breast Cancer
Author String CB Umbricht
Johns Hopkins University, Baltimore, MD
Body Calcitriol (1 α , 25(OH)₂-Vitamin D₃) binds to the vitamin D receptor (VDR) and regulates differentiation of the normal mammary gland, and may therefore be useful in breast cancer treatment or prevention. Many breast cancer cells are, however, resistant to Calcitriol. We have investigated the resistance mechanism and the role of epigenetic silencing of VDR by promoter hypermethylation, and are investigating strategies to reverse or prevent functional inactivation of the Vitamin D pathway in breast cancer. Bisulfite sequencing of the VDR promoter region revealed methylated CpG islands 700 base pairs (bp) upstream as well as near the transcription start site. VDR promoter methylation was reversible by 5'deoxy-azacytidine (AZA) treatment, and this was accompanied by a parallel increase in VDR mRNA levels in breast cancer cell lines. Quantitative methylation-specific PCR analyses confirmed hypermethylation of these CpG islands in primary tumors, and its absence in normal breast tissue. VDR transcripts detected in breast cancers were predominantly 5'-truncated, while normal breast tissue expressed full-length transcripts. Consistent with this observation, genes containing the VDR-responsive element (VDRE), such as cytochrome p450 hydroxylases, p21, or C/EBP were underexpressed in breast cancers compared to normal breast samples. Expression of the active longer transcripts of VDR was restored with AZA treatment, with a concurrent increase in expression of VDRE-containing genes. Thus, promoter methylation-mediated silencing of expression of the functional variants of VDR may reduce expression of downstream effectors of the VDR pathway and contribute to Calcitriol insensitivity in breast cancer. These data suggest that pharmacological reversal of VDR methylation may re-establish breast cancer cell susceptibility to differentiation therapy using Calcitriol. We are currently investigating the effectiveness of alternatives to AZA, such as histone deacetylase (HDAC) inhibitors and soy isoflavones, in reactivating VDR expression and function, with the goal of developing a nontoxic, potentially nutritional approach to breast cancer prevention.

Sources of Research Support: Susan G. Komen Foundation; Department of Defense DAMD17-03-1-0547; NCI P50 CA088843-06A1; Breast Cancer Research Foundation.

Nothing to Disclose: CBU

sort_order 2930
Pub # S67-1
Session Information SYMPOSIUM SESSION: TRANSLATIONAL - Signaling in Mammary Gland Proliferation & Neoplasia (9:30 AM - 11:00 AM)
Title Plasma Membrane Calcium ATPase 2 Regulates Mammary Gland Apoptosis & Neoplasia
Author String JJ Wysolmerski
Yale University School of Medicine, New Haven, CT
Body The plasma membrane calcium-ATPase isoform 2 (PMCA2) is a member of the P-type family of ion transporters, and like other PMCA's, it pumps calcium ions out of cells in response to ATP hydrolysis. PMCA2 is highly expressed in the apical membrane of mammary epithelial cells during lactation, is regulated by the calcium-sensing receptor and is responsible for transporting up to 60-70% of the calcium found in milk. Recently we have found that it is also involved in protecting mammary epithelial cells from apoptosis during lactation. At the initiation of mammary involution, milk stasis leads to a change in the shape of epithelial cells, which, in turn, downregulates PMCA2 expression. Loss of PMCA2 leads to an increase in intracellular calcium, the activation of calpain and mammary epithelial cell apoptosis. In contrast, overexpression of PMCA2 in breast cancer cells lowers intracellular calcium levels, inhibits apoptosis, and leads to the accelerated growth of breast cancer cells in immunocompromised mice. In human patients, PMCA2 expression correlates with HER2 expression and predicts poor outcome. Finally, ablation of the PMCA2 gene inhibits tumor formation in MMTV-Neu mice. These findings support the concept that remodeling of intracellular calcium metabolism is important to the pathophysiology of cancer and suggest that PMCA2, which is vital to calcium transport in lactation, may contribute to the pathophysiology of breast cancer. If these findings are confirmed, then PMCA2 may represent a new target for the development of drugs to treat breast cancer.

Nothing to Disclose: JJW

sort_order 2931
Pub # S67-2
Session Information SYMPOSIUM SESSION: TRANSLATIONAL - Signaling in Mammary Gland Proliferation & Neoplasia (9:30 AM - 11:00 AM)
Title Novel Anti-JAK Therapies Against Breast Cancer
Author String CV Clevenger
Northwestern University, Chicago, IL
Body Using loss-of-function mouse models and emerging small molecular inhibitors, recent studies have implicated the tyrosine kinase Jak2 as a relevant pharmacologic target in human breast cancer. These results have suggested that inhibition of Jak2 expression/activity may have utility both at the therapeutic and chemopreventive levels. In concert with these studies, our lab has documented a critical role in breast cancer cells for the peptidyl prolyl isomerase cyclophilin A (CypA) in the receptor-mediated activation of Jak2. Targeted inhibition of CypA with cyclosporine A (CsA) or its non-immunosuppressive analog NIM811 have revealed significant reductions in breast cancer cell growth, invasion, and tumor progenitor populations in vitro. Pre-clinical studies with these agents or loss of function mouse models have revealed significant to complete inhibition of mammary tumorigenesis and metastasis in vivo. Taken together, these observations validate the clinical relevance of the CypA/Jak2 pathway in breast cancer, resulting in bench to bedside translation.

Sources of Research Support: In part by funding from the AACR and the Komen, Lynn Sage, Avon, and Breast Cancer Research Foundations.

Nothing to Disclose: CVC

sort_order 2932
Pub # S67-3
Session Information SYMPOSIUM SESSION: TRANSLATIONAL - Signaling in Mammary Gland Proliferation & Neoplasia (9:30 AM - 11:00 AM)
Title Role of Musashi1 Signaling in Breast Cancer
Author String RI Glazer
Georgetown University, Washington, DC
Body Musashi1 (Msi1), an evolutionarily conserved RNA-binding protein (RBP), modulates translation by binding to (G/A)U₁₋₃(AGU) motifs in the 3'-UTR of its target mRNAs to disrupt assembly of the 80S ribosomal complex (1). Targets of Msi1 include Numb, a negative regulator of Notch, p21^{Cip1}, an inhibitor of CDKs, and doublecortin, a microtubule-binding protein. Additional targets have also been identified by RBP-IP-Chip analysis (2), suggesting that Msi1 controls a network of signaling molecules involved in apoptosis and proliferation. These functions are consistent with the role of Msi1 as a stem cell regulator that maintains the balance between self-renewal and differentiation.
A similar role for Msi1 pertains to murine mammary epithelial cells, where Msi1 over-expression results in expansion of CD24^{hi}/Sca-1⁺, CD24^{hi}/CD29⁺, CK14⁺/CK18⁺, CK6⁺ and CK19⁺ stem and progenitor cells (3). These lineages are associated with autocrine regulation through secretion of the growth factor Proliferin, a ligand for the G-protein-coupled IGF2 receptor, and loss of DKK3, an inhibitor of the Wnt receptor Frizzled, which result in increased Wnt and Notch signaling.
Msi1 is abundant in most breast cancer cell lines, but low in breast epithelial cells (4). In breast cancer cells, Msi1 controls the expression of the embryonic stem cell markers c-Myc, Nanog, Sox2, Bmi1 and Oct4, which maintain pluripotency (4). This is consistent with the embryonic stem cell-like signature commonly associated with basal type breast cancer, as well as the co-localization of Msi1 with myoepithelial stem/progenitor cells in normal breast tissue. In breast cancer, approximately 40% of primary tumors, particularly those that are ErbB2⁺ and Notch⁺ (5), and all lymph node metastases express high levels of Msi1, which correlates inversely with 5 year survival (4). Interestingly, malignancies with high metastatic potential, such as non-small cell lung cancer, head and neck cancer and melanoma express high levels of Msi1 in a larger percentage of tumors than breast cancer.
Thus, Msi1 is not only a useful modulator of signal transduction in normal stem and progenitor cells, but is a negative prognostic marker for aggressive malignant disease, and perhaps eventually will be useful as a therapeutic target.

(1) Okano, H et al., *Exp Cell Res* 2005; 306:349
(2) de Sousa Abreu R et al., *J Biol Chem* 2009; 284:12125
(3) Wang XY et al., *Mol Cell Biol* 2008; 28:3589
(4) Wang XY et al., *Mol Cancer* 2010; 9:221
(5) Lindsay J et al., *Clin Transl Sci* 2008; 1:107

Sources of Research Support: Charlotte Geyer Foundation and Uniting Against Lung Cancer.

Nothing to Disclose: RIG

sort_order 2933
Pub # S68-1
Session Information SYMPOSIUM SESSION: CLINICAL - Aggressive Pituitary Tumors (9:30 AM - 11:00 AM)
Title Recent Advances in Diagnosis & Treatment of Aggressive Pituitary Tumors & Pituitary Carcinomas
Author String G Raverot
Hospices Civils de Lyon, Lyon, France
Body While generally considered benign, many pituitary tumors (45%) invade the sphenoid or the cavernous sinus and some (15%) are aggressive with high proliferation rate and short postoperative time before recurrence. Only metastatic tumors (0.2%) are considered as malignant. Predicting pituitary tumor behavior remains a challenge. In 2004, the WHO classification pointed out [ldquo]atypical adenomas[rdquo], based on tumor markers (p53 immunoreactivity, MIB-1 proliferative index greater than 3%, and increased mitotic activity) thought to correlate with aggressive pituitary tumor. Using a combination of histological and transcriptomic approaches in human prolactin tumors, we identified prognostic markers (1-2) and genomic alterations associated with PRL tumor aggressiveness. Given the paucity of reported cases, knowledge of the response to treatment and overall prognosis of patients with pituitary aggressive tumors or carcinoma is sparse. Recently, the efficacy of the alkylating chemotherapeutic drug temozolomide in the treatment of these tumors and a possible correlation between anti-tumoral effect and 06-methylguanine-DNA methyltransferase (MGMT) expression has been reported. However, three independent groups, including ours, confirmed the efficacy of temozolomide treatment for some but not all aggressive pituitary tumors or carcinomas and revealed MGMT status as a poor predictor of treatment outcome (3).
Since temozolomide treatment is not effective for all pituitary carcinomas or aggressive adenomas, the development of new therapeutic options is necessary. Evidence suggests that in pituitary adenomas, both the Raf/MEK/ERK and PI3K/Akt/mTOR pathways are upregulated in their initial cascade, implicating a pro-proliferative signal disturbance. As such, mTOR inhibitors, recently shown to have anti-neoplastic activity in several human cancers including neuroendocrine tumors, could be a good alternative for temozolomide-resistant pituitary tumors. Similarly, since HER2 over-expression has been demonstrated in prolactin tumors, the HER2/ErbB2 signaling pathway inhibitor Lapatinib could prove useful.
These recent results combined with the identification of signaling pathways associated with pituitary tumor aggressiveness open new perspectives for the treatment of these tumors, for which no other therapeutic option are available.

1. Wierinckx A, et al. *Endocr Relat Cancer*. 2007 Sep;14(3):887-900.
2. Raverot G, et al. *J Clin Endocrinol Metab*. 2010 Apr;95(4):1708-16.
3. Raverot G, et al. *J Clin Endocrinol Metab*. 2010 Oct;95(10):4592-9.

Sources of Research Support: Grants from the Ministere de la Sante (Programme Hospitalier de Recherche Clinique National n[deg] 27-43 HYPOPRONOS).

Nothing to Disclose: GR

sort_order 2934
Pub # S68-2
Session Information SYMPOSIUM SESSION: CLINICAL - Aggressive Pituitary Tumors (9:30 AM - 11:00 AM)
Title What Does Surgery Offer for Invasive/Aggressive Pituitary Adenomas?
Author String ER Laws
 Brigham & Women's Hospital/Harvard University, Boston, MA
Body

Although the vast majority of Pituitary Adenomas are benign and remain so indefinitely, many have the capability of invading the adjacent parasellar structures. Our studies have demonstrated histologic invasion of the dura in up to 80% of macroadenomas and 15 % of microadenomas. Most common is invasion of the cavernous sinus dura on either side of the lesion. Suprasellar extension of a pituitary tumor may lead to invasion of the diaphragm of the sella. Some tumors, particularly in acromegaly, invade inferiorly in to the sphenoid sinus. These invasive tumors may present with hormonal hypersecretion and/or mass effect. The latter includes loss of vision from chiasmal or optic nerve compression, and diplopia from paresis of cranial nerves responsible for ocular movements. Because many of the dural structures involved cannot safely be removed, some invasive tumor cells are often left behind following surgery and may be responsible for tumor recurrence.

The Goals of Surgical Management - What Can Surgery Accomplish?
 1- Relief of mass effect - restoration of vision, reversal of diplopia
 2- Normalization of hormonal hypersecretion
 3- Characterization of tumor -
 a. Definitive pathology - tumor subtype, immunocytochemistry, EM
 b. Measures of proliferation index (Ki-67, MIB-1), mitotic index, classification as typical or atypical
 c. Other tumor markers - p53, Pit-1, Galanin
 4- Alerts for Aggressive Behavior
 a. Silent ACTH adenoma
 b. ACTH adenoma in Nelson's syndrome
 c. Mammotroph tumors
 d. Acidophil stem cell tumors
 e. Plurihormonal tumors
 5- Tissue for molecular studies pertinent to adjunctive medical management, e.g. dopamine D2 receptor density
 6- Information helpful in targeting radiotherapy/radiosurgery

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 Selman WR, Laws ER Jr, Scheithauer BW, Carpenter SM. The occurrence of dural invasion in pituitary adenomas. *J Neurosurg.* 1986;64:402-407.
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 de Aguiar PH, Aires R, Laws ER, Isolan GR, Logullo A, Patil C, Katznelson L. Labeling index in pituitary adenomas evaluated by means of MIB-1: is there a prognostic role? A critical review. *Neuro Res.* 2010;32(10):1060-71.
 Zada G, Woodmansee WW, Ramkissoon S, Amadio J, Nose V, Laws ER. Atypical pituitary adenomas: incidence, clinical characteristics, and implications. *J Neurosurg.* 2010 Sep 24. [Epub ahead of print]

Nothing to Disclose: ERL

sort_order	2935
Pub #	S68-3
Session Information	SYMPOSIUM SESSION: CLINICAL - Aggressive Pituitary Tumors (9:30 AM - 11:00 AM)
Title	What Can Radiotherapy Offer?
Author String	JS Loeffler Massachusetts General Hospital/Harvard Medical School, Boston, MA
Body	Nothing to Disclose: JSL

sort_order 2936
Pub # S69-1
Session Information SYMPOSIUM SESSION: CLINICAL - Bone Quality: The Holy Frail (9:30 AM - 11:00 AM)
Title Imaging to Assess Bone Quality
Author String ML Bouxsein
Beth Israel Deaconess Medical Center, Boston, MA

Body Fractures resulting from osteoporosis are an enormous and growing concern for public health, as an aging population indicates that the number of fractures worldwide will double or triple in the next 50 years. A fracture occurs when the loads applied to a bone exceed its structural capacity, or strength. Importantly, the ability of a bone to resist fracture depends not only on the amount of bone present, but also on the spatial distribution of the bone mass, the cortical and trabecular microarchitecture, and the intrinsic properties of the materials that comprise the bone. Therefore, whereas low bone mineral density is among the strongest risk factors for fracture, a number of clinical studies have demonstrated the limitations of using measurements of bone mineral density by dual-energy X-ray absorptiometry to assess the risk of fracture and to monitor the response to therapy. Indeed less than 50% of those suffering a hip or non-vertebral fracture had BMD measurements in the osteoporotic range, as assessed by WHO criteria. As a result, new, noninvasive imaging techniques that are capable of assessing various components of bone strength are being developed. These techniques include three-dimensional assessments of bone density, geometry and microarchitecture, as well as integrated measurements of bone strength by engineering analyses. Several studies have demonstrated that deteriorated trabecular microarchitecture, as measured by in vivo imaging, increases fracture risk independent of BMD. Additional studies have shown that certain features of bone geometry, as assessed by 3D quantitative computed tomography are associated with fracture risk. Furthermore, engineering analyses, such as finite element analysis of QCT scans, have shown promise for prediction of bone strength and fracture risk. These techniques and clinical studies will be critically reviewed in this presentation. In summary, bone strength is determined by skeletal traits that cannot be captured solely by BMD measurement. Although new non-invasive imaging techniques show strong potential for assessing bone strength, further development and validation are needed to define their role in the clinical management of individuals with osteoporosis.

Session supported by: Amgen & Lilly USA, LLC

Nothing to Disclose: MLB

sort_order 2937
Pub # S69-2
Session Information SYMPOSIUM SESSION: CLINICAL - Bone Quality: The Holy Frail (9:30 AM - 11:00 AM)
Title Bone Remodeling Assessment & Interpretation
Author String R Eastell
University of Sheffield, Sheffield, UK
Body The assay features of biochemical markers of bone turnover (BTM) have markedly improved in the past few years (Vasikaran 2011). The most sensitive and specific markers of bone formation include serum bone alkaline phosphatase, total osteocalcin (including the intact molecule and the large N-Mid fragment) and the N extension peptide of type I collagen (PINP) assay. Among the various markers of bone resorption, measurements of the urinary excretion N- and C- related telopeptides (NTX and CTX respectively) and of serum CTX are the most sensitive and specific ones. Bone markers can be used to predict the rate of bone loss in postmenopausal women. BTM can be used to assess the risk of fractures in borderline cases. The prediction of fracture risk by BTM independently of BMD level has been confirmed in 3 other independent studies. Bone markers can be used to monitor the efficacy of antiresorptive therapy such as hormone replacement therapy, raloxifene and bisphosphonates. We and others have shown that the short term (3 to 6 months) decrease of bone turnover is significantly correlated with the long terms (2 years) increase in BMD of the spine. In addition, the decrease of urinary NTX and CTX is associated with the risk of vertebral fracture in osteoporotic women treated with risedronate. Similar studies in patients under alendronate or raloxifene show that the short term decrease of bone turnover markers is correlated with the risk of subsequent vertebral and non vertebral fractures. While the increase in BMD over 2 to 3 years explains up to 25% of the efficacy of bisphosphonates to reduce the risk of vertebral and non vertebral fractures, the rapid (3 to 6 months) reduction of bone resorption markers explain up to 70% of their fracture efficacy. Thus, with adequate cut-offs, individual patients can be monitored with bone markers earlier than with DXA. Finally, bone turnover markers can be used to identify response within individuals and so to encourage compliance.

Session supported by: Amgen & Lilly USA, LLC

Vasikaran S et al, Osteoporos Int. 2011; 22: 391

Nothing to Disclose: RE

sort_order 2938
Pub # S69-3
Session Information SYMPOSIUM SESSION: CLINICAL - Bone Quality: The Holy Frail (9:30 AM - 11:00 AM)
Title FRAX Update
Author String ES Siris
Columbia University College of Physicians & Surgeons, New York, NY
Body
FRAX is a tool for estimating absolute 10 year risk of hip and major osteoporotic fractures developed by the World Health Organization. It is based on a [ldquo]mega-analysis[rdquo] of 60,000 women and men studied prospectively from Europe, North America, Asia and Australia with subsequent validation from independent cohorts comprising 230,000 individuals. It is applicable for men and postmenopausal women, age 40 to 90, previously untreated for osteoporosis. FRAX combines femoral neck BMD with validated, easily ascertained clinical risk factors that are largely independent of BMD, providing better risk assessment than BMD alone. FRAX can be performed without BMD, but its inclusion improves risk prediction. Fracture risk assessments are country specific, taking into account fracture rates and mortality rates for individual nations. Countries can establish treatment thresholds for levels of risk for which prescription medication is recommended based on health care resources and societal values.
FRAX is now available online, as an iPhone app, and from software on newer DXA machines, allowing FRAX assessment when BMD is measured. In the US FRAX DXA software includes a filter that calculates risk only in untreated patients when recommendations for treatment are not clear. Since the NOF Guide advises treatment for postmenopausal women and for men [ge]50 with T-scores [le]-2.5 at spine or hip or with prior hip or vertebral fracture, the filter blocks provision of FRAX on such patients. FRAX is reported in those with osteopenia at spine or hip, to identify osteopenic patients at high fracture risk who need treatment and those at low risk who do not.
FRAX has several limitations. Some risk factors are reported as yes/no answers, when levels of risk from them are [ldquo]dose dependent[rdquo]. Falls, lumbar spine BMD and many other established fracture risk factors are not included in FRAX. Thus, fracture risk may sometimes be underestimated. It is also unclear whether osteopenic patients identified as being at increased risk by FRAX will respond to current osteoporosis medications as do patients with BMD T-scores [le]-2.5. Despite these limitations, FRAX, combined with good clinical judgment, offers an improved approach to identifying high risk patients for whom treatment is likely to offer the greatest benefit.

Session supported by: Amgen & Lilly USA, LLC

Nothing to Disclose: ESS

sort_order 2939
Pub # S70-1
Session Information SYMPOSIUM SESSION: CLINICAL - Endocrine Therapies in Developmentally Disabled Children: Medical Challenges & Ethical Dilemmas (9:30 AM - 11:00 AM)
Title When Should We Use Bisphosphonates in Children with Cerebral Palsy?
Author String LK Bachrach
Stanford Medical Center, Stanford, CA
Body Immobilization results in marked muscle and bone weakness. Without the anabolic stimulus of weight-bearing activity, acquisition of bone size, geometry, and strength is compromised. Skeletal health can be further impaired if nutritional deficits, delayed puberty, and anti-convulsant therapy are present as well. The end result is low bone mass, smaller, narrower bones and an increased risk of low impact fractures which occur most commonly in the long bones. An anabolic agent would be ideal to treat skeletal deficits in cerebral palsy (CP) patients, but parathyroid hormone carries a black box warning against pediatric use. Physical therapy and vibratory plates have been used in small studies with limited success. Bisphosphonate therapy has been attempted more frequently (1). In short term observational studies and in three randomized controlled trials (RCTs), pamidronate, risedronate, or etidronate in varying doses has been associated with gains in bone mineral density (BMD) at the lateral femur or spine. Follow up studies have demonstrated that BMD remained greater and fracture rates lower than pretreatment for a year or more post treatment in most children. Although the apparent reduction in fracture rates from observation studies with pamidronate are encouraging, the RCTs were not adequately powered to evaluate the efficacy of bisphosphonates to reduce fractures in CP. For these reasons, current data are inadequate to establish the optimal bisphosphonate, dose and duration of treatment to treat fragility fractures in patients with CP. Less is known about the benefit of bisphosphonate therapy to prevent a first fracture in children with low bone mass alone. Bone densitometry is an imperfect surrogate predictor of fracture risk in children with CP making it hard to select which children would warrant preventative bisphosphonate therapy. Until further research is available, the use of bisphosphonates should be limited to patients with CP meeting the criteria for pediatric osteoporosis established by the Position Development Conferences including low BMD and a long bone fracture of the lower extremity, two long-bone fractures of upper extremity or a vertebral compression fracture (2).

(1) Hough JP et al., Pediatrics 2010; 125: e670
(2) Rauch F et al., J Clin Densitometry 2008; 11: 22

Nothing to Disclose: LKB

sort_order 2940
Pub # S70-2
Session Information SYMPOSIUM SESSION: CLINICAL - Endocrine Therapies in Developmentally Disabled Children: Medical Challenges & Ethical Dilemmas (9:30 AM - 11:00 AM)
Title Growth-Altering Treatments for Disabled Children: Searching for Conceptual Consistency
Author String DB Allen
University of Wisconsin Medical School, Madison, WI
Body Parental and physician concerns about children's growth continue to stimulate interest in and controversy regarding growth-altering therapies. Publication of an account of growth attenuation (GA) using high dose estrogen in a child with profound physical and cognitive disability brought widespread attention to a common and complex issue faced by families caring for similarly affected children namely, the potentially negative effect of the increasing size of a child on the ability of his/her family to provide independent, in-home, and personal care. This talk explores the scientific rationale for, effectiveness and safety of, and ethical considerations bearing on GA of children with profound and permanent cognitive disability, and proposes informed responses to key clinically relevant questions. The analysis suggests: 1) GA is an innovative and sufficiently safe therapy that offers the possibility of an improved quality of life for non-ambulatory children with profound cognitive disability and their families; 2) families caring for a child with profound cognitive disability should be informed in early childhood about the possibility of GA so that, if elected, potential clinically meaningful benefits of GA therapy can be realized; 3) informed consent must acknowledge uncertainty with regard to both the prediction of long-term risks and the magnitude of GA benefit; 4) potential benefits of growth attenuation add a new dimension to management of precocious puberty in children with profound cognitive disabilities; 5) review by an institutional ethics committee is recommended until more data are available on outcomes, and strongly recommended if there is disagreement or doubt about whether such treatment is in the best interests of the child. Ideally, GA therapy should be part of a research protocol. Similarities to quality-of-life justifications offered for treatment of short stature indicate that, to be conceptually consistent, requests for GA should be given respect and commitment of personal resources equal to that afforded growth-promoting therapy.
Nothing to Disclose: DBA

sort_order 2941
Pub # S70-3
Session Information SYMPOSIUM SESSION: CLINICAL - Endocrine Therapies in Developmentally Disabled Children: Medical Challenges & Ethical Dilemmas (9:30 AM - 11:00 AM)
Title Ethical Issues in the Management of Puberty & Fertility in Children with Chronic Disabilities
Author String DS Diekema
Seattle Children's Hospital Research Institute, Seattle, WA
Body Parents and guardians of persons with developmental disabilities may have legitimate concerns that lead to requests for sterilizing procedures involving the developmentally disabled person in their care. At the same time, persons with developmental disabilities must be protected from actions that do not serve their best interests or that might impair their future opportunities. This presentation will review the history of involuntary sterilization in the United States and evaluate the ethical arguments that are relevant to decisions about procedures that result in involuntary sterilization. While other, less permanent forms of contraception or menstrual control might be acceptable, involuntary sterilization ought not be performed on developmentally disabled persons who have the possibility of achieving the capacity for reproductive decision-making, the ability to raise a child, or the capacity to provide valid consent to marriage. Mentally retarded persons who lack capacity in those three areas should be considered for involuntary sterilization only when the procedure is necessary, sterilization would serve the best interests of the mentally retarded person, less intrusive and temporary methods of contraception or control of menstruation are not acceptable alternatives, and procedural safeguards have been implemented to assure a fair decision-making process. Procedural safeguards may require judicial involvement depending on the jurisdictional requirements.
Parents may also raise concerns about puberty, particularly when it occurs precociously. This presentation will also address the ethical issues that might arise surrounding parental requests to alter the pubertal process.

Diekema DS, MRDD Research Reviews 2003; 9: 21-26.

Nothing to Disclose: DSD

sort_order 2942
Pub # OR30-1
Session Information ORAL SESSION: BASIC - The Expanding Universe of Thyroid Biology (11:15 AM-12:45 PM)
Title Thyroid Hormone Receptor Mapping on *Xenopus tropicalis* Genome by ChIA-PET Analysis
Author String N Buisine, P Bilesimo, G Alfama, A Grimaldi, Y Ruan, X Ruan, E Liu, BA Demeneix, LM Sachs
Muséum National d'Histoire Naturelle, Paris, France; Genome Institute of Singapore, Singapore
Body One striking example of how thyroid hormones (THs) regulate vertebrate developmental processes is amphibian metamorphosis. Tadpoles transformation is marked by dramatic TH-induced changes including de novo morphogenesis, tissue remodelling and organ resorption. These changes involve cascades of gene regulation initiated by THs and their receptors (TR). Metamorphosis has close and interesting parallels with the perinatal period in mammals. Metamorphosis is thus an attractive model to decipher the molecular mechanisms controlling the cascades of transcriptional programs dependent on TR/THs signalling. Our aim is to build a genome wide profile of TR binding sites and to map the physical interactions network between DNA bound TR complexes. The latter should provide insight into how the TH responsive genome is organized into high-level three-dimensional structures according to functional input. To this end, the recently developed chromatin interaction analysis by paired-end tag sequencing (ChIA-PET) was used in the context of amphibian metamorphosis. In ChIA-PET, long-range chromatin interactions are captured by formaldehyde crosslinking. Sonicated DNA-protein complexes are enriched by Chromatin immuno-precipitation (ChIP). Tethered DNA fragments in each of the chromatin complexes are connected with DNA linkers by proximity ligation and paired-end tags (PET) corresponding to the end of long DNA fragments are extracted for sequencing on next generation platforms. The resulting ChIA-PET sequences can be accurately mapped to the reference genome, thus demarcating the genomic boundaries of PET-represented DNA fragments and revealing the identities of the target DNA elements, but also revealing relationships between remote chromosomal regions brought together into close spatial proximity by protein factors. ChIA-PET libraries, corresponding to tail fin tissues with treatment with THs, have been constructed and sequenced. Strong TR binding sites have been found and analyzed for THs response elements. DNA array and RNA-Seq data were used to link genomic TR binding sites and T3-response genes by genome mapping. The results highlight enrichment of key gene categories and open new perspectives for functional studies on control of cell fate.
Funded by EU FP6 Crescendo, EU FP7 Ideal, ANR JCJC Trigger, PHC Meriton.
Nothing to Disclose: NB, PB, GA, AG, YR, XR, EL, BAD, LMS

sort_order 2943
Pub # OR30-2
Session Information ORAL SESSION: BASIC - The Expanding Universe of Thyroid Biology (11:15 AM-12:45 PM)
Title Differential Recruitment of Nuclear Co-Regulators Directs the Isoform-Dependent Action of Thyroid Hormone Receptor Mutant
Author String L Fozzatti, C Lu, D-W Kim, S-y Cheng
National Cancer Institute, Bethesda, MD

Body Studies using mice deficient in thyroid hormone receptors (TRs) indicate that the two TR isoforms, TR α 1 and TR β 1, in addition to mediating overlapping biological activities of the thyroid hormone, T3, also mediate distinct functions. Mice harboring an identical knockin dominant negative mutation (denoted PV) at the C-terminus of TR α 1 (Thra1PV mice) or TR β 1 (ThrbPV mice) also exhibit distinct phenotypes. These knockin mice provide an opportunity to understand the molecular basis of isoform-dependent functions in vivo. To test the hypothesis that the distinct functions of TR mutant isoforms are directed by a subset of nuclear regulatory proteins, we first used tandem-affinity chromatography to identify nuclear proteins from HeLa cells that are preferentially associated with TR α 1 mutant (TR α 1PV) or TR β 1 mutant (TR β 1PV). Thirty-three nuclear proteins including nuclear receptor corepressor (NCoR1) and six other nuclear proteins were identified to preferentially associate with TR α 1PV and with TR β 1PV, respectively. Nine common proteins were found to associate with both TR mutants. The involvement of NCoR1 in mediating the distinct phenotype in the liver of Thra1PV and ThrbPV mice was further explored. We showed that NCoR1 preferentially physically interacted with TR α 1PV rather than with TR β 1PV in vitro by coimmunoprecipitation assay. The hepatic mRNA levels of CCAAT/enhancer-binding protein α (C/ebp α), a master regulator of adipogenesis, was shown to be down-regulated in the liver of Thra1PV (~50%) but not in ThrbPV mice. A thyroid hormone response element (TRE) was identified in the promoter (-608/-583) of the mouse C/ebp α gene by gel-shift assays. Chromatin immunoprecipitation assay further demonstrated that NCoR1 was preferentially recruited to the mouse TRE-bound TR α 1PV on a C/ebp α promoter (2- to 2.5-fold increase vs 0.5-fold on TRE-bound TR β 1PV). This preferential recruitment of NCoR1 by TR α 1PV could, at least in part, contribute to the different lipid phenotypic manifestations observed in the liver of these mutant mice. Thus, the present study highlights a novel molecular mechanism by which TR isoforms direct their selective functions via preferential recruitment of a subset of nuclear coregulatory proteins.

Nothing to Disclose: LF, CL, D-WK, S-YC

sort_order

2944

Pub #

OR30-3

Session Information

ORAL SESSION: BASIC - The Expanding Universe of Thyroid Biology (11:15 AM-12:45 PM)

Title

Thyroid Hormone Up-Regulates an Alzheimer Disease-Related Gene Seladin-1 at the Transcriptional Level

Author String

E Ishida, K Hashimoto, A Ozawa, N Shibusawa, T Satoh, S Okada, M Yamada, M Mori
Gunma University Graduate School of Medicine, Maebashi, Japan

Body

Alzheimer's disease (AD) is the most common cause of dementia. Selective AD indicator 1 (Seladin-1) has been identified as a gene down-regulated in the degenerated lesion of AD brain. Up-regulation of Seladin-1 reduces the accumulation of β -amyloid, the oxidative stress and the neuronal death. Seladin-1 encodes 24-dehydrocholesterol reductase, which catalyzes the final step of cholesterol synthesis and reinforces the lipid bilayer of neuron with increased intracellular cholesterol to prevent β -amyloid insertion process. Thus, Seladin-1 could be a promising therapeutic target for AD. Thyroid hormone (TH) also exerts an important effect on development and maintenance of central nervous systems. In a previous report, we demonstrated that a mouse which harbors the [Delta] 337T mutation in thyroid hormone receptor (TR) β gene (TRKI mouse) caused severe neurological dysfunction (e.g. (1)). TH up-regulates Seladin-1 gene expression in human's neuronal cell lines (e.g. (2)), however a molecular mechanism of the regulation has yet to be elucidated. In the current study, we rendered C57/B6 mice thyrotoxic. Seladin-1 gene expression in the forebrain was increased by about three times in thyrotoxic mice compared to that of euthyroid mice. In contrast, TRKI mice showed significantly low gene expression levels of Seladin-1 in the forebrain. Seladin-1 was up-regulated in HTB185 cells derived from human medulloblastoma in a TH dose-dependent manner. Luciferase assays using the human Seladin-1 gene promoter (-1041/+57bp) demonstrated that TH activated the Seladin-1 gene promoter, and the activity was abolished when deleted to -375bp. Site A including Direct Repeat 4 half site in the lesion between -381 and -375bp is responsible for the gene regulation by TH. Mutation in site A in the promoter deteriorated the positive gene regulation by TH. TR β -RXR α heterodimerization was identified on site A by Electromobility shift assay, and Chromatin immunoprecipitation assay revealed the recruitment of TR β to site A. Interestingly, Liver X Receptor (LXR) α was also recruited and bound to the site A. The agonist of LXR TO901317 increased Seladin-1 gene promoter activity to a similar extent as TH. Several lines of data suggested that TR β and LXR α could cross talk on site A competitively. Taken together, we concluded that TH up-regulates Seladin-1 gene expression at the transcriptional level and TR β -LXR α crosstalk could modulate Seladin-1 gene promoter activity.

(1) Hashimoto K et al., Proc Natl Acad Sci 2001; 98:3998

(2) Benvenuti S et al., J Endocrinol 2008; 197:437

Nothing to Disclose: EI, KH, AO, NS, TS, SO, MY, MM

sort_order 2945
Pub # OR30-4
Session Information ORAL SESSION: BASIC - The Expanding Universe of Thyroid Biology (11:15 AM-12:45 PM)
Title Hypothalamic Melanocortin Signaling Regulates Thyroid Hormone Metabolism in the Liver *In Vivo*
Author String KR Vella, P Ramadoss, FD Ye, E Maratos-Flier, AN Hollenberg
Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA
Body Fasting induced suppression of the hypothalamic-pituitary-thyroid hormone (HPT) axis allows for an adaptive response to decrease energy expenditure during food deprivation. Previous studies demonstrate that leptin communicates nutritional status to the HPT axis through thyrotropin-releasing hormone (TRH) expression in the paraventricular nucleus (PVN) of the hypothalamus. Leptin targets TRH neurons either directly through leptin receptors or indirectly by signaling through proopiomelanocortin (POMC) and agouti-related peptide (AgRP)/neuropeptide Y (NPY) neurons from the arcuate nucleus. To evaluate the role of these pathways *in vivo*, we developed double knockout mice (DKO) that lack both the melanocortin 4-receptor (MC4R) and NPY and thus prevent signaling from the arcuate nucleus. Unlike WT mice, DKO mice maintained TRH mRNA expression and thyroid hormone (TH) levels during a fast. Surprisingly, TRH mRNA expression also persisted in fasting mice that lacked only NPY (NPY^{-/-}) whereas TH levels dropped significantly. To explain the adaptive response of TH in NPY^{-/-} despite impaired TRH mRNA repression, we hypothesized that fasting-induced peripheral metabolism of TH was operative in NPY^{-/-} mice, but not in DKO mice. This circuit would allow TH levels to fall independent of TRH and would require the MC4R. Previous studies have shown that the orphan nuclear receptor constitutive androstane receptor (CAR) and its target genes, sulfotransferases (Sult1A1) and UDP-glucuronosyltransferases (UGT1A1), are pivotal to hepatic TH metabolism. Indeed, TH levels in CAR^{-/-} mice do not decrease in response to fasting. Importantly, CAR, Sult1A1, and Ugt1a1 are up regulated in the liver during fasting to increase TH metabolism. To test whether the MC4R and NPY signals regulate CAR and its targets, we evaluated expression of these genes in fed and fasted mice via quantitative RT-PCR (qPCR) in liver tissue. As expected, we found that WT and NPY^{-/-} mice adequately up regulate CAR, Sult1A1 and Ugt1A1 and another CAR target, Cyp2b10 during a fast. Remarkably, CAR and its targets failed to respond to fasting in MC4R^{-/-} and DKO mice. Interestingly, the CAR pathway was blunted in ob/ob mice where MC4R signaling is intact but defective. These data demonstrate for the first time that signaling through the central melanocortin system regulates peripheral thyroid hormone metabolism in the liver and provides an additional role for this pathway in the regulation of energy expenditure.

Sources of Research Support: NIH Grant T32 DK07516 awarded to KRV; NIH Grant DK-078090 awarded to ANH.

Nothing to Disclose: KRV, PR, FDY, EM-F, ANH

sort_order 2946
Pub # OR30-5
Session Information ORAL SESSION: BASIC - The Expanding Universe of Thyroid Biology (11:15 AM-12:45 PM)
Title Interferon-Alpha Induces Thyroiditis by Induction of an Inflammatory Response and by Direct Tissue Cytotoxicity
Author String N Akeno, EP Smith, M Stefan, AK Huber, W Zhang, M Keddache, Y Tomer
University of Cincinnati College of Medicine, Cincinnati, OH; Mount Sinai School of Medicine, New York, NY; Cincinnati Children's Hospital Medical Center, Cincinnati, OH
Body Autoimmune thyroid diseases arise from complex interactions between genetic, epigenetic, and environmental factors. Recently, interferon alpha (IFNa), the most effective therapeutic agent for chronic hepatitis C, has emerged as a major environmental factor triggering thyroiditis. Clinical thyroiditis develops in 5-15% of hepatitis C patients on IFNa and thyroid antibodies develop in 28-40%. Despite the strong association between IFNa and thyroiditis the molecular mechanisms by which IFNa interact with susceptibility genes to trigger thyroiditis are not known. Our aim was to dissect the molecular mechanisms of interferon induced thyroiditis (IIT) using *in vitro* and *in vivo* approaches. We determined that IFNa treatment of thyroid cell lines increased mRNA expression of the major thyroid genes including thyroglobulin (Tg), thyroid stimulating hormone receptor (TSHR), thyroid peroxidase (TPO) and sodium iodide transporter (NIS). Moreover, RNAseq analysis of primary human thyroid cells exposed to IFNa demonstrated that pathways of antigen presentation, pattern recognition receptors and cytokines/chemokines were also stimulated. These changes were accompanied by increased non-apoptotic cell death suggesting direct toxicity of IFNa on thyroid cells. Luciferase reporter assays showed that IFNa can directly activate Tg promoter activity leading to increased levels of transcription. To further examine the effect of IFNa on thyrocytes *in vivo*, we generated transgenic (TG) mice with overexpression of IFNa in the thyroid by placing the mouse IFNa gene under the control of the Tg promoter. Assessment of IFNa plasma levels in TG mice showed no evidence of systemic elevation of IFNa. TG mice were smaller at birth than their wild-type littermates, showed increased neonatal lethality, and failure to thrive. Histological analysis demonstrated marked inflammatory destruction associated with immune cell infiltration of the thyroids beginning at postnatal day 1. T4 and TSH plasma levels also confirmed severe hypothyroidism as a result of the inflammatory destruction of the thyroid. Thyroid transcriptome analysis in the TG mice showed upregulation of pathways similar to those observed in human thyroid cells exposed to IFNa. In conclusion, our *in vitro* and *in vivo* studies demonstrated that IFNa can trigger thyroiditis by direct thyroid toxic effects including thyroid cell necrosis, as well as by stimulating an inflammatory bystander immune response.

Sources of Research Support: In part by grants DK61659, and DK073681 from NIDDK, and by a VA Merit award (to YT).

Nothing to Disclose: NA, EPS, MS, AKH, WZ, MK, YT

sort_order 2947
Pub # OR30-6
Session Information ORAL SESSION: BASIC - The Expanding Universe of Thyroid Biology (11:15 AM-12:45 PM)
Title A Biologically Active Subunit Variant of TSH Is Produced by CD45+ Bone Marrow Macrophages and May Influence Osteoblastogenesis
Author String R Baliram, A Chow, R Latif, M Merad, T Davies, Z Mone
James J Peters VA Medical Center, New York, NY; Mount Sinai School of Medicine, New York, NY; Mount Sinai School of Medicine, New York, NY
Body Our previous studies have shown that TSH influences the physiology and pathophysiology of bone by activating osteoblasts while inhibiting osteoclast activity. Whether this influence is directly exerted by pituitary TSH in vivo is uncertain. Here, we have characterized the functional relevance of a novel form of TSH known to be produced within murine bone marrow. This novel TSH- β subunit (TSH- β v), a splice variant of native TSH- β , deficient in exon 4, was easily detected by RT-PCR in crude bone marrow extract but absent in the pituitary gland. Flow cytometric fractionation of bone marrow cells into myeloid (CD11b⁺) and lymphoid (CD11b⁻) cells demonstrated that the CD11b⁺ cell population was the primary source for the production of TSH- β v. Further sub-fractionation of these lymphoid cells revealed four populations of leukocytes (lymphocytes, monocytes, neutrophils and macrophages). The macrophage sub-population was the primary source of TSH- β v as characterized by qPCR and mass spectrometry of the culture supernatant. 90.9% of bone marrow derived macrophages were F480⁺ and when co-cultured with CHO cells engineered to over express the full length TSH receptor (CHO-TSHR) they induced the generation of intracellular cAMP, a phenomenon not seen in control CHO cells and confirmed the bioactivity of the TSH variant. In order to characterize the regulation of TSH- β v expression, bone marrow cells were cultured with MCSF (10 ng/ml) for 7 days and then stimulated with a variety of cytokines and lymphokines which showed that both TNF- α (10 ng/ml) and MCP-1/CCL2 (10 ng/ml) caused an up-regulation of TSHR- β v expression. In vivo, thyroid hormone treatment of CBA/J mice increased bone marrow TSH- β v transcription in contrast to thyroid hormone suppression of pituitary TSH. These data demonstrated (1) That a native glycoprotein hormone subunit can have significant bioactivity and (2) Since we have shown that TSH is a bone modulating hormone we hypothesize that a local regulatory bone network may be at play, influencing bone cell biology via macrophage TSH- β v gene transcription.

Nothing to Disclose: RB, AC, RL, MM, TD, ZM

sort_order 2948
Pub # OR31-1
Session Information ORAL SESSION: BASIC/TRANSLATIONAL - Adipogenesis, Adiposity & Adipocyte Biology: Novel Findings in Basic Research (11:15 AM-12:45 PM)
Title Deletion of BMP Receptor Type 1A Results in Impaired Brown Adipocyte Development
Author String TJ Schulz, P Huang, LE McDougall, TL Huang, Y Mishina, E Gussoni, Y-H Tseng
Joslin Diabetes Center, Boston, MA; Children's Hospital, Boston, MA; University of Michigan, Ann Arbor, MI

Body Brown adipose tissue dissipates energy in the form of heat and has therefore been proposed as a target for anti-obesity therapies. Recently, it has been demonstrated that brown fat cells located in different anatomical locations come from different developmental origins. Preformed brown fat present at birth arises from myf5-positive progenitors, whereas myf5-negative populations of progenitors found in skeletal muscle and white adipose tissue are highly inducible to differentiate into brown adipocytes. The developmental fate of these progenitors is tightly regulated by inductive cues. We and others recently demonstrated that bone morphogenetic proteins (BMPs) play an important role in adipose cell fate decision and differentiation. Cellular responses to BMPs are relayed by hetero-oligomeric complexes of type 1 and type 2 BMP receptors (BMPRs). Type 1A BMPR (BMPRIA) has previously been implicated in adipocyte differentiation. To determine the role of BMPRIA in brown fat development, we generated a mouse model in which BMPRIA is deleted in cells expressing myf5 by use of the CRE/loxP system. Interscapular brown fat mass was significantly reduced in knockout (KO) mice, while there was no effect on white fat. KO mice retained their ability to induce brown fat formation in white fat in response to beta3-adrenergic stimulation, which is consistent with the notion that brown fat cells located in white fat come from a distinct developmental origin. Isolated brown preadipocytes lacking BMPRIA displayed a near complete blockage of differentiation, and a blunted response to induction by BMP7. To further examine the impact of deletion of BMPRIA in different fat depots, we generated a second mouse model with fat-specific deletion of BMPRIA: CRE-expression was placed under the control of the aP2 promoter, achieving deletion of BMPRIA in mature adipocytes only. While KO mice displayed a significant reduction in interscapular brown adipose tissue, only a trend towards decreased white fat mass was observed. Expression of white fat markers was unaltered, but expression of UCP1 was decreased in white fat, suggesting that the small population of inducible brown adipocytes residing within this fat type were affected by deletion of BMPRIA. In summary, these findings establish an essential role of BMPRIA in the development of brown fat depots, and suggest that targeting BMP signaling may present a strategy to counteract obesity by increasing brown fat mass and function.

Nothing to Disclose: TJS, PH, LEM, TLH, YM, EG, Y-HT

sort_order 2949
Pub # OR31-2
Session Information ORAL SESSION: BASIC/TRANSLATIONAL - Adipogenesis, Adiposity & Adipocyte Biology: Novel Findings in Basic Research (11:15 AM-12:45 PM)
Title SUMO-1 Function in Regulation of Adipogenesis
Author String L Mikkonen, J Hirvonen, OA Janne
University of Helsinki, Helsinki, Finland

Body SUMOylation is a dynamic process involving the covalent attachment of SUMO to target proteins. The SUMO family consists of four related proteins. We have previously generated a Sumo1 null mouse whose phenotype under normal conditions was indistinguishable from that of wild-type (WT) littermates, at least in part, due to compensation by other SUMO paralogs for the lack of SUMO-1 [1]. Since distinct SUMO paralogs have been implicated in the regulation of several nuclear receptors, including PPARs, we have studied the role of Sumo1 in adipocyte differentiation. Sumo1 null mouse embryonic fibroblasts (MEFs) and mesenchymal stem cells (MSCs) differentiated into adipocytes less efficiently than WT cells after 12 days, as judged by Oil Red O staining and decreased expression of mRNAs encoding the adipocyte markers aP2 and Pparg in Sumo1 null cells. In addition, expression of Fsp27, a gene important in the regulation of lipid droplets and fat storage, and a direct target gene of PPAR γ , was attenuated during differentiation of Sumo1 null MEFs to adipocytes. PPAR γ protein levels were markedly reduced in Sumo1 null adipocytes compared to WT ones differentiated from MEFs. To study the role of sumoylation in PPAR γ signalling further, we created a 3T3-L1 preadipocyte cell line stably expressing shRNA targeting Sumo1. With approximately 80% silenced Sumo1 gene, as measured by Sumo1 mRNA and protein levels, we saw a reduction in the efficiency of adipocyte differentiation and significantly attenuated loading of PPAR γ protein onto the PPRE at the aP2 promoter in mature adipocytes, indicative of defective function of PPAR γ in the absence of SUMO-1. These in vitro results suggested that the function of PPAR γ , the master regulator of adipogenesis, could be modulated by SUMO-1 not only in transrepression, as shown before [2], but also in transcriptional activation. To test this hypothesis in vivo, we treated Sumo1 null mice with rosiglitazone and measured Pparg mRNA levels in white adipose tissue, where PPAR γ is known to activate its own transcription. In contrast to WT mice, rosiglitazone treatment failed to increase Pparg mRNA expression in Sumo1 null mice. Taken together, these data indicate that SUMO-1 is required for normal PPAR γ function both in vitro and in vivo.

- (1) Zhang F-P et al., Mol Cell Biol 2008; 28: 5381.
- (2) Ghisletti S et al., Mol Cell 2007; 25:57.

Sources of Research Support: CRESCENDO; Sigrid Juselius Foundation; Academy of Finland.

Nothing to Disclose: LM, JH, OAJ

sort_order 2950
Pub # OR31-3
Session Information ORAL SESSION: BASIC/TRANSLATIONAL - Adipogenesis, Adiposity & Adipocyte Biology: Novel Findings in Basic Research (11:15 AM-12:45 PM)
Title Deletion of the Mitochondrial Transcription Factor A (TFAM) in Adipose Tissue Protects Mice from Age- and Diet-Induced Obesity and Insulin Resistance
Author String C Vernochet, O Bezy, Y Macotela, B Emanuelli, N Larson, CR Kahn

Body

Joslin Diabetes Center, Boston, MA; Max Planck Institute for Biology of Ageing, Cologne, Germany

Mitochondrial dysfunction in adipose tissue has been reported in obesity and type 2 diabetes, but whether this dysfunction participates in the development or is a result of these disorders remains an open question. Mitochondrial transcription factor A (Tfam) plays a key role in mitochondrial function by controlling both mtDNA stability and transcription. Tfam expression is high in brown adipose tissue (BAT), lower in perigonadal white adipose tissue (PG) and very low in subcutaneous white adipose tissue (SC) of mice. Upon High fat diet (HFD), Tfam mRNA and protein levels decrease in all adipose depots. C3H10T1/2 mesenchymal stem cells with a stable 90% knockdown (KD) for Tfam exhibit decreased mtDNA copy number, drastically impaired basal and maximal respiratory mitochondrial capacity, but increased mitochondria volume and reactive oxygen (ROS) production. These cells also have reduced adipogenic capacity as assessed by triglyceride accumulation and lower expression of the key adipocyte transcription factors PPAR γ and C/EBP α . To investigate the physiological relevance of mitochondrial impairment in adipose tissue, we generated a mouse model deficient for Tfam specifically in adipocytes (FAT-Tfam-KO) using Cre-lox technology. In FAT-Tfam-KO mice, Tfam mRNA levels are reduced by 72% in BAT, 51% in PG fat and 40% in SC fat. One-year-old FAT-Tfam-KO mice are leaner both on normal chow diet (CD) and HFD, protected from hyperinsulinemia and more insulin sensitive than their control littermates. FAT-Tfam-KO mice also had increased oxygen consumption and food intake on both CD and HFD with no significant change in spontaneous activity. Interestingly, Tfam deficiency did not affect all adipose depots equally. On chow diet, BAT and PG fat mass is decreased in FAT-Tfam-KO (42% and 29%), but the SC depot showed an even greater decrease (79%). On HFD fed mice, BAT mass is the more affected by FAT-Tfam-KO (83%), while SC fat mass was decreased by 54%, and PG mass was decreased only 32%. Thus, Tfam deletion has differential effects on adipose depots mass and protects mice from obesity and insulin resistance. These data highlight Tfam and mitochondria differential role in fat depots dynamic in response to aging or HFD. Our results also suggest that fat mitochondria dysfunction can modify the development of obesity and establish adipose tissue mitochondria as a potential therapeutic target for this disorder.

Nothing to Disclose: CV, OB, YM, BE, NGL, CRK

sort_order 2951
Pub # OR31-4
Session Information ORAL SESSION: BASIC/TRANSLATIONAL - Adipogenesis, Adiposity & Adipocyte Biology: Novel Findings in Basic Research (11:15 AM-12:45 PM)
Title Enhanced Adipogenic and Lipogenic Signatures in White Adipose Tissue of Offspring Exposed to Maternal Obesity *In Utero*
Author String K Shankar, Y Zhong, P Kang, SJ Borengasser, MJ Ronis, TM Badger
ACNC, Little Rock, AR; University of Arkansas for Medical Sciences, Little Rock, AR; University of Arkansas for Medical Sciences, Little Rock, AR
Body The risk of obesity throughout life is subject to programming beginning early in development. Exposure to maternal obesity (MO) at conception and during gestation increases the risk of obesity in adult-life. MO was induced in female Sprague Dawley rats via overfeeding of liquid diets (30% excess calories). Exposure to MO was restricted only to gestation by cross-fostering pups to lean dams at birth. Male offspring from obese rat dams gain greater body weight ($p < 0.005$), fat mass and develop insulin resistance when fed high-fat diets (45% fat). Hepatic microarray analyses at postnatal day (PND) 21 revealed a reprogramming of lipogenic and lipid degradative pathways following exposure to MO. In this report we examined global gene expression changes in white adipose tissue (WAT) using microarrays, adipogenic potential of WAT stromal vascular (SV) cells and expression of insulin signaling components. Exposure to maternal obesity altered the expression of 258 transcripts in the offspring WAT at PND21. In offspring of obese dams, the expression of lipogenic transcripts regulated by SREBP-1 was up-regulated akin to the regulation in the liver. Real-time PCR confirmed increased expression of FASN (3-fold), SREBP-1 (1.7-fold), ChREBP (2.5-fold), ACLY (4.5-fold), ELOVL6 (3.6-fold), and adiponutrin (4.8-fold) in the WAT of offspring of obese dams ($p < 0.05$). Protein expression of lipogenic proteins including SREBP-1, FASN and GAPDH was confirmed to be elevated in obese-dam offspring, along with increased levels of Glut-4 protein (1.5-fold, $p < 0.05$), suggesting increased glucose flux into WAT adipocytes driving lipogenesis. However, insulin-signaling components (IR- β , pAKT and total AKT, pAS160, pERK and total ERK) were unchanged in total WAT lysates. Protein expression of adipogenic factors PPAR- γ , C/EBP- α and C/EBP- β was increased ($p < 0.05$) in WAT tissues of offspring from obese dams. *Ex vivo* adipogenic differentiation of SV cells using hormonal cocktail revealed greater differentiation in offspring of obese dams. This was confirmed by enhanced mRNA expression of leptin, FASN, FABP4 and PPAR- γ and decreased expression of Pref-1 mRNA in cells cultured from offspring of obese dams. Our findings suggest that MO programs increased adipogenic potential of SV cells combined with increased lipogenic gene expression in WAT. These changes may underlie greater adiposity and obesity risk in the offspring later in life.

Sources of Research Support: ARS-CRIS 6251-51000-005-00D and R01-DK084225.

Nothing to Disclose: KS, YZ, PK, SJB, MJR, TMB

sort_order

2952

Pub #

OR31-5

Session Information

ORAL SESSION: BASIC/TRANSLATIONAL - Adipogenesis, Adiposity & Adipocyte Biology: Novel Findings in Basic Research (11:15 AM-12:45 PM)

Title

GH-Stimulated Lipolysis Is Disrupted in Mice with Adipocyte-Specific Deletion of JAK2, Leading to GH-Dependent Obesity

Author String

SM Nordstrom, JL Tran, BC Sos, K-U Wagner, EJ Weiss
University of California, San Francisco, San Francisco, CA; University of Nebraska Medical Center, Omaha, NE

Body

We recently reported fatty liver (FL) in mice with conditional deletion of JAK2 in hepatocytes (JAK2L). FL was due to both an increase in the hepatic uptake of free fatty acids (FFA) and an increase in FFA levels as the result of increased GH-stimulated lipolysis. By crossing JAK2L mice to GH-deficient "little" mice, we showed that elimination of GH secretion was sufficient to rescue the FL phenotype in JAK2L animals. However, the mechanism by which GH promotes lipolysis remains unclear; it may act directly on adipocytes by interfering with intracellular signaling, indirectly via macrophages or other cells, or through the actions of IGF-1. To determine the relative contribution of direct GH signaling in adipocytes on GH-stimulated lipolysis, we generated mice with conditional deletion of JAK2 in adipocytes (JAK2A) and crossed them to JAK2L mice. Since we had shown that the loss of GH secretion resulted in normalization of FL in JAK2L mice, we reasoned that JAK2L/A mice would allow us to determine whether the effects of GH on promoting lipolysis were due to direct or indirect effects on adipocytes. In agreement with our previous report, JAK2L mice had profound FL with a 5.8 fold increase in liver TG ($P < 0.0001$) and a 1.3 fold increase in liver mass ($P < 0.01$) vs WT. Strikingly, the livers of JAK2L/A were normalized, with measures of liver TG and liver mass that were comparable to WT ($P > 0.05$). While the fat mass, percent body fat, and epididymal fat pad weight were similar in JAK2L, JAK2A, and WT mice, there was a 2.3 fold increase in fat mass and percent body fat, and a 1.8 fold increase in fat pad weight in JAK2L/A mice vs WT ($P < 0.0001$). Thus, JAK2A animals with normal GH levels had no changes in adiposity as compared to WT, but in the compound JAK2L/A mutant mice with high circulating GH there was a paradoxical and significant increase in adiposity. To determine how GH administration would affect fat mass in JAK2A mice, we administered a short course of high dose GH to a cohort of JAK2A and WT mice; strikingly, we found that there was a 1.6 fold increase in fat mass ($P < 0.05$) and percent body fat ($P < 0.01$) in response to GH treatment in JAK2A versus WT mice. In summary, these data suggest that direct GH signaling in adipocytes is necessary for GH-stimulated lipolysis. Disrupting GH signaling in adipocytes has important consequences on fat metabolism leading to paradoxical obesity in response to GH.

Sources of Research Support: UCSF Liver Center pilot/feasibility grant P30 DK026743 awarded to EJW; NIH Grant CA117930 awarded to KW; NHLBI training grant awarded to SMN.

Nothing to Disclose: SMN, JLT, BCS, K-UW, EJW

sort_order 2953
Pub # OR31-6
Session Information ORAL SESSION: BASIC/TRANSLATIONAL - Adipogenesis, Adiposity & Adipocyte Biology: Novel Findings in Basic Research (11:15 AM-12:45 PM)
Title Targeted Deletion of Adipocytes by Apoptosis Leads to Adipose Tissue Recruitment of Alternatively Activated M2-Macrophages
Author String P Fischer-Posovszky, Q Wang, IW Asterholm, JM Rutkowski, M Wabitsch, PE Scherer
The University of Texas Southwestern Medical Center, Dallas, TX; University of Ulm, Ulm, Germany
Body
Introduction: Obesity is associated with an infiltration of macrophages into adipose tissue. The excessive accumulation of fat causes a phenotypic switch of macrophages from an alternatively activated M2-like phenotype towards a pro-inflammatory M1 phenotype.
Macrophages are generally responsible for clearing old, pathological and dead cells from tissues. In this study we investigate the role of fat cell apoptosis in adipose tissue macrophage accumulation.
Methods: We took advantage of the FAT-ATTAC (apoptosis through targeted activation of caspase-8) mouse model. Apoptosis of adipocytes was induced by administration of a FK1012 analog leading to the dimerization of a membrane-bound, adipocyte-specific caspase 8-FKBP fusion protein.
Results: After 2 weeks of dimerizer treatment we detected markedly reduced levels of adipose tissue and a robust down-regulation of circulating adipokines. qPCR and immunohistochemistry on epididymal and inguinal fat depots revealed an increase of the macrophage markers F4/80 and CD11c. Using polychromatic flow cytometry we detected an up-regulation of the alternatively activated M2 macrophage markers, CD206 and CD301, on F4/80 positive macrophages.
Conclusion: Apoptosis of adipocytes caused an accumulation of alternatively activated, anti-inflammatory M2 macrophages. We conclude that apoptosis of adipocytes is a healthy process contributing to normal tissue homeostasis without causing a pro-inflammatory milieu. Other and/or additional factors are responsible for switching towards a M1 pro-inflammatory macrophage phenotype observed in obesity.

Sources of Research Support: German Research Association (FI1007/1); Margarete von Wrangell fellowship awarded to PFP.

Nothing to Disclose: PF-P, QW, IWA, JMR, MW, PES

sort_order 2954
Pub # OR32-1
Session Information ORAL SESSION: BASIC/TRANSLATIONAL - Mechanisms in Adrenal Development & Cardiovascular Endocrinology (11:15 AM-12:45 PM)
Title Tcf21-Expressing Cells in the Adrenal Capsule Give Rise to Differentiated Adrenocortical Cells
Author String MA Wood, I Garg, A Acharya, MD Tallquist, GD Hammer
University of Michigan, Ann Arbor, MI; University of Texas Southwestern Medical Center, Dallas, TX
Body
Recent data support a model whereby the adrenal capsule serves as a bona fide stem/progenitor cell population that gives rise to *Nr5a1*-expressing subcapsular cells and differentiated adrenocortical cells. The mechanisms by which *Nr5a1* is repressed in the capsular cell and/or activated in the cortical cell are unknown. The expression of *Nr5a1* is controlled in part by the binding of the differentiation-regulating transcription factors, Upstream stimulatory factors 1 and 2 (*Usf1* and *Usf2*), to an E-box element in the *Nr5a1* proximal promoter. Our studies have focused on transcription factor 21 (*Tcf21*), an E-box binding protein, which is thought to inhibit *Nr5a1* promoter activity, although the exact mechanism is unknown. We propose that *Tcf21* is a negative regulator of *Usf*-mediated *Nr5a1* expression in the quiescent capsular stem/progenitor cells of the adrenal gland and that regulated loss of *Tcf21* inhibition drives adrenocortical cell differentiation. In our model, *Nr5a1*⁽⁻⁾/*Tcf21*⁽⁺⁾ progenitor cells give rise to *Nr5a1*⁽⁺⁾/*Tcf21*⁽⁻⁾ cells. We have characterized *Tcf21* promoter activity in the adrenal capsule of mice expressing *LacZ* driven by the *Tcf21* promoter. In the postnatal adrenal gland, *Tcf21* promoter activity is present in the majority of cells in the capsule until around 10 days after birth when the number of cells with *Tcf21* promoter activity gradually decreases until puberty. *LacZ* expression has not been found in cells of the underlying adrenal cortex. Current studies have been initiated to determine if *Tcf21*⁽⁺⁾/*Nr5a1*⁽⁻⁾ capsular cells give rise to *Nr5a1*⁽⁺⁾ adrenocortical cells. Lineage tracing studies are using mice in which the *Tcf21* promoter, driven by tamoxifen-inducible Cre recombinase, yields YFP expression in all progeny of *Tcf21*-expressing cells. Preliminary studies indicate that treatment with tamoxifen as early as E9.5 induces the expression of YFP in the capsule. YFP expression can later be detected in an increasingly centripetal population of adrenocortical cells as late as two months after birth. These results indicate that capsular cells, in which the *Tcf21* promoter was once active, are able to give rise to cells in the adrenal cortex. Our data provide evidence that *Tcf21*⁽⁺⁾/*Nr5a1*⁽⁻⁾ cells of the adrenal capsule give rise to *Nr5a1*⁽⁺⁾/*Tcf21*⁽⁻⁾ adrenocortical cells and support our hypothesis that the adrenal capsule is a niche for *Nr5a1*⁽⁻⁾ stem/progenitor cells that serve to regulate the homeostatic expansion of *Nr5a1*⁽⁺⁾ adrenocortical cells.

Sources of Research Support: National Institutes of Health (NIH) Grant DK062027 (to G.D.H.) and Grant P30DK079328 (to M.D.T./UT Southwestern O'Brien Kidney Research Core Center) from National Institute of Diabetes and Digestive and Kidney Diseases, Grant CA134606 from the National Cancer Institute (to G.D.H.); M.A.W. was supported, by NIH Grant T32 DK07245 from the Training Program in Endocrinology and T32 HD007048 from the Training Program in Reproductive Sciences at the University of Michigan.

Disclosures: GDH: Ad Hoc Consultant & Study Investigator, OSI; Ad Hoc Consultant, Orphagen, HRA Pharma; Study Investigator, Corcept. Nothing to Disclose: MAW, IG, AA, MDT

sort_order

2955

Pub #

OR32-2

Session Information

ORAL SESSION: BASIC/TRANSLATIONAL - Mechanisms in Adrenal Development & Cardiovascular Endocrinology (11:15 AM-12:45 PM)

Title

Zona Fasciculata Cells Arise from the Zona Glomerulosa

Author String

BD Freedman, DL Carlone, NA Guagliardo, PQ Barrett, JA Majzoub, DT Breault
Children's Hospital Boston, Boston, MA; University of Virginia School of Medicine, Charlottesville, VA

Body

The adrenal cortex has extensive regenerative capacity but the molecular and cellular mechanisms by which its concentric layers arise postnatally and are maintained throughout life are poorly understood. A better understanding of adrenal gland zonation and maintenance should culminate in new treatment options for patients with adrenal disorders. The best supported model of adrenal zonation is the centripetal or cell migration theory. We hypothesize that functional zona Glomerulosa (zG) cells are required for ongoing zona Fasciculata (zF) formation and function. To test this hypothesis, we created a genetically engineered mouse line in which Cre recombinase is expressed under the control of the zG-specific aldosterone synthase (AS) gene locus (AS-Cre). We used homologous recombination to replace the AS coding sequence. Heterozygous AS-Cre mice do not exhibit haploinsufficiency and have levels of aldosterone and plasma renin activity comparable to wildtype littermates. In contrast, homozygous AS-Cre mice are functional knockouts with aldosterone deficiency. To follow adrenal lineage development, we performed cell fate mapping studies by crossing heterozygous AS-Cre mice with Cre-reporter lines to selectively and permanently mark zG cells. Histological and whole mount analyses demonstrated single permanently labeled zG cells at postnatal day 1, and by 3 weeks of age, nearly all zG cells were labeled. Interestingly, by 5 weeks of age, there was also significant labeling of zF cells, as radial linear stripes that emanated from the zG. This centripetal labeling pattern continued to progress with ongoing adrenocortical remodeling. These data indicate that zG cells contribute to the maintenance of the zF zone, and provide strong support for the centripetal model of adrenal zonation. Lineage-ablation studies are underway to evaluate the effect of zG depletion on zonation and zF function. We speculate that ablation of the zG will result in mineralocorticoid as well as glucocorticoid deficiency, demonstrating a functional link between these zones. Future studies will investigate whether transdifferentiation of zG into zF cells is a fundamental property of adrenocortical zonation and maintenance.

Nothing to Disclose: BDF, DLC, NAG, PQB, JAM, DTB

sort_order 2956
Pub # OR32-3
Session Information ORAL SESSION: BASIC/TRANSLATIONAL - Mechanisms in Adrenal Development & Cardiovascular Endocrinology (11:15 AM-12:45 PM)
Title A New Presentation of Chimeric CYP11B1/CYP11B2 Gene with Low Prevalence of Primary Aldosteronism and Atypical Gene Segregation Pattern
Author String CA Carvajal, CM Campino, JE Tichauer, CP Valdivia, R Bancalari, M Aglony, A Martinez, H Garcia, V Giadrosich, PA Salman, PL Trejo, R Baudrand, CE Fardella
P Universidad Catolica de Chile, Santiago, Chile; P Universidad Catolica de Chile, Santiago, Chile; Universidad de Valparaiso, Santiago, Chile
Body Familial Hyperaldosteronism type I (FH-I) is an autosomal dominant disorder causing hypertension, cardiac hypertrophy and cerebrovascular abnormalities. FH-I is caused by an unequal cross-over of the gene encoding steroid 11 β -hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2), giving rise to a chimeric CYP11B1/CYP11B2 gene (CG) gene that displays aldosterone synthase activity showing synthesis of abnormal corticosteroids as free 18-hydroxycortisol (18OH-F). Aim: To describe a family carrying a new subtype of FH-I in relation to its inheritance and clinical-biochemical parameters. Subjects and Methods: We studied 4 generations of a family with hispanic-american ethnicity, being the index case a teenager of 15 years-old (III-10), who debuted with hypertension, hyperaldosteronism and normokalemia. The others members of the family were 27 from generation (Gen) I, II, III and IV. In all of them the arterial blood pressure (ABP) was measured and classified by hypertension (HT) stages. We measured serum aldosterone (Aldo) and plasma renin activity (PRA), calculated the Aldo to PRA ratio (ARR) and urinary free 18OH-F (NV (X \pm SD)=99.3 \pm 17.2 [μ g/g Creatinine]). We identified the CG by XL-PCR, and further analyses were performed by sequencing. Statistical analysis by exact binomial method to predict inheritance pattern was made. Results: We studied 28 subjects; 16/28 adults and 12/28 children (3 younger than 2 years-old). The prevalence of HT, primary aldosteronism (PA), CG and 18OH-F are the following: Gen-II HT: 100% (5/5), PA: 20% (1/5), CG: 100% (5/5), high 18OH-F: 100% (5/5); Gen-III HT: 64% (9/14), PA: 64% (9/14), CG: 100% (14/14), high 18OH-F: 100% (14/14); Gen-IV HT: 25% (2/8), PA: 38% (3/8), CG: 62% (5/8), high 18OH-F: 84% (5/6). Sequence analysis showed the unequal cross-over of CYP11B1/CYP11B2 in a region of 50 bp between intron 3 CYP11B1 (C.2937-40) and exon 4 CYP11B2 (C.2937+10). Statistical analysis showed that 100% of CG inheritance in Gen-II and III was not due to random segregation ($p < 0.001$). Conclusion: We describe a family with a CG and high 18 OH-F suggesting a FH-I. However, there are two differences with the classical FH-I syndrome: 1) The presence of PA was near to 50% of affected patients; 2) The inheritance of CG was close to 100% in the offspring, showing a different gene segregation pattern. These findings suggesting a new presentation of chimeric CYP11B1/CYP11B2 gene from the previously described.

Sources of Research Support: FONDECYT (1100356), FONDEF (D0811087) and NMII (P07/088-F) Chilean Grants.

Nothing to Disclose: CAC, CMC, JET, CPV, RB, MA, AM, HG, VG, PAS, PLT, RB, CEF

sort_order 2957
Pub # OR32-4
Session Information ORAL SESSION: BASIC/TRANSLATIONAL - Mechanisms in Adrenal Development & Cardiovascular Endocrinology (11:15 AM-12:45 PM)
Title Study of the Role of KCNK3 and KCNK9 in the Pathogenesis of Primary Aldosteronism
Author String S Boulkroun, SK Tareen, H Perdry, J-F Golib Dzib, O Karam, B Samson-Couterie, C Simian, S Bendahou, A Benecke, J Barhanin, X Jeunemaitre, M-C Zennaro
INSERM, Paris, France; University Paris Descartes, Paris, France; Hopital Europeen Georges Pompidou, Paris, France; UMR-S0669, Villejuif, France; INSERM, Villejuif, France; IHES, Bures sur Yvette, France; CNRS, Nice, France; University Nice-Sophia Antipolis, Nice, France
Body Primary aldosteronism (PAL) is the most common form of secondary hypertension due to autonomous aldosterone production. The two principal causes are Aldosterone Producing Adenoma (APA) and Bilateral Adrenal Hyperplasia (BAH). But if the causes are known, the molecular etiology of primary aldosteronism remains elusive. In mouse models, the genetic deletion of TWIK-related acid-sensitive K (TASK)-1 and TASK-3 channels removes an important background K current that results in a marked depolarization of adrenal zona glomerulosa cell membrane potential, leading to the autonomous overproduction of aldosterone. The importance of TASK channel dysfunction in human primary aldosteronism is uncertain, motivating their molecular analysis. Expression of *KCNK3* and *KCNK9*, coding for TASK1 and TASK3 respectively, was investigated by *in situ* hybridization in 6 control adrenal glands and 20 adrenals from patients with APA. In control adrenal, the *KCNK3* gene is highly expressed in the three layers of the adrenal cortex, while the expression of *KCNK9* is barely detectable, and restricted to zona glomerulosa. In APA, *KCNK3* expression is detected in a majority of patients, while *KCNK9* expression is low and heterogeneous among samples. Strikingly, *KCNK9* is highly expressed in the hyperplastic peritumoral zona glomerulosa, indicating a possible positive feed-back regulation of KCNK9 expression by high aldosterone or low potassium. Transcriptome profiling performed on 43 APA and 11 control adrenals showed a slight, but significantly increased expression of *KCNK3* in adenomas compared to controls that is positively correlated to CYP11B2 expression. Comparison of allelic distribution in a large case control study showed a significant association PAL (both APA and BAH) with single nucleotide polymorphisms in the *KCNK3* gene. However, sequencing of both *KCNK3* and *KCNK9* coding exons and exon-intron junctions in 825 patients did not reveal the presence of rare functional coding sequence variants, nor did we identify any somatic mutation in 40 tumoral DNA samples. Taken together, genetic studies indicate an involvement of *KCNK3* (TASK1) in the pathogenesis of PAL. Quantitative alterations of *KCNK3* expression observed in APA may be a primary phenomenon or secondary to increased aldosterone production; alternatively, they might result from deregulation of master transcriptional regulators or upstream signaling cascades.

Sources of Research Support: The Agence Nationale pour la Recherche (Physiopath 2007; Genopath 2008); The Fondation pour la Recherche sur l'Hypertension Arterielle (AO 2007); Institutional funding from INSERM.

Nothing to Disclose: SB, SKT, HP, J-FGD, OK, BS-C, CS, SB, AB, JB, XJ, M-CZ

sort_order

2958

Pub #

OR32-5

Session Information

ORAL SESSION: BASIC/TRANSLATIONAL - Mechanisms in Adrenal Development & Cardiovascular Endocrinology (11:15 AM-12:45 PM)

Title

Mechanisms of Aldosterone-Stimulated Atherosclerosis: A Potential Role for Placental Growth Factor

Author String

AP McGraw, C Nowlin, H Nickerson, NN Mohammad, P Carmeliet, IZ Jaffe

Body

Tufts Medical Center, Boston, MA; Vlaams Instituut voor Biotechnologie, Leuven, Belgium; Katholieke Universiteit Leuven, Leuven, Belgium; Tufts Medical Center, Boston, MA

Increasing evidence supports that the steroid hormone aldosterone (aldo) and its receptor, the mineralocorticoid receptor (MR), act directly in the vasculature to promote cardiovascular disease in humans. In clinical trials, MR antagonists reduce mortality, heart attacks, and strokes out of proportion to modest effects on blood pressure, and recent trials of the lipid-regulating drug Torcetrapib revealed unexpected increases in mortality and atherosclerosis, a chronic inflammatory disease of the vasculature, that correlated with off-target increases in aldo levels. In animal models, aldo increases atherosclerotic burden by unknown mechanisms. To explore the role of aldo in the mechanism of atherosclerosis, we characterized the effects of aldo infusion on plaque burden, distribution, and composition over time in the ApoE^{-/-} mouse model of atherosclerosis. Aldo infusion to levels found in patients with cardiovascular disease had no effect on traditional cardiac risk factors, but significantly increased atherosclerotic plaque size in areas of turbulent flow where early plaques form, including the aortic root (1.8-fold, $p < 0.001$ at 4 weeks) and the aortic arch (2.3-fold, $p < 0.01$ at 8 weeks). Aldo did not affect lesion size at either timepoint in the descending aorta, a laminar blood flow region where atherosclerosis is less common in humans. In addition, aortic root plaques in aldo-treated animals contain more macrophages (2.2-fold, $p = 0.03$) and more lipids (2.1-fold, $p = 0.003$), and exhibit a trend towards lower collagen content (0.8-fold, $p = 0.4$). These data demonstrate that aldo promotes development of early, highly inflammatory atherosclerotic lesions in areas of turbulent flow. In humans, this plaque phenotype is associated with increased risk of rupture, the cause of heart attack and stroke. To begin to address the mechanism, we performed gene expression profiling on vascular tissue to identify aldo-regulated vascular genes. One of these genes is the vascular endothelial growth factor family member placental growth factor (PGF), which is known to recruit macrophages and promote atherogenesis. We demonstrate that in human vessels, PGF expression is enhanced in atherosclerotic vessels and is inhibited by MR antagonists. PGF expression is also enhanced, both at baseline and with aldo, in the aortic arch compared to the descending aorta. The role of PGF in aldosterone-stimulated atherosclerosis is being explored in ApoE^{-/-}/PGF^{-/-} mice.

Sources of Research Support: NIH Grant 5R01HL095590-02 awarded to IZJ; American Heart Association 11POST5390010 awarded to APM.

Nothing to Disclose: APM, CN, HN, NNM, PC, IZJ

sort_order 2959
Pub # OR32-6
Session Information ORAL SESSION: BASIC/TRANSLATIONAL - Mechanisms in Adrenal Development & Cardiovascular Endocrinology (11:15 AM-12:45 PM)
Title Phenotype, SLC12A3 Genotype and Outcome of Adult Hypokalemic Patients with Inappropriate Kaliuresis Suggesting Gitelman Syndrome (GS)
Author String M-C Vantghem, A-S Balavoine, P Bataille, P Vanhille, R Azar, B Soudan, C Noel, J-L Wemeau, X Jeunemaître, R Vargas-Poussou
Lille University Hospital, Lille, France; Centre Hospitalier Général de Boulogne/Mer, Boulogne/Mer, France; Centre Hospitalier Général de Valenciennes, Valenciennes, France; Centre Hospitalier Général de Dunkerque, Dunkerque, France; Lille University Hospital, Lille, France; Lille University Hospital, Lille, France; Hôpital Européen Georges Pompidou, Lille, France
Body GS is a rare tubulopathy caused by SLC12A3 gene mutations which encodes the renal thiazide-sensitive sodium chloride co-transporter NCC, leading to hypokalemic alkalosis, secondary hyperaldosteronism, hypomagnesemia and hypocalciuria, usually diagnosed in young adults. The aim of this study was to assess the prevalence of SLC12A3 gene mutations in adult hypokalemic patients with inappropriate kaliuresis, to compare the phenotype of homozygous, heterozygous and non-mutated patients, and to determine the efficiency of treatment on blood potassium levels. Methods: Clinical and laboratory follow-up, and genetic data were recorded in 26 patients. Results: Screening of SLC12A3 gene allowed the detection of 2 mutated alleles in 15 patients (group 1, 6 homozygous and 9 compound heterozygous), one heterozygous mutation in 6 (group 2), and no mutations in 5 patients (group 3). There was no statistical difference in clinical symptoms at diagnosis between the 3 groups. Systolic blood pressure tended to be lower in patients of group 1 ($p=0.16$). Unexpectedly, hypertension was detected in 4 patients (in 1, GS was diagnosed before the age of 40 and in 3 after this age). Five patients of group 1 and 2 of group 2 had severe manifestations of GS (in group 1: symptomatic chondrocalcinosis $n=2$, growth retardation $n=2$, severe cardiac arrhythmia $n=1$; in group 2: cardiac syncope $n=1$, chondrocalcinosis $n=1$). The brother of another patient of group 1 died suddenly at the age of 23 with the same biological abnormalities as his sister. Significant differences were observed between the 3 groups in: blood potassium ($p=0.005$), chloride ($p=0.03$), magnesium ($p=0.02$), and supine aldosterone ($p=0.039$), 24H-urine chloride and magnesium levels ($p=0.04$) as well as glomerular filtration rate assessed with MDRD ($p=0.02$). Mean blood potassium levels increased from 2.8 ± 0.3 , 3.5 ± 0.5 , 3.2 ± 0.3 before treatment to 3.2 ± 0.5 , 3.7 ± 0.6 and 3.7 ± 0.3 mmol/l with treatment in groups 1, 2 and 3 respectively ($p=0.003$ for group 1). Conclusion: In adult patients referred for renal hypokalemia, we confirmed the presence of mutations of the SLC12A3 gene in 80% of cases (1). GS was more severe in patients with 2 mutated alleles. Patients with only one heterozygous mutation have mild phenotype; a second mutation or functional polymorphism cannot be excluded in this group. High blood pressure should not let the diagnosis be discarded, especially in older patients.

1) Vargas-Poussou R et al., *J Am Soc Nephrol* 2011, in press
Nothing to Disclose: M-CV, A-SB, PB, PV, RA, BS, CN, J-LW, XJ, RV-P

sort_order 2960
Pub # OR33-1
Session Information ORAL SESSION: BASIC/TRANSLATIONAL - Novel Insights into Hypothalamic Signaling (11:15 AM-12:45 PM)
Title Rapid Onset of Hypothalamic Inflammation, Reactive Gliosis and Microglial Accumulation during High-Fat Diet-Induced Obesity
Author String JP Thaler, C-X Yi, BH Hwang, X Zhao, SJ Guyenet, DA Sarruf, GJ Morton, HT Nguyen, JD Fischer, DG Baskin, BE Wisse, MH Tschop, MW Schwartz
University of Washington, Seattle, WA; Metabolic Disease Institute at University of Cincinnati-College of Medicine, Cincinnati, OH; Veterans Affairs Puget Sound Health Care System, Seattle, WA
Body Hypothalamic inflammation is a recently described phenomenon that occurs during consumption of high fat diets (HFD) and is hypothesized to promote diet-induced obesity (DIO) by causing resistance to leptin and other adiposity-related inputs. Since evidence supporting this hypothesis was generated in animals with established DIO, it remains unclear whether hypothalamic inflammation occurs early enough to play a causal role in HFD-induced obesity. We report that whereas inflammation in peripheral tissues develops only after months of HFD consumption, low-grade inflammation is evident in both rat and mouse hypothalamus within the first wk of HFD exposure. This increase in inflammatory gene expression is initially transient (~7 d) and coincides temporally with the early onset of both HFD-induced excessive energy intake and hypothalamic leptin resistance. Remarkably, this early phase of the response to HFD in both rats and mice is accompanied by an accumulation of enlarged microglia and reactive astrocytes within the mediobasal hypothalamus (MBH), a region containing key neurocircuits regulating energy homeostasis. The combination of altered astrocyte cell structure and microglial involvement is characteristic of "gliosis," a histopathological hallmark of acute neuronal injury. While the astrocyte component of MBH gliosis resolves over a similar time frame as hypothalamic inflammation, microglia continue to accumulate in the MBH over months of HFD consumption. These results suggest that the initial gliosis response may be protective, limiting HFD-induced neuronal injury and inflammation. Consistent with this hypothesis, microglia isolated from the MBH show reduced inflammatory gene expression in the first wk of HFD feeding, but late appear to perpetuate hypothalamic inflammation. These findings collectively support an "acute neuronal injury" model of DIO, in which the defense of elevated body weight results from fixed injury to neurons responsible for energy homeostasis, and suggest that interventions to avert or reverse neuronal damage have important potential in obesity treatment and prevention.
Nothing to Disclose: JPT, C-XY, BHH, XZ, SJG, DAS, GJM, HTN, JDF, DGB, BEW, MHT, MWS

sort_order

2961

Pub #

OR33-2

Session Information

ORAL SESSION: BASIC/TRANSLATIONAL - Novel Insights into Hypothalamic Signaling (11:15 AM-12:45 PM)

Title

Leptin Action Via Nos1-Expressing Hypothalamic LepRb Neurons Is Crucial for Energy Balance and Reproduction

Author String

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Body

The adipocyte-derived hormone leptin acts in the brain to suppress feeding and permit energy utilization by a variety of processes, including reproduction. The lack of leptin or its receptor (LepRb) promotes hyperphagic obesity and impaired fertility, among other phenotypes. While leptin action via hypothalamic arcuate nucleus (ARC) neuron containing proopiomelanocortin (POMC) or Agouti-related peptide (AgRP) has been studied extensively, these represent a minority of CNS LepRb neurons. Roles for other hypothalamic LepRb neurons remain poorly defined. Here, we investigate roles for leptin action in neuronal nitric oxide synthase (NOS1)-expressing LepRb neurons. We generated and utilized NOS1-cre mice to delete LepRb from NOS1 neurons (LepRb-NOS1KO mice), which represent approximately 15-20% of hypothalamic LepRb neurons. Most LepRb/NOS1 neurons lie in the ventral premammillary nucleus (PMv), although more modest numbers lie in a few other hypothalamic sites. We compared LepRb-NOS1KO mice to normal controls and mice completely null for LepRb (LepRb-KO). We find that while LepRb-NOS1KO females are modestly heavier than controls, the metabolic phenotype of LepRb-NOS1KO males is indistinguishable from that of LepRb-KO males, with pronounced hyperphagic diabetes, decreased energy expenditure, and florid diabetes. In LepRb-NOS1KO females, puberty was delayed and estrus cycling disrupted independent of adiposity. ARC LepRb signaling and gene expression was unaltered in either LepRb-NOS1KO males or females. Thus, hypothalamic LepRb/NOS1 neurons act independently of the ARC POMC/AgRP circuitry to play a crucial role in the control of the reproductive axis in females and a dominant role in the modulation of energy balance in males.

Nothing to Disclose: MLG-Y, RLL, MGM

sort_order 2962
Pub # OR33-3
Session Information ORAL SESSION: BASIC/TRANSLATIONAL - Novel Insights into Hypothalamic Signaling (11:15 AM-12:45 PM)
Title Neuronal POMC Expression and Body Weight Are Synergistically Regulated by Distal Upstream Enhancers nPE1 and nPE2
Author String DD Lam, V Otero-Corchon, FSJ de Souza, K Meece, SL Wardlaw, M Rubinstein, MJ Low
University of Michigan, Ann Arbor, MI; University of Buenos Aires, Buenos Aires, Argentina; Columbia University, New York, NY
Body Products of the proopiomelanocortin (Pomc) gene play an important role in regulating body weight, and disruption of Pomc function results in severe obesity. Previously, we identified distal upstream enhancers of the Pomc gene, called neuronal Pomc enhancers 1 and 2 (nPE1 and nPE2). These enhancers appear to specifically control Pomc transcription in the arcuate nucleus of the hypothalamus (ARC), since each enhancer drives transgene expression to Pomc cells in the ARC but not the pituitary. Moreover, deletion of both enhancers disrupts ARC but not pituitary transgene expression. To probe the functional importance of the enhancers, we generated and characterized mice bearing specific homozygous deletions of nPE1 ([Delta]1 mice), nPE2 ([Delta]2 mice), or both ([Delta]1[Delta]2 mice). The nPE-deficient mice were generated by Cre-mediated excision of a LoxP-flanked neomycin selection cassette (Fneo) at the respective enhancer site. Prior to excision of the neomycin cassette, Fneo[Delta]1[Delta]2 mice had drastic reductions in Pomc transcription (<0.4% of wild-type ARC Pomc mRNA levels) and accordingly developed severe obesity. Deletion of nPE2 did not substantially affect ARC Pomc transcription as measured by qRT-PCR of dissected hypothalamus. In contrast, [Delta]1 mice retained only 20-25% of wild-type Pomc mRNA levels and 25-30% of wild-type levels of Pomc-derived peptide α -melanocyte stimulating hormone (α -MSH) measured by RIA. [Delta]1[Delta]2 mice retained just 2-3% of wild-type ARC Pomc mRNA levels and 10-15% of wild-type α -MSH levels, indicating that the two enhancers may interact synergistically. Anterior pituitary Pomc mRNA levels were more than two-fold higher in [Delta]1[Delta]2 mice than wild-types, possibly due to lack of indirect inhibitory effects of ARC Pomc products on pituitary Pomc expression. The phenotype of nPE-deficient mice closely reflected the extent of Pomc disruption. [Delta]2 mice showed no discernable altered phenotype, [Delta]1 mice showed moderate obesity, and [Delta]1[Delta]2 mice showed severe obesity approximating that of Fneo[Delta]1[Delta]2 mice. Both male and female [Delta]1[Delta]2 and Fneo[Delta]1[Delta]2 mice displayed fasting hyperglycemia, but only females were glucose intolerant. [Delta]1 mice exhibited normal glucose homeostasis. In summary, our data show that two distal enhancers play a synergistic role in controlling transcription of Pomc in ARC neurons but not in pituitary cells. Disruption of the enhancers causes a severe obesity phenotype, indicating that these enhancers are critical for the normal regulation of energy balance.

Sources of Research Support: NIH Grant DK068400 awarded to MJL; NIH Grant DK080003 awarded to SLW.

Nothing to Disclose: DDL, VO-C, FSJdS, KM, SLW, MR, MJL.

sort_order 2963
Pub # OR33-4
Session Information ORAL SESSION: BASIC/TRANSLATIONAL - Novel Insights into Hypothalamic Signaling (11:15 AM-12:45 PM)
Title Deficiency of PTP1B in Leptin Receptor-Expressing Cells Leads to Decreased Body Weight and Improved Glucose Homeostasis
Author String RC Tsou, DE Zimmer, BC De Jonghe, KK Bence
University of Pennsylvania, School of Veterinary Medicine, Philadelphia, PA
Body Protein tyrosine phosphatase 1B (PTP1B) is a ubiquitously expressed protein tyrosine phosphatase, implicated in the negative regulation of leptin and insulin signaling. PTP1B^{-/-} mice, as well as whole brain- and POMC neuron-specific PTP1B^{-/-} mice, possess a lean metabolic phenotype attributed at least partially to improved hypothalamic leptin sensitivity. Interestingly, mice lacking both leptin and PTP1B (ob/ob;PTP1B^{-/-}) show an intermediate body weight phenotype compared to animals lacking leptin only (ob/ob), suggesting that PTP1B may have important leptin-independent metabolic effects. In this study, we generated leptin receptor (Lepr) expressing cell-specific PTP1B^{-/-} mice and compared them with whole body PTP1B^{-/-} mice and Lepr-Cre only wild type controls (WT) in an array of metabolic phenotyping measures. Lepr-specific PTP1B^{-/-} mice (Lepr-PTP1B^{-/-}) have significantly reduced body weight when maintained on high-fat diet (HFD) compared to Lepr-Cre only WT controls. Lepr-PTP1B^{-/-} mice also show a trend toward decreased body weight compared to WT controls when maintained on a normal chow diet. Interestingly, the reduction in body weight of Lepr-PTP1B^{-/-} mice on HFD was comparable to that of whole-body PTP1B^{-/-} mice, suggesting that PTP1B's metabolic effects may be restricted to its activity within leptin receptor-expressing cells. However, serum leptin levels in Lepr-PTP1B^{-/-} mice were significantly higher than in whole-body PTP1B^{-/-} mice, despite similar body weights, suggesting that PTP1B may play an important tissue-specific role in regulating leptin levels. Compared to WT animals, food intake was unchanged in Lepr-PTP1B^{-/-} mice on chow or HFD, suggesting that the reduced body weight is most likely due to increased energy expenditure as previously shown in whole-body and neuron-specific PTP1B^{-/-} mice. Additionally, Lepr-PTP1B^{-/-} mice show enhanced glucose tolerance and improved insulin sensitivity compared to WT controls, but are not as glucose tolerant as whole-body PTP1B^{-/-} mice on HFD. Overall these results demonstrate that deficiency of PTP1B in Lepr-expressing cells, in large part, underlies the metabolic phenotypes seen in previous PTP1B-deficient models. Whether the metabolic improvements in Lepr-PTP1B^{-/-} mice are due exclusively to regulation of the leptin receptor *per se*, however, remains to be determined.

Sources of Research Support: NIH grant DK082417 awarded to KKB.

Nothing to Disclose: RCT, DEZ, BCDJ, KKB

sort_order 2964
Pub # OR33-5
Session Information ORAL SESSION: BASIC/TRANSLATIONAL - Novel Insights into Hypothalamic Signaling (11:15 AM-12:45 PM)
Title MicroRNA Ablation in POMC Neurons Leads to Severe Obesity and Glucocorticoid Deficiency
Author String Y Greenman, Y Kuperman, I Navon, Y Keshet, S Rodrig-Haramati, S Gil, N Stern, A Chen
Tel Aviv-Sourasky Medical Center and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; The Weizmann Institute of Science, Rehovot, Israel
Body MicroRNAs have important roles in neuronal differentiation and survival, as well as in neuronal plasticity in the mature nervous system. To investigate the role of miRNA in the central hub connecting stress response and appetite regulation, we generated a transgenic mouse model in which Dicer was specifically deleted from POMC expressing neurons and cells, using a cre-lox system. Mice are born phenotypically normal and at the expected genetic ratio. On PND1, POMC-mRNA expression is similar in wild type and Dicer-KO mice but at six weeks of age no POMC neurons could be detected in the arcuate nucleus by immunostaining, indicating that miRNAs are essential for survival of these neurons. Similarly, POMC-mRNA expression in the hypothalamus of dicer-KO mice was reduced by 96% from the levels in WT animals ($p=0.0009$). AgRP, Leptin receptor and NPY mRNA levels were reduced by 87% ($p=0.003$), 32% ($p=0.02$), and 26% ($p=0.09$) respectively. POMC and CRFR1 mRNA levels were undetectable in the anterior pituitary gland of Dicer-KO mice. Consequently, basal and stress-induced corticosterone levels were undetectable in these mice. Weight gain and fat mass were significantly more prominent in Dicer-KO mice: 15-20 week- old Dicer $-/-$ and $+/-$ males weighted 42 ± 2.9 and 32 ± 0.5 g respectively ($p=0.003$) and had $21.1\pm 3.4\%$ and $9.3\pm 0.9\%$ fat mass ($p=0.0029$). Interestingly, although free thyroxine levels were similar between the groups, total tri-iodothyronine levels were significantly higher in the Dicer-KO (45.4 ± 3.7 ng/ml) in comparison to heterozygotes (29.3 ± 3.8 ng/ml) and wild type mice (32.7 ± 4.4 ng/ml; $p=0.017$). As could be expected, $-/-$ were glucose intolerant, responding with higher glucose levels after a glucose load (357 ± 34 vs 247 ± 13 mg% at 30 min ($p=0.007$)). Nevertheless, total ($p=0.009$), HDL ($p=0.003$) and LDL ($p=0.001$) cholesterol levels were significant lower in Dicer-KO, whereas there were no differences in triglyceride values. In conclusion, postnatal POMC neuronal death due to microRNA ablation leads to development of obesity and increased fat mass despite glucocorticoid deficiency.
Nothing to Disclose: YG, YK, IN, YK, SR-H, SG, NS, AC

sort_order 2965
Pub # OR33-6
Session Information ORAL SESSION: BASIC/TRANSLATIONAL - Novel Insights into Hypothalamic Signaling (11:15 AM-12:45 PM)
Title Biophysical Properties of KISS1 Neurons
Author String R Frazao, RM Cravo, J Donato, Jr, JK Elmquist, JM Zigman, KW Williams, CF Elias
The University of Texas Southwestern Medical Center at Dallas, Dallas, TX
Body Mice with disruption of kisspeptin receptor or Kiss1 genes do not undergo puberty. Both sexes are infertile, with poor gonadal growth and impaired gametogenesis. Neurons expressing Kiss1 mRNA are distributed in the anteroventral periventricular nucleus (AVPV), the anterior periventricular nucleus (PeN) and the arcuate nucleus (ARC). In these sites, Kiss1 mRNA is differentially regulated by estrogen. The goal of the present work is to determine the electrophysiological properties of identified Kiss1 neurons and whether changing levels of estrogen acutely modifies the cellular activity of Kiss1 neurons. In order to better identify Kiss1 neurons, we generated transgenic mice expressing Cre-recombinase driven by Kiss1 regulatory elements. These mice (Kiss1-Cre) were crossed with Rosa26GFP mice, which express the green fluorescent protein (GFP) in a Cre-dependent manner. GFP neurons in hypothalamic slice preparations from female mice in diestrus were targeted for whole cell patch-clamp recordings. When K⁺ was used as the major cation in the recording pipette AVPV Kiss1 neurons had a resting membrane potential (RMP) of -50.6 ± 2.6 mV (n=5) and PeN Kiss1 neurons resting at -59.4 ± 1.1 mV (n=5). ARC Kiss1 neurons had a RMP of -53.4 ± 1.8 mV (n=9). Within Kiss1 neurons of the AVPV and PeN the frequency and amplitude of spontaneous inhibitory postsynaptic current (sIPSC) was 0.3 ± 0.06 Hz and 31.1 ± 2.7 pA (n=24); and in the ARC was 0.14 ± 0.02 Hz and 24.7 ± 3.6 pA (n=12). The frequency and amplitude of spontaneous excitatory postsynaptic current (sEPSC) within Kiss1 neurons in the AVPV/PeN was 0.8 ± 0.09 Hz and 20.2 ± 1.1 pA (n=24); and in the ARC was 0.5 ± 0.08 Hz and 18.8 ± 1.3 pA (n=14). The sEPSC and sIPSC observed in Kiss1 neurons of the AVPV, PeN and ARC could be blocked by application of ionotropic glutamate receptor antagonists (Kynurenic acid, CNQX, and AP5) or GABAA receptor antagonists (picrotoxin), respectively. We next assessed if lack of estrogen (ovariectomized mice) induces biophysical changes in Kiss1 neurons. The sIPSC and sEPSC frequency and amplitude were increased in Kiss1 neurons only in the ARC. Our findings suggest that Kiss1 neurons located in specific hypothalamic sites show distinct electrophysiological properties. Our results also indicate that changes in circulating levels of estrogen induce biophysical changes in Kiss1 neurons in the ARC. Future experiments are aimed at further delineating the physiological relevance of our findings.

Sources of Research Support: NIH Grant K01 DK087780 to KWW, R01 HD061539 to CFE, National Council for Scientific and Technological Development (CNPq-Brazil) 201804/2008-5 to RF, Regent's Scholar Research Award and the President's Council Research Award (UTSW).

Nothing to Disclose: RF, RMC, JD, JKE, JMZ, KWW, CFE

sort_order 2966
Pub # OR34-1
Session Information ORAL SESSION: TRANSLATIONAL - Sexual Differentiation & Reproductive Development: Influences of Endocrine-Disrupting Chemicals & Genetics (11:15 AM-12:45 PM)
Title *In Utero* Exposure to Bisphenol A (BPA) in Late Pregnancy Alters Uterine Expression of *HOX* and *WNT* Genes in Female Rhesus Monkeys at Birth
Author String KC Calhoun, E Padilla-Banks, PA Hunt, CA VandeVoort, CJ Williams
The University of North Carolina, Chapel Hill, NC; National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC; Washington State University, Pullman, WA; University of California, Davis, CA
Body There is ubiquitous human exposure to bisphenol A (BPA), a component of polycarbonate plastics that is widely employed in the food and medical industries. BPA is detected in the urine of 90% of Americans aged 6-60, with levels highest in children. In rodents, BPA is an [endocrine disruptor] that has estrogenic activity in the female reproductive tract (FRT) and can alter the timing of pubertal onset. Much less is known regarding whether or not BPA is an endocrine disruptor in humans. We used Rhesus monkeys to test the hypothesis that prenatal exposure to BPA alters development of the primate FRT because these monkeys are similar to humans with regard to BPA physiology, pharmacology and metabolism. Pregnant Rhesus monkeys carrying a single female fetus were exposed to BPA orally (400 ug/kg/day) or via subcutaneous capsules (~140 ug/kg/day) from gestational day 100 until the day of delivery, a time period similar to the third trimester of human pregnancy. These dosing regimens aimed to achieve serum BPA levels found in adult women (1-2 ng/ml). The uteri of the offspring were harvested on the day of birth and then examined histologically and by microarray analysis. There were no gross uterine abnormalities observed. Histological analysis revealed subtle differences in epithelial glandular morphogenesis in subcutaneous BPA-exposed females as compared to controls. Of the >19,000 genes on the Agilent Rhesus monkey microarray, 883 genes were significantly altered (p<0.01; corrected for multiple comparisons) in orally-dosed animals as compared to controls. Microarray data for the subcutaneous exposure group is pending. Expression of a remarkable number of homeobox transcription factors was significantly altered in oral BPA-exposed animals. Indeed, 5 of 36 homeotic complex (*HoxA-D*) genes present on the microarray, including *HOXA13* and *HOXC9*, were altered more than 1.5-fold. Appropriate expression of *HOX* genes is critical for embryonic axis patterning including differentiation of the rudimentary FRT into oviduct, uterus, and cervix. Mutations of *HOXA13* in humans are associated with [hand foot-genital syndrome], which includes Mullerian anomalies. Another gene important for FRT development, the secreted signaling factor *WNT4*, was upregulated 1.6-fold. These findings suggest that fetal primate exposure to BPA alters expression of critical uterine genes and places females at risk for abnormal FRT development and diminished reproductive function.

Nothing to Disclose: KCC, EP-B, PAH, CAV, CJW

sort_order 2967
Pub # OR34-2
Session Information ORAL SESSION: TRANSLATIONAL - Sexual Differentiation & Reproductive Development: Influences of Endocrine-Disrupting Chemicals & Genetics (11:15 AM-12:45 PM)
Title Estrogenic EDCs Rapidly Alter Cardiomyocyte Mechanics Via Activation of Estrogen Receptor beta
Author String Y Chen, M Dong, SM Belcher, H-S Wang
University of Cincinnati, Cincinnati, OH
Body Estrogenic endocrine-disrupting chemicals (EDCs) are a structurally diverse group of compounds that mimic, or antagonize the effects of endogenous estrogens. Xenoestrogens are man-made environmental contaminants with estrogenic properties; phytoestrogens are naturally occurring estrogenic compounds. The effect of EDC exposure on the heart is currently poorly understood. In earlier studies, we showed that rapid exposure to low-doses of bisphenol A (BPA) promoted arrhythmogenic triggered activities in cardiac myocytes, and resulted in increased ventricular arrhythmias in whole hearts. In the present study, we examined the rapid actions of a range of estrogen EDCs in rat ventricular myocytes. Using myocyte contractility as an index of Ca²⁺ handling, the dose-dependencies of the actions of these estrogens were compared. 17beta-estrodial (E2) rapidly stimulated myocyte contractility and had a U-shaped dose-response curve with a most efficacious dose at 1 nM. Among the phytoestrogens tested, equol, but not genistein and daidzein, had an inverted U dose response curve. Interestingly, in contrast to the reported 1,000- to 10,000-fold less potency of phytoestrogens in genomic estrogenic activity compared with E2, equol stimulated myocyte contractility with a most efficacious dose at 1 pM, 1,000 times more potent than E2. BPA and 17alpha-ethynylestradiol (EE2) were found to have near-identical dose-dependent effects as E2, while diethylstilbestrol (DES) was the most potent among the estrogens tested. The rapid actions of the tested estrogenic EDCs were blocked by PHTPP, an estrogen receptor (ER) beta blocker, but not affected by ER alpha blocker. These estrogens, particularly equol and DES, rapidly enhanced SR Ca²⁺ reuptake and spontaneous [Ca²⁺]_i leak from the SR. These Ca²⁺ handling alterations were demonstrated in our previous studies to underlie the pro-arrhythmic effect of BPA, and are believed to be a key factor for arrhythmogenesis in cardiac diseases. There is growing interest in the potential health effects of dietary phytoestrogens. The strong potency of equol in rapidly altering myocyte Ca²⁺ handling has important implication for the cardiac actions and safety of phytoestrogens. We also demonstrate that cardiac myocytes provide a highly sensitive system for in vitro detection and testing of the rapid actions of estrogenic EDCs.

Nothing to Disclose: YC, MD, SMB, H-SW

sort_order 2968
Pub # OR34-3
Session Information ORAL SESSION: TRANSLATIONAL - Sexual Differentiation & Reproductive Development: Influences of Endocrine-Disrupting Chemicals & Genetics (11:15 AM-12:45 PM)
Title The Dietary Polyphenol Metabolite Enterolactone Activates Estrogen Signaling in Reproductive and Non-Reproductive Tissues and Regulates the Expression of Circadian Genes in Mice
Author String P Damdimpoulou, T Nurmi, A Salminen, M Yli-Heikkilä, AE Dandimopoulos, M Poutanen, P van der Saag, L Strauss, S Makela
University of Turku, Turku, Finland; Karolinska Institutet, Huddinge, Sweden; University of Eastern Finland, Kuopio, Finland; University of Turku, Turku, Finland; University of Turku, Turku, Finland; Royal Netherlands Academy of Arts and Sciences, Utrecht, Netherlands
Body Enterolactone is an enterolignan produced by gut microbiota from dietary plant lignans. Epidemiological and experimental studies have suggested that dietary lignans and enterolactone may prevent the development of breast and prostate cancer, as well as cardiovascular disease. These effects are believed to, at least in part, involve modulation of the estrogen receptor activity. However, surprisingly little is known about the in vivo estrogenicity of enterolactone. Using conventional and estrogen reporter mouse models, we investigated enterolactone's target tissues and genes, in addition to the response kinetics. Using luciferase as a reporter, the estrogen response across various mouse tissues was quantified in gonadectomized 3xERE-luc reporter mice following a single dose of enterolactone (10 mg/kg). A significant response was detected in half of the studied tissues, with following relative activity: vagina>uterus>adipose tissue>urinary bladder>pituitary gland>liver in females and pituitary gland>adrenal gland>liver>bone in males. Microarray analysis of uterine gene expression revealed that enterolactone modulated the expression of only 1 % of 17 β -estradiol target genes. Majority of enterolactone induced genes were traditional estrogen targets; however, members of the circadian signaling pathway (Clock, bMal, Per3) were also detected. Interestingly, these genes were not affected in the liver, the most extensively characterized peripheral clock tissue. The kinetic analyses revealed that enterolactone undergoes a rapid phase II metabolism when injected as a pure compound: 30 min after injection 98% of circulating enterolactone was present as conjugates. Moreover, enterolactone is efficiently excreted, as the concentration in serum fell >200-fold within the first 24 hours. In vivo imaging of female 3xERE-luc mice showed that the estrogen response exhibits similar kinetics: highest luciferase activity was detected immediately after enterolactone administration, and the response returned to baseline within 24 hours. We conclude that enterolactone activates estrogen signaling in a range of reproductive and non-reproductive tissues in both mouse genders. The observed responses were transient, which may depend on the rapid metabolism of the compound. Finally, the regulation of clock genes suggests that enterolactone may represent a link between diet, gut microbiota and the circadian signaling pathway.

Sources of Research Support: CASCADE Network of Excellence (FOOD-CT-2004-506319); Academy of Finland (123382).
Nothing to Disclose: PD, TN, AS, MY-HI, AED, MP, vdS, LS, SM

sort_order 2969
Pub # OR34-4
Session Information ORAL SESSION: TRANSLATIONAL - Sexual Differentiation & Reproductive Development: Influences of Endocrine-Disrupting Chemicals & Genetics (11:15 AM-12:45 PM)
Title Unique Gene Expression Profiles in the Mammary Gland of Prepubertal and Adult Female Rats Treated with Estradiol or Soy Protein Isolate (SPI)
Author String MJ Ronis, R Singhal, K Shankar, J Badeaux, TM Badger
University of Arkansas for Medical Sciences, Little Rock, AR
Body Concerns have arisen regarding infertility and increased breast cancer risk in women consuming soy foods, primarily because of the perceived estrogenicity of soy isoflavones such as genistein and daidzein. Two studies were conducted in mammary gland to determine if consumption of soy products induces a gene expression profile similar to that of estradiol. In Experiment 1, Sprague-Dawley rats (N = 20/group) were fed AIN-93G diets with casein or SPI from PND30. From PND50-64, rats (N = 10/group) were ovariectomized and infused s.c. with 5 mg/kg/d 17 β -estradiol (E2) to restore physiological levels. In Experiment 2, intact female rats were fed AIN-93G or SPI from PND21-33 or were additionally infused s.c. with 10 mg/kg/d E2 (N = 10/group). Mammary glands were collected and total mRNA isolated for microarray analysis. Array data were normalized using GeneSpring. Statistical analysis of genes expressed greater than 1.5-fold in Experiment 1 revealed 651 genes regulated by E2 (P < 0.05) compared to 27 genes regulated by SPI with only 6 in common between the two treatments. In Experiment 2, 391 genes were regulated by E2 (P < 0.05) and 71 by SPI with only 17 genes in common. Data were confirmed by real time RT-PCR and suggest that gene signatures of E2 and SPI in the mammary gland have little overlap in either adults or prior to puberty. Sub-sets of 164 and 116 E2-regulated genes were significantly modulated by SPI feeding in the E2 + SPI vs. E2 + casein groups. There was little evidence of additive effects, and particularly in the adults, SPI feeding actually antagonized E2 actions. In Experiment 1, SPI feeding inhibited E2-mediated induction of cyclin D1, the oncogene c-myc, several c-myc regulated genes and E2 induction of ER β -specific genes, such as Kns12 and Top2a. These data suggest that foods such as SPI, which are complex mixtures of proteins, peptides and many phytochemicals, are not estrogenic. In fact, anti-estrogenic actions of SPI on mammary cyclin D1 and c-myc pathways are consistent with epidemiological data demonstrating reduced breast cancer risk in Asian soy consumers.

Sources of Research Support: USDA CRIS 6251-51000-007-03S.

Nothing to Disclose: MJR, RS, KS, JB, TMB

sort_order 2970
Pub # OR34-5
Session Information ORAL SESSION: TRANSLATIONAL - Sexual Differentiation & Reproductive Development: Influences of Endocrine-Disrupting Chemicals & Genetics (11:15 AM-12:45 PM)
Title Exome Sequencing Reveals a Novel Cause of 46,XY Disorder of Sex Development (DSD)
Author String A Bashambo, V Karageorgou, D Lourenco, J Bignon-Topalovic, R Brauner, K McElreavey
Institut Pasteur, Paris, France; Université Paris Descartes and AP-HP, H[ocirc]pital Bic[ecirc]tre, Le Kremlin-Bic[ecirc]tre, France
Body
Exome sequencing has emerged as a very powerful tool to identify the genetic basis of rare human Mendelian disorders. This approach is particularly attractive for mutation detection in cases of Disorder of Sex Development (DSD). These conditions are refractory to classic genetic approaches. Conventional linkage analysis is difficult since familial cases are rare. A candidate gene approach has also had limited success since sex-determination, as a developmental process, is not well conserved in evolution. It has been estimated that a specific molecular diagnosis is identified in only around 20% of cases of DSD. We have therefore performed exome enrichment and high throughput sequencing using the SOLiD system on six cases of DSD. Overall, the data showed that there was a correct analyses of 96% of the Agilent High Quality Exome with >x20 coverage. The average exome coverage was x200. The power of the technique is demonstrated by one patient of north African origin who presented with ambiguous external genitalia and a 46,XY karyotype. She also had learning difficulties. Data analyses indicated that this individual carried two independent mutations in the FOG2 gene. Murine studies have previously demonstrated that Fog2 plays an essential role in gonadogenesis. The first mutation we identified is a homozygous p.M544I amino acid change. This mutation was inherited from both her normal parents, who are first cousins. The second mutation is a de novo heterozygous p.R260E mutation. This mutation is located within the N-terminal zinc finger domain. Both mutations, predicted to be damaging by in silico analysis, were not detected by sequence analysis in more than 300 ancestry-matched controls. In-vitro analysis of the biological activity of the mutant proteins revealed that the protein carrying both the mutations exhibited a quantitative and qualitative reduction in its function, suggesting that both mutations together contribute to the phenotype. Our data demonstrate the power of exome sequencing to detect pathogenic mutations in individuals presenting with gonadal anomalies and we identified a novel genetic cause of DSD.

Sources of Research Support: Grants from the Agence Nationale de la Recherche-GIS Institut des Maladies Rares; by a research grant (1-FY07-490) from the March of Dimes Foundation; by a research grant from the EuroDSD in the European Community's Seventh Framework Programme FP7/2007-2013 under grant agreement n[deg] 201444, by a research grant from the Portuguese Foundation for Science and Technology.

Nothing to Disclose: AB, VK, DL, JB-T, RB, KM

sort_order

2971

Pub #

OR34-6

Session Information

ORAL SESSION: TRANSLATIONAL - Sexual Differentiation & Reproductive Development: Influences of Endocrine-Disrupting Chemicals & Genetics (11:15 AM-12:45 PM)

Title

First Description of NANOS3 Mutation in Two Sisters with Primary Amenorrhea

Author String

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Body

Background: Primary ovarian insufficiency (POI) is a disorder associated with female infertility affecting 1 to 2% of women under 40 years old. POI may be characterized by primary amenorrhea (PA) or secondary amenorrhea (SA) in women with postpubertal onset. Several genetic mechanisms involved in proliferation and or survival of primordial germ cells (PGCs) are involved in POI pathogenesis. Mutations in *NANOS3*, a RNA-binding protein in mice result in impaired proliferation or dead of the PGCs leading to infertility in those animals. Previous study comprising 168 Caucasian and Chinese infertile women did not find mutations (1). **Objective:** Our aim was to investigate the presence of mutations in *NANOS3* in Brazilian women with POI. **Patients:** 40 women with POI, 27 with primary amenorrhea, six familial cases, all of them presenting 46,XX karyotype and elevated levels of FSH and LH. **Methods:** Genomic DNA was extracted from peripheral leukocytes, PCR amplified and sequenced. **Results:** We identified the new homozygous missense mutation (c.359G>A) in exon 1 of *NANOS3*, which changes an acid to basic amino acid (E120K), located within the zinc finger domain in two sisters with primary amenorrhea; in these patients, FSH levels were 150 and 61 U/L and LH levels were 63 and 21 U/L, respectively and the ovaries were not visualized at ultrasound. This mutation was absent in 100 female control. Two previously described SNPs, rs2016163 and rs897790 were also identified in our cohort. **Conclusions:** We report here the first mutation in *NANOS3* in women with primary amenorrhea suggesting that the capacity of *Nanos3* to prevent PGCs apoptosis in mice is also true for human beings.

(1) Qin Y et al.Fertil Steril, 2007

Nothing to Disclose: MGS, AZM, EEMFC, MYN, CNM, SD, BBM

sort_order 2972
Pub # OR35-1
Session Information ORAL SESSION: CLINICAL/TRANSLATIONAL - Male Reproductive Endocrinology: Testosterone across the Ages (11:15 AM-12:45 PM)
Title Older Men Reporting Excellent Asymptomatic Health Exhibit No Decline in Serum Testosterone, Dihydrotestosterone or Estradiol with Age: The Healthy Man Study
Author String G Sartorius, S Spasevska, A Idan, L Turner, C Allan, LP Ly, A Conway, RI McLachlan, DJ Handelsman
ANZAC Research Institute, University of Sydney, Sydney, Australia; Monash Medical Centre, Melbourne, Australia
Body Declining blood testosterone (T) during male ageing is well known from observational studies, mostly cross-sectional and obtaining only a single T measurement. Although such studies are unable to ascribe causality, some believe this represents a symptomatic age-related androgen deficiency contributing to deteriorating health of older men. We evaluated within-subject variability and effects of age and obesity (BMI) on blood T in older men reporting excellent asymptomatic health. Men over 40 years (n=325; age - 60 (median), 52 (Q1) - 67 (Q3) yr; height - 176, 171-181 cm; weight 81.8, 74.7-88.9 kg; BMI 26.3, 24.7-28.6 kg/m²) were recruited from two centres to provide history, physical examination and 9 blood samples at fixed time intervals (3 at 20 min intervals days 1 (fasting) & 2 (non-fasting), 1 on days 7, 30 and 90) over 3 months. Serum samples (n=2900, >99% completion) had steroids (T, DHT, estradiol (E2)) measured by LC-MS/MS. Serum TT did not vary (repeated measures ANOVA) within a single day, between weeks or at 3 month intervals but exhibited a small but significant decrease at 1 month. Higher within-subject variability in serum T in non-fasting (10.8% vs 4.9%, p<0.001) would require larger sample size for studies using non-fasting sera. The effects of age and obesity (BMI) were estimated (linear mixed model ANOVA) with adjustments for fasting state and centre. Serum T did not vary with age (p=0.76) but was significantly increased by fasting (+1.5 nmol/L vs non-fasting, p<0.0001) and decreased by obesity (-0.35 nmol/L per unit BMI, p<0.0001). Serum DHT increased with age (+0.011 nmol/L per year of age, p=0.001) and fasting (+0.14 nmol/L, P<0.0001) but decreased with obesity (-0.05 nmol/L per unit BMI, p<0.0001). Serum E2 did not vary with age (p=0.31) or obesity (p=0.12) but increased on fasting (+14 pmol/L, p<0.0001). Hence, among older men reporting excellent asymptomatic health, age has no effect on serum T or E2 with a minor increase in DHT while obesity decreases serum androgens (T, DHT) but not E2. Fasting produces a consistent increase in serum T, DHT and E2. These finding suggests that (a) fasting systematically over-estimates ambient serum T, DHT and E2 and (b) the modest age-related decline in blood T associated with non-specific symptoms may be due to accumulating co-morbidities of ageing rather than representing an androgen deficiency state contributing to adverse health features of male ageing.

Sources of Research Support: MBF (BUPA) Foundation.

Disclosures: RIM: Speaker, Schering Plough; Consultant, Acrux Australia, Bayer Australia Pty. Ltd.; Research Funding, Bayer Schering Pharma. Nothing to Disclose: GS, SS, AI, LT, CA, LPL, AJC, DJH

sort_order 2973
Pub # OR35-2
Session Information ORAL SESSION: CLINICAL/TRANSLATIONAL - Male Reproductive Endocrinology: Testosterone across the Ages (11:15 AM-12:45 PM)
Title Long-Term Testosterone Replacement Improves Survival in Men with Type 2 Diabetes and Hypogonadism
Author String V Muraleedharan, H Marsh, KS Channer, HT Jones
Barnsley Hospital NHS Foundation Trust, Barnsley, UK; University of Sheffield, Sheffield, UK; Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK; Sheffield Hallam University, Sheffield, UK
Body Background: Low testosterone levels in men have been shown to be associated with increased mortality. Men with type 2 diabetes are known to have a high prevalence of testosterone deficiency. We have previously presented data demonstrating an increased mortality in men with type 2 diabetes and low testosterone¹. No long term data has been published regarding the effect of testosterone replacement (TRT) in men with type 2 diabetes and hypogonadism.
Aim: We report a 6 year follow up study to examine the effect of baseline testosterone and testosterone replacement in hypogonadal men on all cause mortality in men with type 2 diabetes.
Methods: A total of 585 patients with type 2 diabetes who had testosterone levels performed between 2002 and 2005 were followed up for a mean period of 5.8years (SD1.3). After excluding death in first 6 months (n=4), patients were analysed in three groups. (1)Total Testosterone (TT) >10.4nmol/l (300ng/dl) (2) TT 12 months duration (Testosterone gel, or i.m. testosterone undecanoate).
Results: Of 581 patients analysed, 343 (59%) had TT levels >10.4nmol/l and 238(41%) had low TT. Mean age was 59.45 (SD10.8). Mean duration of TRT was 41.6 (SD+20.7) months. 60 patients received TRT for >12 months 51 of these having treatment >2 years. The low TT group were more likely to have poor diabetes control (A1c 7.5±1.3 vs. 7.1±1.4 p=0.002) and higher weight(102±21.5 vs. 95.3±18.4 p<0.0001) than normal TT group. In the low TT group treated and non-treated were equally matched for age, weight, HbA1c, smoking status, pre-existing CV disease, statin and ACEi/ARB use.
There were 72 (12.4%) deaths. The mortality rate was highest in low TT without treatment (33/182-19.2%) compared with normal TT (31/343-9%) and lowest in the TRT group (5/60-8.3%). Survival was significantly decreased in subjects with low TT without TRT (p=0.001 log rank) as compared to normal TT. In the Cox Regression model the multi-variate adjusted hazard ratio was 2.2 (95%CI 1.3- 3.7 p=0.001) for low TT without TRT. The treated group had an improved mean survival of 86.2(SE1.6) months as compared to 83.8(SE1.8) in the untreated group (p=0.048 log rank).
Conclusions: Men with type 2 diabetes and low testosterone have a significantly increased mortality. This study provides evidence which indicates that long-term TRT in hypogonadal men with type2 diabetes improves survival.

1. Muraleedharan, V., Marsh, H and Jones, T H (2010). Endocrine Reviews Supplement 1(June 2010, 31[3]: S863.

Nothing to Disclose: VM, HM, KSC, HTJ

sort_order

2974

Pub #

OR35-3

Session Information

ORAL SESSION: CLINICAL/TRANSLATIONAL - Male Reproductive Endocrinology: Testosterone across the Ages (11:15 AM-12:45 PM)

Title

Endogenous Testosterone and All-Cause and Cardiovascular Disease Mortality in Men: A Systematic Review and Meta-Analysis

Author String

AB Araujo, JM Dixon, EA Suarez, DS Allen, MH Murad, AT Wang, GA Wittert
New England Research Institutes, Inc, Watertown, MA; Mayo Clinic, Rochester, MN; The University of Adelaide, Adelaide, Australia

Body

Low testosterone (T) levels have been associated with obesity, diabetes, metabolic syndrome, insulin resistance, impaired glucose tolerance, and dyslipidemia, among other outcomes that reduce survival in men. In the past few years, several studies have reported an association between endogenous T levels and all-cause and cause-specific mortality. The objective of this analysis was to perform a systematic review and meta-analysis of population-based studies to estimate the association between T and mortality. We searched MEDLINE (1966-Dec 2010) and EMBASE (1988-Dec 2010) and reviewed reference lists from included studies. Independently and in duplicate, we assessed the methodological quality of the eligible studies and collected data on variables of interest, including study characteristics (author, publication year, study design, number subjects, length of follow-up, T collection/assay procedures, adjustment for covariates, etc.); sample characteristics (mean age, BMI, current smokers, and T level, number of deaths (overall and CVD)); and study results (relative risk (RR) of death per SD or in quantiles and 95% confidence intervals (CI)). A total of 820 studies were identified and 777 were excluded after abstract screening. Of the 43 articles selected for full-text review, 29 were excluded and 14 studies including 18,492 subjects were included in the meta-analysis (N=13 for all-cause and N=9 for CVD mortality). Mean age and T level of the subjects were 60 y and 479 ng/dL and they were followed for 9.5 y on average. Meta-analysis showed that the RRs of all-cause and CVD mortality were 1.12 (95% CI: 1.04-1.21) and 1.31 (95% CI: 1.26-1.35) per SD decrease in total T. Low versus higher T levels (generally, lowest (e.g., quartile 1) versus highest (e.g., quartile 4) category) were associated with RRs of 1.37 (95% CI: 1.13-1.67) and 1.26 (95% CI: 0.95-1.68) for all-cause and CVD mortality, respectively. Given significant heterogeneity between studies, summary estimates may be biased. Higher RRs for low T were more likely to be observed in studies that included older ($p < .001$) subjects with lower T levels ($p = .02$) and lower prevalence of smoking ($p = .03$) who were followed for less time ($p < .001$) and whose blood was sampled throughout the day ($p = .02$). In conclusion, low endogenous T levels are associated with increased risk of death in population-based studies of men, but findings depend substantially upon characteristics of the subjects and study methods.

Sources of Research Support: Award Number R01AG020727 from the National Institute on Aging. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Aging or the National Institutes of Health.

Nothing to Disclose: ABA, JMD, EAS, DSA, MHM, ATW, GAW

sort_order

2975

Pub #

OR35-4

Session Information

ORAL SESSION: CLINICAL/TRANSLATIONAL - Male Reproductive Endocrinology: Testosterone across the Ages (11:15 AM-12:45 PM)

Title

Hypogonadism with Estrogen Removal (HER): Effects of Androgens and Estrogens on Prostate-Specific Antigen in Young Adult Men

Author String

JC Pallais, H Lee, EW Yu, S-AM Burnett-Bowie, BZ Leder, CW Hahn, NE Perros, CV Barry, JS Finkelstein
Massachusetts General Hospital, Boston, MA; Massachusetts General Hospital, Boston, MA

Body

Using a GnRH agonist and different doses of testosterone (T) add-back, we had previously shown that lowering T levels below baseline reduced PSA levels whereas increasing T levels above baseline did not alter PSA levels in young men. **Methods:** To determine if these effects are due to T itself or to its conversion to estrogen (E), we recruited 2 cohorts of healthy men age 20-50. All men received goserelin acetate (Zoladex[reg], AstraZeneca LP, 3.6 mg q4wk) to suppress endogenous T and E. Men in Cohort 1 (T/E+, n=198) were randomized to treatment with 1 of 5 doses of T gel (AndroGel [reg], Abbott) daily for 16 weeks (G1-placebo; G2-1.25g; G3-2.5g; G4-5g; G5-10g). Men in Cohort 2 (T/E-, n=200) were randomized to the same T doses plus anastrozole (Arimidex[reg], AstraZeneca LP, 1 mg/d) to block T to E conversion. A third control cohort (n=35) received only placebo medications. Serum PSA levels were measured at baseline and every 4 wks for 16 wks. Within the T/E- cohort, changes in PSA between T dose groups were evaluated to assess independent T effects. PSA changes between same T dose groups were compared across the T/E+ and T/E- cohorts to assess independent E effects. **Results:** Mean serum T levels in Groups 1-5 were 44, 187, 332, 538, and 829 ng/dL in the T/E+ cohort, 41, 186, 339, 435, and 786 ng/dL in the T/E- cohort (P=NS at each dose between cohorts), and 584 ng/dL in the control cohort (P=NS vs men receiving 5g of T in the T/E+ and T/E- cohorts). Within both the T/E+ and T/E- cohorts, there was a strong dose response relationship between T doses and change in PSA. The percent changes in PSA in Groups 1-5 of the T/E+ and T/E- cohorts were -59%, -38%, -28%, -18%, and -1% and -52%, -42%, -24%, -15%, and -6%, respectively. Compared with the percent change in PSA in the control cohort (2%), PSA values decreased in men in both cohorts treated with less than 5g of T, but did not change in those receiving more than 5g of T. Aromatase inhibition had no effect on PSA changes at any T dose when compared across the T/E+ and T/E- cohorts. **Conclusions:** Androgens regulate PSA levels in a dose-dependent manner in healthy young men. Prostate responsiveness is more sensitive to androgen deficiency rather than excess, at least in the short term. E does not appear to be involved in the hormonal regulation of PSA at T levels ranging from pre-pubertal to the upper end of the reference range.

Sources of Research Support: NIH Grants R01 AG030545, K24 KD02759, and RR-1066 and an investigator-initiated grant from Abbott. AndroGel[reg] was provided at no cost by Abbott; Zoladex [reg] and Arimidex[reg] were provided at no cost by AstraZeneca Pharmaceuticals LP.

Disclosures: BZL: Consultant, Amgen; Principal Investigator, Amgen; Lilly USA, LLC. JSF: Principal Investigator, AstraZeneca; Solvay Pharmaceuticals, Inc. Nothing to Disclose: JCP, HL, EWY, S-AMB-B, CWH, NEP, CVB

sort_order 2976
Pub # OR35-5
Session Information ORAL SESSION: CLINICAL/TRANSLATIONAL - Male Reproductive Endocrinology: Testosterone across the Ages (11:15 AM-12:45 PM)
Title Kisspeptin 10 Infusion Increases LH Pulse Frequency, Pulse Size and Testosterone Secretion in Men
Author String JT George, JD Veldhuis, RA Anderson, RP Millar
The Queen's Medical Research Institute, Edinburgh, UK; Mayo Clinic, Rochester, MN; The Queen's Medical Research Institute, Edinburgh, UK; Division of Medical Biochemistry, University of Cape Town, Cape Town, South Africa
Body
Introduction: Neuroendocrine mechanisms regulating GnRH and thus LH pulse frequency are yet to be fully delineated. Injection of the hypothalamic neuropeptide kisspeptin stimulates LH secretion in men whilst kisspeptin antagonists decrease LH pulse frequency in animal models. We hypothesised that kisspeptin-10 (Kp10) infusion increases LH pulse frequency in the human male.
Methods:
Experiment 1: Four healthy men received an iv infusion of Kp10 (4mcg/kg/hr) for 22.5 hours following 9 hours of frequent (10 min interval) baseline serum sampling. Further sampling was carried out for 9 hours on the second day of the infusion. 100 mcg GnRH was administered an hour before the end of the infusion.
Experiment 2: Four healthy men received a lower dose (1.5 mcg/kg/hr) iv Kp10 infusion for 9 hours, 5 days after baseline sampling. Serum samples were obtained at 10 min intervals. LH pulses were identified using deconvolution analysis.
Results:
Experiment 1: Kp10 infusion at 4 mcg/kg/hr effected a rise in mean LH from 5.4 ± 0.7 (Mean \pm SEM) to 20.8 ± 4.9 IU/L ($p < 0.05$, $n=4$) with resultant increase in testosterone from 16.6 ± 2.4 to 24.0 ± 2.5 nmol/L ($p < 0.001$). GnRH co-administration elicited a further three-fold rise in serum LH ($p < 0.05$ vs. Kp10 alone) with a peak LH of 57.0 ± 17.8 IU/L. LH pulses were readily apparent preinfusion, but were obscured by the high LH secretion rate during Kp10 administration. FSH remained unchanged.
Experiment 2: Mean LH increased significantly from 5.2 ± 0.8 to 14.1 ± 1.7 IU/L during the lower dose infusion ($p < 0.01$, $n=4$). The increase was progressive from 7.2 ± 2.3 IU/L in the first 90 minutes of infusion to 20.4 ± 3.5 IU/L in the last 90 minutes ($p < 0.05$), while FSH increased from 3.8 ± 0.8 to 6.6 ± 0.8 IU/L ($P < 0.01$) over the corresponding time intervals. LH pulse frequency increased from 0.7 ± 0.1 to 1.0 ± 0.2 pulses/hr, ($p < 0.05$). LH secreted per pulse also increased from 3.9 ± 0.4 to 12.8 ± 2.6 IU/L ($P < 0.05$). Pulsatile LH secretion as a proportion of total LH secretion increased from $41.3 \pm 5.7\%$ to $69.5 \pm 5.9\%$ during Kp10 infusion.
Conclusions: Continuous infusion of kisspeptin-10 increases LH pulse frequency and secretory mass per pulse, and thus testosterone secretion. There was no evidence of desensitisation during infusion for up to 22.5hr. These data suggest kisspeptin is a key regulator of pulsatile GnRH secretion in man. Potential therapeutic applications include reproductive disorders characterised by decreased LH pulse frequency such as late onset male hypogonadism.

Sources of Research Support: Funded by Experimental Medicine grant G0701682 from the Medical Research Council (UK).

Nothing to Disclose: JTG, JDV, RAA, RPM

sort_order 2977
Pub # OR35-6
Session Information ORAL SESSION: CLINICAL/TRANSLATIONAL - Male Reproductive Endocrinology: Testosterone across the Ages (11:15 AM-12:45 PM)
Title Insulin-Like Peptide 3, a Novel Marker of Leydig Cell Function during Minipuberty
Author String S Cabrol, I Fennoy, JL Ross, C Bouvattier, M Leguy, M Roger, N Lahlou
Hopital Armand Trousseau, Pierre & Marie Curie University, Paris, France; Columbia University, New York, NY; Thomas Jefferson University, Philadelphia, PA; Hopital Saint Vincent de Paul, Paris-
Descartes University, Paris, France; CHU Cochin, Paris-Descartes University, Paris, France; CHU Cochin, Paris-Descartes University, Paris, France
Body Insulin-like peptide 3 (INSL3) is a peptide hormone belonging to the relaxin family, produced in mammals by the testis and ovary. In male fetuses it plays an important role in testis descent through its effect on gubernaculum differentiation and some cases of cryptorchidism have been related to a mutation either in the INSL3 gene or the receptor gene. Its secretion markedly increases during pubertal development, but its function after birth is not fully understood.
Since low serum levels of INSL3 have been reported in postpubertal males with Klinefelter (KS) syndrome, we compared INSL3 levels during minipuberty in 50 normal infants and in 50 infants with prenatally identified XXY karyotype. In addition to gonadotropins, testosterone, and the Sertoli cell markers inhibin B (INHB) and anti-Mullerian hormone (AMH) were also measured in the same infants.
In normal infants aged 16 -152 days (n=32) INSL3 levels ranged from undetectable level (<11 pg/ml) to 180 pg/ml (median 88), and in infants aged 153 - 750 days (n=18) from undetectable level to 80 pg/ml (median 32). In age-matched infants with XXY karyotype, INSL3 levels were 26-222 (median 92) at 16-152 days of age (n=32) and <11-110 pg/ml (median 39) at 153-750 days of age (n=18). There was no significant difference between control and KS infants. During minipuberty (first five months of life) INSL3 levels were significantly higher (p<0.01) than in older infants. INHB and AMH levels were similar in control and KS infants. Testosterone levels in KS were within normal range although the majority of values were below the median of controls.
In control and KS infants, INSL3 levels were positively correlated with LH levels (Spearman r=0.73 and 0.67, respectively, p<0.01) and with testosterone levels (r=0.72 and 0.57, respectively, p<0.01). On the other hand, INHB levels were highly correlated with FSH levels both in controls and infants with XXY karyotype, while there was no correlation (r=0) between the other Sertoli cell peptide hormone AMH and FSH. Similarly there was no correlation of AMH with testosterone levels, by contrast with the negative correlation reported in pubertal males.
These data give evidence that INSL3 production is sensitive to the stimulating action of LH during minipuberty and is therefore a reliable marker of Leydig cell activity. It is expected that INSL3 measurements within the first year of life will provide useful information on testis function in pituitary gonadal axis disorders.

Sources of Research Support: IREM grant 2010.

Nothing to Disclose: SC, IF, JLR, CB, M-CL, MR, NL

sort_order 2978
Pub # OR36-1
Session Information ORAL SESSION: CLINICAL - Acromegaly & Gigantism: Some Interesting Aspects (11:15 AM-12:45 PM)
Title A Case of Gigantism Associated with a Missense Mutation in the *SOCS2* Gene
Author String K Suda, G Iguchi, M Yamamoto, AE Handayaniingsih, H Nishizawa, M Takahashi, Y Okimura, H Kaji, K Chihara, Y Takahashi
Kobe University Graduate School of Medicine, Kobe, Japan; Kobe Women's University, Kobe, Japan; University of Hyogo, Akashi, Japan; Hyogo Prefectural Kakogawa Medical Center, Kakogawa, Japan
Body Suppressor of cytokine signaling (SOCS) 2 negatively regulates GH-IGF-I signaling and a targeted disruption in mice results in a gigantism. A 20-year-old Japanese man presented tall stature with a height of 188.2 cm (+3.18 SD score) and a weight of 100.6kg (+3.35 SD score). He manifested prognathism, jaw malocclusion and hyperhidrosis, which are compatible with gigantism caused by GH producing pituitary tumor. Endocrinological data demonstrated that basal GH levels were within normal range and a GH nadir during an oral glucose tolerance test was suppressed to normal range. Serum IGF-I levels were around upper limit of the normal range. MRI examination revealed no abnormal findings in the pituitary. To elucidate the pathophysiology, we analyzed *SOCS2* gene in the patient and found a heterozygous missense mutation, which converted Ser to Asn at a position of the 52th amino acid that localized in the SH2 domain of SOCS2. Given that *SOCS2* heterozygous knockout male mice showed a significant overgrowth and the striking similarity in the phenotype and endocrinological findings between the patients and the mice, although the functional analysis of the mutation is now under investigation, it is hypothesized that the mutation in *SOCS2* gene may be causally associated with gigantism without GH-producing pituitary tumor.

Nothing to Disclose: KS, GI, MY, AEH, HN, MT, YO, HK, KC, YT

sort_order

2979

Pub #

OR36-2

Session Information

ORAL SESSION: CLINICAL - Acromegaly & Gigantism: Some Interesting Aspects (11:15 AM-12:45 PM)

Title

Impact of Germline AIP Mutations on Tumor Characteristics and Management in Young Acromegalic Patients: Results of an Age- and Tumor-Diameter-Matched Cohort Study

Author String

MA Tichomirowa, M Theodoropoulou, AF Daly, M-L Jaffrain Rea, LA Naves, RS Auriemma, P Petrossians, A Beckers

Body

University of Liège, Belgium; Max Planck Institute of Psychiatry, Munich, Germany; University of L'Aquila and Neuromed, Pozzilli, Italy; University of Brasilia, Brasilia, Brazil

Background: Mutations in the aryl hydrocarbon receptor interacting protein (AIPmut) occur in 15-25% of familial isolated pituitary adenoma (FIPA) kindreds and less commonly in unselected sporadic pituitary adenomas cohorts (1). Pituitary adenoma patients with AIPmut are younger at disease onset and diagnosis than those with normal AIP sequences; they present most frequently with large somatotropinomas and require a greater relative treatment burden to achieve control (2). It is not known if these clinical features may be attributable to the large tumor size or to intrinsic tumor characteristic caused by AIPmut.

Methods: To investigate this question, we compared disease and treatment characteristics in two cohorts of somatotropinoma patients, with and without AIPmut, that were matched for age at first symptoms (<30 years old) and tumor size (macroadenoma). The AIPmut group comprised 57 patients, who were compared with 70 age-matched AIPmut negative controls. All patients had macroadenomas that caused symptoms before the age of 30.

Results: The AIPmut group had a significantly higher male-to-female ratio (2.4 vs. 0.8; $P=0.008$), younger mean age at diagnosis (20.6 ± 6.4 vs. 23.8 ± 5.2 yr, $P=0.008$) and disease onset (17.3 ± 5.7 , vs. 20.1 ± 6.2 , $P=0.028$). There were no statistical differences in maximal tumor diameter ($P=0.23$), prevalence of extension ($P=0.82$) or invasiveness ($P=1$), GH ($P=0.075$) and IGF-1 ($p=0.28$) levels at diagnosis. A trend toward poorer long-term disease control was observed in the AIPmut group (67.9% vs. 74.5%) which was associated with higher re-operation rate (28.6% vs. 16.7%); this was not statistically significant ($P=0.68$ and $P=0.49$ respectively). In contrast, disease control rates with somatostatin analog (SSA) treatment was significantly lower in patients with AIPmut compared with controls (18.5% vs. 53.0%; $P=0.014$).

Conclusion: Germline AIPmut in acromegalic tumors shows a male predominance and positively associates with younger age at presentation even when compared with age- and tumor diameter-matched AIPmut-negative acromegalic patients. Although no significant differences were observed in the tumor characteristics and remission rate between the two acromegalic patient groups, AIPmut status reduced the response rate to SSA treatment. These results further underline the clinical importance of AIP genetic status as a potential marker of poorer therapeutic response, particularly in young acromegalic patients.

1. Tichomirowa MA et al J Intern Med. 2009 Jul;266(1):5-18.

2. Daly AF et al. J Clin Endocrinol Metab 2010 Nov;95(11):E373-83.

Nothing to Disclose: MAT, MT, AFD, M-LJR, LAN, RSA, PP, AB

sort_order 2980
Pub # OR36-3
Session Information ORAL SESSION: CLINICAL - Acromegaly & Gigantism: Some Interesting Aspects (11:15 AM-12:45 PM)
Title Predicting Long-Term Remission by Measuring Immediate Postoperative Growth Hormone Levels and Oral Glucose Tolerance Test in Acromegaly
Author String EH Kim, EJ Lee, SH Kim
Yonsei University College of Medicine, Seoul, Republic of Korea; Yonsei University College of Medicine, Seoul, Republic of Korea
Body
Context: The suppression of the growth hormone (GH) in an oral glucose tolerance test (OGTT) has been accepted as the most reliable parameter for determining remission of acromegaly.
Objectives: We evaluated the role of immediate postoperative GH level and 1-wk postoperative OGTT as early predictive tools of long-term surgical remission.
Methods: One hundred ninety-four acromegalic patients who were followed up for longer than 1.5 yr (mean duration, 3.80 ± 0.17 yr), with at least three postoperative OGTTs, were evaluated. GH was measured 2, 6, 12, 18, 24, 48, 72 h postoperatively and an OGTT was performed 1 wk after surgery, every 6 months for the first 3 yr and annually thereafter.
Results: One hundred seventy-seven patients underwent gross total resection and long-term remission was achieved in 153 (153/177, 86.4%). The GH level at 24 h after surgery showed the highest predictive power for long-term remission. Long-term remission was observed in 125/127 (98.4%) patients with a nadir GH level < 1.0 mg/liter in an early postoperative OGTT. However, long-term remission was also observed in patients (28/67, 41.8%) with nadir GH levels higher than 1.0 mg/liter. One-week postoperative OGTT had a sensitivity of 81.7% and specificity of 95.1% for predicting remission.
Conclusions: Immediate postoperative GH level is a very good predictor of long-term outcome in acromegaly. One-week postoperative OGTT is also a good predictor with high specificity. These findings may provide critical information for the determination of adjuvant treatment after surgery.
Nothing to Disclose: EHK, EJJ, SHK

sort_order 2981
Pub # OR36-4
Session Information ORAL SESSION: CLINICAL - Acromegaly & Gigantism: Some Interesting Aspects (11:15 AM-12:45 PM)
Title Efficacy of Weekly Pegvisomant Monotherapy, in Patients Previously Controlled with Combined Somatostatin Analog and Pegvisomant Therapy
Author String RD O'Connor, AJ van der Lely, M Madsen, JOL Jorgensen, SJCMN Neggers
Erasmus University Medical Center Rotterdam, Rotterdam, Netherlands; Aarhus University Hospital, Aarhus, Denmark
Body
Introduction: Daily administration of Pegvisomant normalizes Insulin Like Growth Factor-1 (IGF-1) levels >71% of acromegalics [1]. Few studies have assessed the efficacy of weekly administration. We assessed the efficacy of weekly pegvisomant for 12 months, after withdrawal of long-acting somatostatin analogs (SSA) in acromegalics previously controlled on combination therapy.
Design: 15 Subjects (8 males, age 58(35-80) (median(range))yrs on combination therapy of high-dose SSA and weekly pegvisomant and IGF-1 levels within the normal range for >6 months, were enrolled. IGF-1 at baseline was 0.62(0.3-0.84) times the upper limit of normal (ULN) and the weekly dose of pegvisomant was 60(30-80)mg. SSA treatment was stopped for 12 months. IGF-1, HbA1c, growth hormone (GH) and pegvisomant concentrations were assessed at baseline and there after every 6 weeks. When IGF-1 levels increased, pegvisomant dose was increased by 20mg weekly. Dosages were divided into two injections per week when pegvisomant exceeded 80mg.
Results: Baseline pegvisomant and GH serum levels were 2988(252-19440) and 2.99(0.19-15.95)mcg/l respectively. After 12 months, in 73.3% of subjects IGF-1 levels remained controlled under monotherapy of pegvisomant. One patient restarted SSA, during the study-period, due to an increase in signs and symptoms of acromegaly. After 12 months, IGF-1 was 0.83(0.30-1.75)ULN, while the cumulative weekly pegvisomant dose increased to 80(50-120)mg. Pegvisomant and GH levels increased to 4356(1116-21276) and 6.36(0.180-31.45)mcg/l. Pegvisomant levels tended to be different between subjects in whom IGF-1 remained normal and those who did not: 5544(1116-21276) vs. 3848(1296-4392)mcg/l, although the weekly pegvisomant dose was the same. HbA1c decreased from 6.0(5.1-9.2) to 5.9(5.0-9.1)% (p=0.02).
Conclusion: After cessation of SSA treatment in acromegalic subjects on combination therapy, weekly pegvisomant could control 73.3% of patients. Pegvisomant levels seems to be lower in patients with an elevated IGF-1 than in patients with a normal IGF-1, with similar subcutaneous administration dosages. Future research on the relation between levels of pegvisomant and the administered dose is necessary and might help to predict treatment outcome. Future research on the relation between levels of pegvisomant and the administered dose is necessary and might help to predict treatment outcome.
1. Buchfelder, M., et al., The German ACROSTUDY: past and present. Eur J Endocrinol, 2009. 161 Suppl 1: p. S3-S10.
2. Higham, C.E., et al., Successful use of weekly pegvisomant administration in patients with acromegaly. Eur J Endocrinol, 2009. 161(1): p. 21-5.
Nothing to Disclose: RDO, AJvdL, MM, JOLJ, SJCMN

sort_order 2982
Pub # OR36-5
Session Information ORAL SESSION: CLINICAL - Acromegaly & Gigantism: Some Interesting Aspects (11:15 AM-12:45 PM)
Title Octreotide LAR Withdrawal after Long-Term Treatment of Acromegaly
Author String J Rabago, C Ramirez, M Mercado
Centro Medico Nacional, S XXI, Instituto Mexicano del Seguro Social, Mexico City, Mexico
Body
Introduction: Somatostatin analogs (SA) are the most commonly used drugs in the treatment of acromegaly. Targeted against sst2 and to a lesser extent sst5, they achieve a safe GH and a normal IGF-1 in 35-55% of patients. Although the standard octreotide LAR dose is 20 mg every 4 weeks, in many patients the injection interval can be spaced up to q. 8 to 12 weeks. Based on these observations and the scenario of prolactinomas treated with DA, where 15 to 25% of patients can come off the medication after several years, we hypothesized that SA could be withdrawn in selected patients.
Objective: To evaluate the feasibility of discontinuing SA in well-controlled acromegalic patients.
Methods: Of 258 acromegalic patients treated with octreotide LAR, we selected those who met the following criteria: Primary or secondary octreotide LAR treatment for at least 2 yrs with an administration interval of q. 8 weeks or greater for at least the previous year; disease control documented by, a basal GH [Ie] 1.5 ng/mL and an IGF-1 [Ie] 1.2 x the ULN for age and gender; and a residual tumor on an MRI [Ie] 8 mm. Our Ethics Committee approved the study and all patients signed an informed consent. Octreotide LAR was stopped in eligible patients and serum GH and IGF-1 were measured monthly. After completing 4 months without the SA, patients underwent an OGTT with GH measurements as well as basal IGF-1 and an MRI. If either the GH or the IGF-1 at any of the monthly follow-ups were above 1.5 ng/mL or 1.2 times the ULN, respectively, the patient was withdrawn from the study and returned to his/her previous treatment regime.
Results: Fourteen patients (11 women and 3 men, median age 56 years) met the inclusion criteria, all but one had undergone pituitary surgery; median duration of SA treatment was 3.5 to 5 years. Injection intervals were q. 8 weeks in 2, q. 10 weeks in 8 and q. 12 weeks in 4 patients. Eleven patients recurred after 3 to 4 months of having stopped the SA; 3 showed elevations of both GH and IGF-1, one had an elevated GH but her IGF-1 remained normal and 7 kept a GH [Ie] 1.5 ng/mL but their IGF-1 rose. None of these 11 patients had clinical recurrence or tumor re-growth. Thus, 21.4% patients remain off SA; they all had a nadir GH < 1 ng/mL. No clinical or biochemical features correlated with the probability of a successful SA withdrawal.
Conclusion: In a minority of patients treated with SA, the medication can be stopped. These patients need long term surveillance.

Disclosures: MM: Consultant, Speaker, Novartis Pharmaceuticals. Nothing to Disclose: JR, CR

sort_order 2983
Pub # OR36-6
Session Information ORAL SESSION: CLINICAL - Acromegaly & Gigantism: Some Interesting Aspects (11:15 AM-12:45 PM)
Title Aggressive Sparsely Granulated Somatotroph Adenoma of the Pituitary Responding Favorably to Temozolomide
Author String C Steele, F Roncaroli, A Baborie, N Syed, D Husband, KSV Das, M Javadpour, I Macfarlane, C Daousi
University Hospital Aintree, Liverpool, UK; Imperial College London, London, UK; The Walton Centre for Neurology and Neurosurgery, Liverpool, UK; Clatterbridge Centre for Oncology, Bebington, UK
Body
Background: It has become increasingly recognized that temozolomide (TMZ), an alkylating chemotherapeutic agent, can be of value in the treatment of some aggressive pituitary adenomas and carcinomas resistant to conventional multimodality treatment.
Clinical Case: A 34 year-old woman presented in 1997 with symptoms of acute pituitary apoplexy, including deteriorating vision, necessitating emergency transsphenoidal surgery (TSS). Histology was consistent with a sparsely granulated somatotroph adenoma. IGF-1 and GH were raised but thyroid hormones and prolactin were normal. Following her TSS her acromegaly remained active, with evidence of residual adenoma on MRI. Radiotherapy was arranged and long-acting somatostatin analogue treatment started. For 9 years, serial pituitary MRIs showed static appearances of the residual adenoma and her acromegaly remained biochemically controlled on medical therapy. Between 2006-2009 there were several massive, symptomatic recurrences of her adenoma. She underwent repeat TSS and three craniotomies, including one as an emergency due to brainstem compression. Whole body CT scan in 2009 showed no evidence of metastases. In June 2009 she was commenced on oral TMZ, 150 mg/kg/m² given for 5 days in 28-day cycles. There was significant tumor shrinkage within 3 months which was maintained until the end of her 12-cycle treatment during which no further debulking became necessary and her seizure control improved. Off license treatment with TMZ was discontinued in June 2010, and repeat MRI in December 2010 showed possible increase in size of the residual tumor and further TMZ treatment is being considered. Neither the primary tumor and recurrences showed the features of atypical adenoma. Surgical specimens obtained in 2008 and 2009 showed no MGMT (O6-methylguanine-DNA methyltransferase) expression on immunohistochemistry. DNA extracted from the tumor obtained in 2009 showed high promoter methylation by methylation-specific-PCR.
Conclusion: This is the first case of an invasive GH adenoma successfully treated with TMZ. One reported case of a mixed GH-PRL-secreting carcinoma had responded favourably to TMZ, but another case of an aggressive GH adenoma had a poor response after a 3-month trial. Our case adds to existing literature that patients with aggressive adenomas or carcinomas who are resistant to conventional treatment should be submitted to a trial of TMZ. In our case MGMT status was also a good predictor of treatment outcome.

Nothing to Disclose: CS, FR, AB, NS, DH, KSVD, MJ, IM, CD

sort_order 2984
Pub # OR37-1
Session Information ORAL SESSION: CLINICAL - Adrenal Insufficiency, Congenital Adrenal Hyperplasia & Adrenal Tumors (11:15 AM-12:45 PM)
Title Measurements of Serum DHEA and DHEA-Sulfate Levels Improve the Accuracy of the Low-Dose Cosyntropin Test (LDC) in Diagnosis of Central Adrenal Insufficiency (AI)
Author String L Sayyed Kassem, K EISibai, J Chaiban, D Abdelmannan, BM Arafah
University Hospitals Case Medical Center, Cleveland, OH; Case Western Reserve University, Cleveland, OH; Louis Stokes Cleveland Veterans Medical Center, Cleveland, OH
Body
The diagnosis of central AI continues to be challenging especially when it is partial. We recently demonstrated the value of measuring serum DHEA-S in establishing the diagnosis of central AI (1). In that study, we showed that a normal age and gender-adjusted serum DHEA-S level makes the diagnosis of AI untenable. In the current investigation, we examine the diagnostic value of measuring serum DHEA along with serum cortisol levels during LDC in healthy subjects (HS; n=61) and in patients with pituitary masses (n=147). Impaired HPA (IHPA) function was defined on the basis of clinical symptoms, low AM basal serum cortisol (<5.0 ug/dl), subnormal LDC-stimulated cortisol (<18 ug/dl) or a subnormal response to insulin-hypoglycemia (<18.5 ug/dl). Patients of all groups and normal subjects were of similar ages and gender. Of the 147 patients, 93 had NL HPA while 54 had IHPA function.
Patients with NL HPA had normal LDC-stimulated serum cortisol (28.3±5.9 ug/dL) and DHEA (7.1±4.9 ng/ml) levels and NL baseline serum DHEA-S levels. In the latter 2 groups (HS & NL HPA), the baseline DHEA/Cortisol molar ratios were similar (35.7±28.1 VS 43.7±28.9) and were unchanged with LDC stimulation (35.3±21.7 VS 47.9±34.5). In contrast, patients with IHPA function had significantly lower baseline DHEA-S levels (24.8±20.5), LDC-stimulated cortisol (16.8±4.3 ug/dL) and DHEA (2.1±1.7 ng/ml). Patients with IHPA had significantly higher Cortisol/DHEA molar ratio at baseline (84.4±124) that increased further after LDC stimulation (145.4±238).
Normal HPA function is characterized by equimolar secretion of cortisol and DHEA in response to LDC stimulation. In contrast, patients with impaired HPA (central AI) have a greater loss of DHEA secretion than cortisol that is magnified after LDC stimulation. Importantly, although 18 of the 54 patients with IHPA had an LDC-stimulated serum cortisol level of >18.5 ug/dL (20.4±1.6 ug/dL), their baseline serum DHEA-S (24.7±15) and LDC-stimulated DHEA levels (1.42±0.83) were quite low. As expected, LDC stimulation in these patients resulted in a significant increase in the cortisol/DHEA molar ratio (baseline: 74.5±64.3, peak: 233.8±278).
The data indicate that measurements of serum DHEA levels during LDC stimulation provide valuable additional information that improves the diagnostic accuracy of LDC in patients suspected to have partial central AI. We recommend the inclusion of DHEA and DHEA-S measurements in the laboratory assessment of HPA function.
(1) Nasrallah MP, Arafah BM, J Clin Endocrinol Metab 2003;88(11):5293
Nothing to Disclose: LSK, KE, JC, DA, BMA

sort_order

2985

Pub #

OR37-2

Session Information

ORAL SESSION: CLINICAL - Adrenal Insufficiency, Congenital Adrenal Hyperplasia & Adrenal Tumors (11:15 AM-12:45 PM)

Title

Predictive Value of Timed Serum Cortisol and ACTH Measurements for the Quality of Daytime Glucocorticoid Substitution in Addison Disease

Author String

E Rousseau, G Trzepla, H Lefebvre, J-I Wemeau, R Desailoud, J-J Parienti, A Coquerel, Y Reznik
CHU de Caen, Caen, France; CHU de Rouen, Rouen, France; CHU de Lille, Lille, France; CHU d'Amiens, Amiens, France

Body

Chronic glucocorticoid (GC) replacement by hydrocortisone (HC) may lead to under or over-replacement and the subsequent increase in morbidity and mortality previously observed in patients with secondary or primary adrenal insufficiency (AI). GC substitution is adjusted on clinical grounds which exhibit poor sensitivity for the detection of under or over-replacement. The measurement of daytime serum cortisol and ACTH may help assessing the adequacy of HC replacement but no previous study have defined the predictive value of such biochemical criteria for the quality of GC substitution.

In the present study, 27 patients with primary AI were given HC thrice daily in fasting conditions on three occasions at doses of 6, 10 and 14 mg/m²/day respectively. Blood samples were drawn hourly from 0800 to 1900 h for cortisol and ACTH measurements. 29 control subjects matched for age, BMI and sex to AI patients were also studied for cortisol daytime hourly measurements in order to define the physiological range of diurnal plasma cortisol concentrations. Timed point cortisol concentrations and cortisol area under curve (AUC) were compared between both groups in order to determine the % of AI patients well, under- or over-replaced in comparison with control subjects. Finally, the predictive value of cortisol and ACTH measurements for the quality of HC replacement was studied.

Results : the comparison of cortisol AUC in AI patients at different HC doses and in control subjects showed that 81.5% patients receiving 6 mg/m²/day were well-replaced, while most patients receiving 10 and 14 mg/m²/day were over-replaced (81.5% and 96.3% respectively). Correlation coefficient R² between single-point cortisol concentration and cortisol AUC_{8-19h} was 0.87 for 10h cortisol (p<0.0001), while 10h, 14h and 18h cortisol concentrations best predicted cortisol AUC_{8-12h}, AUC_{12-16h} and AUC_{16-19h} respectively (p<0.0001). ROC curve analysis showed that cortisol concentration measured at 10h was the best predictor of well- or over- HC replacement with a C index of 0.97 (95% sensitivity, 86% specificity) at a cut-off of 160 ng/ml (440 nmol/L). The predictive value of ACTH decrease from baseline after HC replacement ([Delta] 8-14h) was less efficient with a C index of 0.89 at a cut-off of - 86%.

In conclusion, an HC dose of 6 mg/m²/day is the most appropriate to reach the physiological target, and single-point cortisol measurement may help adjusting HC dose in order to avoid over-replacement.

Nothing to Disclose: ER, GT, HL, J-LW, RD, J-JP, AC, YR

sort_order 2986
Pub # OR37-3
Session Information ORAL SESSION: CLINICAL - Adrenal Insufficiency, Congenital Adrenal Hyperplasia & Adrenal Tumors (11:15 AM-12:45 PM)
Title An Atypical Case of Familial Glucocorticoid Deficiency *without* Pigmentation Caused by Coexistent Homozygous Mutations in MC2R (T152K) and MC1R (R160W)
Author String S Turan, Z Atay, C Hughes, T Guran, B Haliloglu, B Abdullah, LA Metherell
Marmara University, Istanbul, UK; William Harvey Research Institute, Barts and the London School of Medicine, London, UK
Body Familial glucocorticoid deficiency (FGD) is a rare autosomal recessive disorder characterised by unresponsiveness to ACTH and isolated cortisol deficiency. FGD is caused by mutations in genes encoding the ACTH receptor [melanocortin 2 receptor (MC2R)], its accessory protein (MRAP) or the steroidogenic acute regulatory protein (StAR). One significant feature is generalized skin hyperpigmentation which is thought to be due to elevated ACTH acting on the melanocortin 1 receptor (MC1R). MC1R plays a central role in the regulation of skin pigmentation, is expressed in melanocytes and binds α -MSH and ACTH with similar affinity. MC1R activation increases the ratio of black, strongly photoprotective eumelanins to reddish, poorly photoprotective pheomelanins. Several MC1R variants are associated with red hair/fair skin.
The index case presented aged 4y with hypoglycaemia after prolonged fasting during a respiratory tract infection. She had further hypoglycaemic attacks and was diagnosed with hypocortisolemia at 6 (14nmol/l during hypoglycaemia) and hypercorticotropinemia (ACTH >1250 pg/ml). Her parents were consanguineous and she had one unaffected sister. Her physical examination was normal except her height and weight were greater than the 97th centile for age. Interestingly, she had no hyperpigmentation despite very high ACTH levels. Nucleotide sequence analysis revealed homozygous mutations c.478C>T in *MC1R* and c.455C>A in *MC2R* leading to R160W and T152K changes in the proteins respectively.
The R160W MC1R change has previously been implicated in a red hair/pale skin phenotype and the T152K change in *MC2R* is novel. Both parents were heterozygous for the mutations and her unaffected sister was heterozygous for the *MC1R* mutation and had a wild-type *MC2R*.
We report an unusual case of FGD without hyperpigmentation due to co-existent *MC1R/MC2R* mutations. This case is important as it clearly demonstrates for the first time that the assumption that skin pigmentation is caused by the action of ACTH on the MC1R is correct.
Nothing to Disclose: ST, ZA, CH, TG, BH, BA, LAM

sort_order 2987
Pub # OR37-4
Session Information ORAL SESSION: CLINICAL - Adrenal Insufficiency, Congenital Adrenal Hyperplasia & Adrenal Tumors (11:15 AM-12:45 PM)
Title A Novel Homozygous Q334X Mutation in *HSD3B2* Gene Causing Classic 3 β -Hydroxysteroid Dehydrogenase Deficiency
Author String DD Jeandron, T Sahakitrungruang
Childrens Hospital Los Angeles, Los Angeles, CA; Chulalongkorn University, Bangkok, Thailand
Body
Context: 3 β -hydroxysteroid dehydrogenase, type 2 enzyme (3 β HSD2) is the principal isoform in the adrenals and gonads, encoded by the *HSD3B2* gene. Genetic defects in *HSD3B2* cause the rare form of congenital adrenal hyperplasia known as [ldquo]3 β HSD deficiency.[rdquo] In its classic form, affected individuals have salt wasting episodes early in infancy and genetic males have underdeveloped male genitalia. Genetic females can have mild virilization or normal genitalia. The presence of peripheral type 1, 3 β HSD activity often complicates the hormonal diagnosis of this disorder.
Objective: We describe a 46,XX non-virilized girl who presented with elevated 17-hydroxyprogesterone (17OHP) and salt-losing at early infancy and perform mutation analysis of the *HSD3B2* gene.
Patients and Methods: A 46,XX phenotypic female presented with positive newborn screening for 21-hydroxylase deficiency (17OHP 185.77 nmol/l (normal <180) at 39 hours of life), and later developed salt-wasting crisis on DOL 13. Hormone levels drawn just after hydrocortisone bolus and fluid resuscitation showed PRA 2738 ng/dl/hr (normal range 200-3500), androstenedione 2408 ng/dl (normal range 18-80), 17OHP 10,800 ng/dl (normal range 40-200), and progesterone 1240 ng/dl. Physical exam showed increased pigmentation of the areola and labia, no clitoromegaly, and no posterior fusion of the labial folds. She was started on hydrocortisone, fludrocortisone, and sodium chloride. Sequencing of the *CYP21* gene showed the patient carried heterozygote V281L mutation, which did not explain the clinical phenotypes. The entire coding regions of the *HSD3B2* gene were then assessed by polymerase chain reaction (PCR) and sequencing analysis.
Results: The patient was homozygous for the novel nonsense mutation Q334X, inherited from both parents.
Conclusions: We reported the novel mutation of *HSD3B2* gene, Q334X responsible for classic 3 β HSD deficiency and further illustrated that the clinical and hormonal phenotypes could be complicated in this disorder.
Nothing to Disclose: DDJ, TS

sort_order

2988

Pub #

OR37-5

Session Information

ORAL SESSION: CLINICAL - Adrenal Insufficiency, Congenital Adrenal Hyperplasia & Adrenal Tumors (11:15 AM-12:45 PM)

Title

Mineralocorticoid and Androgen Changes after Bilateral Adrenalectomy for Massive Myelolipomas in Monozygotic Twin Men with 21-Hydroxylase Deficiency

Author String

AS Heyliger, FE Nwariaku, NP Krone, RJ Auchus

UT Southwestern Medical Center, Dallas, TX; UT Southwestern Medical Center, Dallas, TX; University of Birmingham, Birmingham, UK

Body

Adrenal myelolipomas (AM) are non-steroidogenic adrenal tumors composed of mature adipose and hematopoietic elements. AM usually present in the fifth to seventh decade of life as small hypodense masses found incidentally on computed tomography (CT) scans, but others can be very large. The incidence of AM is higher in adrenal disorders including Cushing's disease, Conn's syndrome, and 21-hydroxylase deficiency (21OHD). The mechanism of AM development is unknown, but a both trophic hormone excess and genetic predisposition appear necessary. We describe identical twin brothers with 21OHD who both developed bilateral AM at age 47. One brother was genotyped by direct sequencing and multiplex ligand-dependent probe amplification (MLPA) as a compound heterozygote for classical alleles (del/R356W). Both patients were intermittently compliant with adrenal replacement therapy in the prior 2 decades and had testicular adrenal rest tumors. Both patients had CT scans for abdominal and back discomfort, which showed large heterogeneous adrenal masses consisting of fat and soft tissue elements typical of AM. Twin #1 had an 11 x 10 cm mass in the left adrenal and two 3 cm nodules in an enlarged right adrenal. After an open left adrenalectomy, progressive growth of the right adrenal masses prompted laparoscopic adrenalectomy. Twin #2 had a 7.4 x 5.3 x 6.8 cm left adrenal mass and two 1.5 cm masses in an enlarged right adrenal. After an open left adrenalectomy, the patient's preference to avoid a second open procedure prompted laparoscopic right adrenalectomy 4 months later. Postoperatively, Twin #1 developed hot flashes, fatigue, and symptomatic orthostatic hypotension with high plasma renin activity and low testosterone. The symptoms and blood pressure responded to increased fludrocortisone and testosterone replacement. Twin #2 had a markedly elevated serum 11-deoxycorticosterone (DOC) of 207 ng/dL preoperatively and undetectable DOC after the second surgery. The simultaneous bilateral AMs in monozygotic twins with 21OHD provide evidence for a strong genetic predisposition for these tumors in 21OHD. The profound hormonal changes postoperatively demonstrate that the adrenals of men with 21OHD can produce more testosterone than the testes and that extra-adrenal conversion of adrenal progesterone to DOC can significantly contribute to volume maintenance in adults with 21OHD. These findings provide insight to tailoring hormone replacement for adults with 21OHD.

Sources of Research Support: Clinical scientist award in translational research from the Burroughs-Wellcome Fund (to RJA).

Nothing to Disclose: ASH, FEN, NPK, RJA

sort_order 2989
Pub # OR37-6
Session Information ORAL SESSION: CLINICAL - Adrenal Insufficiency, Congenital Adrenal Hyperplasia & Adrenal Tumors (11:15 AM-12:45 PM)
Title Beckwith-Wiedemann Syndrome in Adults: 3 New Cases Presenting with Virilizing Adrenocortical Tumors
Author String F Bertoin, M Patey, M Sardinoux, S Rossignol, R Libe, B Delemer
CHU de Reims, Reims, France; CHU de Reims, Reims, France; CHU de Montpellier, Montpellier, France; Hopital Trousseau, APHP, Paris, France; Hopital Cochin AP-HP, Paris, France
Body
Background: Beckwith-Wiedemann syndrome (BWS) is a pediatric overgrowth syndrome associated with fetal macrosomia, macroglossia and abdominal wall defects. It mainly predisposes to Wilm's tumor, but other embryonic tumors and adrenal tumors may be detected in infants and children. Most of these tumors occur before 5 years old. Therefore it is suggested that clinical follow up could be stopped after the first decade.
BWS arises from epigenetic and/or genetic alterations in the imprinted gene cluster on chromosome11p15 which encodes for growth regulatory genes or tumor suppressor genes. Some alterations lead to an over expression of IGF2, a growth factor also implicated in the pathogenesis of adrenocortical tumors and a hallmark of their malignant status.
Clinical case: We report three young adult women with BWS, referred for a sudden hirsutism. Hormonal evaluation showed an isolated hyperandrogenemia in all of them. Medical imaging revealed adrenal tumors in all three cases but with distinct pathologic patterns: one double adenoma and two adrenal carcinomas of undetermined malignancy with a Weiss score of 3. Two women also developed large breast fibroadenomas.
We add here three new adult manifestations of the Beckwith-Wiedemann syndrome and comment the hormonal homology between our three patients with an isolated rise of the testosterone level between 1.31 ng/mL and 2.7 ng/mL (normal range < 0.8 ng/mL) but two different pathologic patterns.
Conclusion: Isolated adrenal hyperandrogenemia in our three Beckwith-Wiedemann adult patients was the same mode of presentation of adrenal tumors of either benign or of undetermined prognosis. Our three cases plead in favour of a lifelong follow-up in Beckwith-Wiedemann patients even if advances in epigenotyping allow paediatricians to simplify the cancer screening protocol during infancy and childhood.
Nothing to Disclose: FB, MP, MS, SR, RL, BD

sort_order

2990

Pub #

OR38-1

Session Information

ORAL SESSION: CLINICAL - Genetic & Physiologic Predictors of Obesity (11:15 AM-12:45 PM)

Title

Central Lipid Metabolism Is Linked to Peripheral Glucose and Energy Homeostasis in Humans

Author String

R Jumpertz, A Guijarro, D Piomelli, J Krakoff

National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Phoenix, AZ, University of California, Irvine, Irvine, CA

Body

Background: Recent experiments in rodents have demonstrated that central administration of oleic acid results in reduced hepatic glucose production and deletion of an enzyme responsible for the synthesis of very-long-chain saturated fatty acids (ELOVL3) leads to increased metabolic rate when animals are at rest (1,2). Objective: We aimed to investigate whether central fatty acids and metabolizing enzyme activities are linked to peripheral glucose regulation and energy expenditure in humans. Methods: Twenty-nine (14 males) individuals with a wide range of adiposity (BMI: 20.8-46.0) were admitted to our metabolic research unit. Lumbar punctures were performed for fatty acid profiling of cerebrospinal fluid (CSF). Body fat percentage was measured by dual-energy x-ray absorptiometry, glucose regulation by an oral glucose tolerance test and 24 h (24EE) and sleep energy expenditure (SLEEP) were measured by indirect calorimetry in a metabolic chamber. SLEEP and 24EE were adjusted for age, sex, race, fat mass, fat free mass, fasting and two hour glucose concentrations. Fatty acid fractions (% of measured fatty acids) were used for correlation analyses. Delta-5-desaturase (D5D) was estimated by the product/substrate ratio 20:4[omega]6/20:3[omega]6. Results: CSF oleic acid (18:1) and eicosenoic acid (20:1) were negatively associated with glucose area under the curve (AUC) ($r=-0.38$, $p<0.05$, $r=-0.37$, $p<0.05$). Individuals with CSF D5D activity [ge] 4.5 (median) had significantly lower glucose AUC but similar insulin AUC ($p=0.03$, $p=0.75$) vs. individuals with D5D activity <4.5 indicating decreased insulin sensitivity in individuals with lower D5D activity in the CNS. Interestingly, very-long-chain saturated fatty acids (arachidic [20:0], linoceric [24:0] and cerotic acid [26:0]) in CSF were strongly negatively associated with adjusted SLEEP ($r=0.59$, $p<0.01$; $r=0.66$, $p<0.001$; $r=0.67$, $p<0.001$) but not adjusted 24EE. Conclusion: We show for the first time in humans that central fatty acids and metabolizing enzyme activities are linked to peripheral glucose homeostasis and very-long-chain saturated fatty acids in the CSF correlate strongly with lower energy expenditure during sleep. These data are strikingly consistent with observations made in animal experiments and set the base for future studies in humans targeting the role of central lipid metabolism in peripheral glucose and energy regulation.

(1) Obici S et al., Diabetes 2002; 51:271

(2) Zdravec D et al., FASEB 2010; 24:4366

Sources of Research Support: NIDDK Intramural Research Program.

Nothing to Disclose: RJ, AG, DP, JK

sort_order 2991
Pub # OR38-2
Session Information ORAL SESSION: CLINICAL - Genetic & Physiologic Predictors of Obesity (11:15 AM-12:45 PM)
Title Growth Hormone Secretagogue Receptor (GHSR) Gene Polymorphisms: Association with Food Intake and Metabolic Features in Obese Children and Adolescents
Author String T Arthur, S Deram, SM Diniz, I Guazzelli, E Frazzatto, SF Villares
University of São Paulo Medical School, São Paulo, Brazil
Body **INTRODUCTION:** Ghrelin, a hormone-releasing peptide, enhances appetite and increases food intake in healthy men. The endogenous ligand ghrelin is the growth hormone secretagogue receptor (GHSR), and effects of ghrelin are mediated via the GHSR. Ghrelin and the GHSR are believed to have important roles in energy homeostasis and metabolic parameters. Common polymorphisms in GHSR have been associated with obesity. The GHSR gene 477G/A (rs572169) polymorphism is a good candidate for susceptibility to obesity, and subjects carrying the minor A allele had a higher dietary restraint and more disinhibition than subjects homozygous for the G allele.
OBJECTIVE: Determine possible associations between the 477G/A (rs572169) polymorphism of GHSR with energy intake, macronutrient intakes and metabolic features in obese children and adolescents.
METHODS: A total of 347 obese children and adolescents (37.2% boys; aged 10.6±1.4 years, BMI 30.5±4.7 kg/m², ZBMI 2.3±0.3, 46.3% pubertal) were genotyped for GHSR by PCR. Metabolic measures were obtained and energy and macronutrient intakes were assessed by using 3-day food records. The statistical analysis was performed with Independent-samples T test by SPSS software.
RESULTS: The population was in Hardy-Weinberg equilibrium (GG: 67.4%, GA:29.7%, AA:2.9%, p=0.74). GG children had higher energy intake than children carrying the A allele (GA+AA) (2127.7±641.2 Kcal vs. 1815.3±562.0 Kcal, p=0.006) and carbohydrate intake (261.0±86.9 g vs. 218.0±71.5 g, p=0.005). GG carrier had also a higher total cholesterol (160.7±31.2 mg/dL vs. 152.5±27.4 mg/dL, p=0.02), higher LDLc (98.8±27.1 mg/dL vs. 89.7±25.7 mg/dL, p=0.003) and lower HDLc (41.1±8.8 mg/dL vs. 43.5±10.1, p= 0.03) when compared with children carrying the A allele.
CONCLUSIONS: The results support the notion that the studied 477 G/A (rs572169) polymorphism of GHSR may be involved in obesity, food intake and with a more severe metabolic profile in obese children and adolescents. Our findings also suggest a complex genotype - environmental interactions on obesity risk.
Nothing to Disclose: TA, SD, SMD, IG, EF, SFV

sort_order

2992

Pub #

OR38-3

Session Information

ORAL SESSION: CLINICAL - Genetic & Physiologic Predictors of Obesity (11:15 AM-12:45 PM)

Title

Excessive Gestational Weight Gain in Women without Gestational Diabetes Mellitus Is Associated with Increased Neonatal Fat Mass and Hyperinsulinemia

Author String

J Josefsen, BE Metzger

Northwestern Feinberg School of Medicine, Chicago, IL; Northwestern Feinberg School of Medicine, Chicago, IL

Body

Previous studies have found associations between excessive gestational weight gain (GWG) and increased offspring weight for age in the newborn period and in childhood. Studies associating excessive GWG with increased offspring fat mass either failed to adjust for maternal diabetes status during pregnancy, a known risk factor for offspring obesity, or used imprecise methodologies, such as skinfold thickness to measure fat mass. Our objective was to determine if women with normal glucose tolerance who gain weight beyond the 2009 Institute of Medicine guidelines (based on pre-pregnancy BMI) have newborns with increased fat mass. Healthy weight and obese pregnant women (pre-pregnancy BMI 18-25 or ≥ 30 kg/m²) were recruited if their 50-g glucose challenge test was < 130 mg/dl. All women had singleton pregnancies, were normotensive, and delivered at term. A maternal fasting blood sample was collected at 36-38 weeks gestation and cord blood was collected at birth. Neonatal length, weight, abdominal circumference and body composition analysis by air displacement plethysmography was measured within 48 hours of birth. Weight gain during pregnancy was calculated by subtracting self-reported pre-pregnancy weight from weight at the last prenatal visit. Of 56 mother-infant pairs (20 obese, 36 healthy weight), 31 women stayed within weight gain guidelines and 25 women exceeded the guidelines. Between the 2 groups, there was no significant difference in the maternal age, ethnicity, education level, parity, type of delivery, gestational age or gender of the newborn. Obese women were more likely than healthy weight women to gain beyond recommended guidelines (70% vs. 31%). Maternal fasting glucose, C-peptide (marker of insulin secretion) and leptin were significantly higher in the excessive GWG group. Newborns of mothers with excessive GWG had significantly higher fat mass (490 vs. 390 g, $p=0.04$) and they tended to weigh more (3.61 vs. 3.38 kg, $p=0.1$). Neonatal length, abdominal circumference, cord blood glucose and leptin were similar between the groups, but cord blood C-peptide was significantly higher in the excessive GWG group (1.16 vs. 0.84 ng/mL, $p=0.03$). Excessive gestational weight gain, in the absence of diabetes, is associated with increased neonatal adiposity even if birth weight is normal. Associations between neonatal adiposity and risk of childhood obesity require prospective studies.

Sources of Research Support: Eleanor Wood Prince Grant Initiative: A Project of the Women's Board of Northwestern Memorial Hospital.

Nothing to Disclose: JJ, BEM

sort_order

2993

Pub #

OR38-4

Session Information

ORAL SESSION: CLINICAL - Genetic & Physiologic Predictors of Obesity (11:15 AM-12:45 PM)

Title

A Novel *ADIPOQ* Mutation (p.M40K) Results in Impaired High-Molecular-Weight Adiponectin and Associates with Obesity and Early-Onset Metabolic Syndrome

Author String

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School of Medicine of Ribeirao Preto - University of São Paulo, Ribeirao Preto, Brazil; School of Medicine of Ribeirao Preto - University of São Paulo, Ribeirao Preto, Brazil

Body

Aim: To describe a novel *ADIPOQ* mutation associated with early onset obesity and metabolic syndrome (MetS). **Subjects and Methods:** A subset of 14 individuals with severe hypoadiponectinemia (<3 [micro]g/mL) identified in a cohort of 710 young adults followed since birth was screened for *ADIPOQ* mutations. Anthropometric and biochemical assessments were further performed in subjects carrying *ADIPOQ* mutations. **Results:** A novel heterozygous missense mutation (c.T119A/p.M40K) in exon 2 of *ADIPOQ* was identified in a 24 yrs-old male with hypoadiponectinemia (RIA: 2.4 [micro]g/mL), childhood onset obesity (BMI=32.9kg/m² and waist=111.5cm) and insulin resistance (IR) (HOMA-IR=4.7). At the age of 32 yrs obesity (BMI=39.6kg/m²; waist=125cm) and IR had worsened (HOMA-IR=7.8). He also developed severe hypertension (180/120 mmHg) and dyslipidemia (tryglicerides, total-, LDL- and HDL-cholesterol= 2; 7; 4.8 and 1.3 mmol/L, respectively). MRI showed markedly elevated visceral (169 cm²) and subcutaneous fat (550 cm²), hepatomegaly with severe steatosis (mean liver fat= 40±6%) and ultrasound revealed increased carotid artery intima-media thickness. ELISA adiponectin isoforms measurements revealed low total adiponectinemia (2.3 [micro]g/mL; RV= 3.4 - 9) with markedly reduction of the high molecular weight isoform (HMW: 0.24 [micro]g/mL; RV= 2.2 -4.1). The *ADIPOQ* p.M40K mutation was also found in 3 out of 6 family members, all of them presenting obesity, IR and dyslipidemia. This mutation was not present in 200 healthy subjects. The affected codon is well conserved across species and *in silico* analysis indicated a possible damage effect of this mutation. This aminoacid change results in polarity and conformational changes and likely impairs the formation of disulfide bonds responsible for oligomerization of the HMW. Indeed, when compared to control subjects paired for age and sex (n=4), *ADIPOQ* p.M40K carriers present marked reduction of the HMW (0.3±0.1 vs. 3±1.1 [micro]g/mL; p=0.01) and similar low molecular weight (LMW) levels (2.3±0.8 vs. 1.6±0.7 [micro]g/mL; NS), indicating decreased oligomerization into HMW isoform. **Conclusion:** the novel *ADIPOQ* mutation (p.M40K) found in a Brazilian family associates with obesity, early onset MetS and hypoadiponectinemia due to HMW adiponectin deficiency.

Sources of Research Support: Fundacao de Amparo a Pesquisa do Estado de Sao Paulo - FAPESP, grant 2009/17095-9.

Nothing to Disclose: ACB, MC, JEJ, VCC, MAB, HB, SRA

sort_order 2994
Pub # OR38-5
Session Information ORAL SESSION: CLINICAL - Genetic & Physiologic Predictors of Obesity (11:15 AM-12:45 PM)
Title Reward Deficiency Syndrome (RDS) and Hypodopaminergic Genes as Potential Antecedents to Obesity: KB220-Z[trade] Induced "Dopamine Sensitivity" and Anti-Craving Behavior
Author String K Blum, E Stice, Y Liu, J Giordano, S Morse, BW Downs, RL Waite, M Madigan, ER Braverman, UJ Damle, M Oscar-Berman, A Bowirrat, J Thompson, C Allen, A Smollen
University of Florida College of Medicine, Gainesville, FL; Oregon Research Institute, Eugene, OR; G&G Holistic Addiction Treatment Center, North Miami Beach, FL; LifeGen, Inc, San Diego, CA
Weill Cornell College of Medicine, New York, NY; PATH Foundation NY, New York, NY; Boston University School of Medicine & Boston VA Healthcare System, Boston, MA; Ziv Government
Medical Center, Safed, Israel; Brain Enhancement Solutions & Technologies, Orlando, FL; Synaptic Connections Research Institute and Welcome Home Vets, Charleston, SC; University of Colorado,
Denver, CO
Body Individuals addicted to food or psychoactive substances show a blunted response in dopamine-based reward circuitry ([ldquo]dopamine resistance[rdquo]) due in part to an association with the DRD2
Taq A1 allele. A natural non-addicting, safe putative D2 agonist may aid in recovery from Reward Deficiency Syndrome. We have used qEEG and fMRI imaging to investigate the impact of oral
KB220-Z[trade] (Metalloglycoside[trade] variant) on meso-limbic system activation. In a randomized triple-blind placebo controlled study, QEEG showed positive outcomes by establishing
normalization of reward circuitry in abstinent psychostimulant abusers. Based on our qEEG studies, we cautiously suggest that long-term activation of dopaminergic receptors will lead to D2 receptor
proliferation and enhanced "dopamine sensitivity," thus reducing aberrant craving behavior in DRD2 A1 carriers especially. We also genotyped 14 psychostimulant abusers to classify the severity of
Substance Use Disorder risk. Based on 6 candidate genes (DRD2; DAT1; COMT; DRD4; MAO A; Serotonin Transporter genes), each addict had at least one risk allele. Based on a proposed Genetic
Addiction Risk Score (GARS), we found that 72% had moderate to severe addiction risk. Utilizing fMRI imaging, we found that, at rest, KB220Z compared to placebo significantly activates
dopaminergic pathways in three brain regions: the caudate, accumbens, and putamen. Significant results were observed for weight loss, appetite suppression, reduction in sugar craving, snacking, late
night eating (all p<0.01), increased perception of overeating and happiness, enhanced quality of sleep (all p<0.05), and increased energy (p<0.001). Polymorphic correlates were obtained for a number
of genes (LEP, PPAR-gamma2, MTHFR, 5-HT2A, and DRD2 genes) with positive clinical parameters tested in this study. Only the DRD2 gene polymorphism (A1 allele) had a significant Pearson
correlation with days on treatment (r=0.42, p=0.045). Since stress induces overeating, we evaluated KB220-Z in a double-blind placebo randomized controlled study of stress in patients in an addiction
recovery clinic. Patients receiving KB220-Z had significantly reduced stress a significantly reduced stress response as measured by skin conductance level compared to placebo. Two factor ANOVA
yielded significant differences in Time (p<0.001) and Treatment (p<.0025), as well as Time-by-Treatment interaction (p <0.01). KB220-Z awaits PET scan results to determine its chronic effects on D2
receptor numbers.

Disclosures: KB: Chairman of the Board and Chief Scientific Officer, LifeGen Inc, Reward Deficiency Solutions Inc. JG: Stockholder, HappyGen. BWD: Scientific Board Member, LifeGen Inc,
Reward Deficiency Solutions Inc. RLW: Owner, LifeGen Inc; Officer, Reward Deficiency Solutions Inc. MM: Stockholder, LifeGen Inc. AB: Stockholder, LifeGen Inc. Nothing to Disclose: ES, YL,
SM, ERB, UJD, MO-B, JT, CA, AS

sort_order 2995
Pub # OR38-6
Session Information ORAL SESSION: CLINICAL - Genetic & Physiologic Predictors of Obesity (11:15 AM-12:45 PM)
Title Differences in Sweet Taste Perception in African-Americans and Caucasians
Author String AR DuFlo, R Muniyappa, G Hall, J Lemons, S Aney, KY Chen, LM Bartoshuk, MC Skarulis
National Institute of Diabetes & Digestive & Kidney Diseases, NIH, Bethesda, MD; University of Florida, Gainesville, FL
Body **Background:** Interindividual differences in consumption of sugar is influenced by perceived sweetness intensity which is subject to genetic variability and may play a role in increased preference for sweets. Studies suggest that a higher desire for sweets in African Americans may contribute to the elevated rates of obesity and diabetes in this population. However, little is known regarding racial differences in sweet perception.
Objective: To determine if perceived sweetness intensity was different between African American (AA) and Caucasian (W) enrolled in a study to extensively phenotype non-treatment seeking lean, overweight, and obese adults.
Methods: In a cross-sectional study of AA (n = 84; Women = 50, Men = 34; age, range: 21-62 yr) and W (n = 88; Women = 58, Men = 30; age, range: 20-69 yr), we measured perceived taste intensity of supra-threshold concentrations of sucrose using the general Labeled Magnitude Scale (gLMS). Adiposity was measured by BMI and DEXA (total body fat percent, TBF and total truncal fat percent, TTF); insulin sensitivity, by FSIVGTT (S_I); and resting energy expenditure (REE), by whole room indirect calorimeters.
Results: While there were no significant differences in age, BMI, TBF, TTF, or REE between the groups, AA were less insulin sensitive than W (S_I: 3.1 ± 2.3 vs. 5.7 ± 3.7, p < 0.0001). Bivariate [Spearman's rho (rs)] analyses revealed that age (rs = 0.26), BMI (rs = 0.16), TBF (rs = 0.22), TTF (rs = 0.19), and S_I (rs = -0.18), but not REE (rs = -0.06), were related (P<0.05) to sucrose taste intensity scores. Neither sex nor race significantly affected these relationships. Stepwise regression analyses revealed that the strongest independent predictors of sweet taste intensity were age and TBF, accounting for 15% of its variation. After adjusting for age and TBF, AA had a higher sweet taste intensity scores than W (ANCOVA with post-hoc t test, adjusted means ± SE: 50 ± 3 vs. 41 ± 3, p = 0.02).
Conclusions: These results suggest that independent of age and total body fat content, sweet perception intensity scores are higher in African Americans when compared with Caucasians. Whether, the higher sweetness perception contributes to increased liking of sweets and increased prevalence of insulin resistance and obesity in African Americans requires further investigation.
Nothing to Disclose: ARD, RM, GH, JL, SA, KYC, LMB, MCS

sort_order 2996
Pub # OR39-1
Session Information ORAL SESSION: CLINICAL - MODY & More (11:15 AM-12:45 PM)
Title Monogenic Diabetes Is Often Unrecognized in Childhood
Author String S Ghanny, L Nie, D Tan, S Perez, I Predescu, S Bhandari, E Jacobson-Dickman, I Kazachkova, F Lachawan, A Bhangoo, S Ten
Infants and Children's Hospital of Brooklyn at Maimonides and SUNY, Brooklyn, NY; SUNY Downstate, Brooklyn, NY
Body **Background:** Monogenic diabetes(MD) is often unrecognized in childhood, especially among children with IDDM. The major distinguishing feature in monogenic diabetes is an AD inheritance of DM. The most common genes to be affected in these patients include GCK, HNF1A and HNF4A. Mutations in the HNF1A gene have been seen to cause 58% of MD. Patients with mutations of HNF1A respond well to sulfonylurea therapy¹.
Objective: To study mutations or deletions in the GCK, HNF1A, HNF4A patients with AD inherited DM in 3 generations.
Methods: We evaluated islet cell antibodies and family history in 100 families with DM. 30 families out of 100 had 3 consecutive generations of DM. Protein coding regions of GCK, HNF1A and HNF4A were sequenced.
Results: Analysis of the first 10 families revealed, 7 cases had mutations in HNF1A. Analysis of 20 cases is pending, 4 of them also had (+) islet cell antibodies.
Patient 1: Hispanic, age of onset of DM:20 y, HbA1C(diagnosis):6, HNF1A Mutation: E1:c.74C>G,102A>C, E4:c.887G>C
Patient 2: Ashkenazi Jew, age of onset of DM:16y, HbA1C(diagnosis):8, HNF1A Mutation: E1:c.74C>G, c.316C>T
Patient 3: Caribbean American, age of onset of DM:11y, HbA1C(diagnosis):13.6, HNF1A mutation: E10: c.1830T>A.
Patient 4: African American, age of onset of DM:14y, HbA1C(diagnosis):14, HNF1A mutation: Intron:(5+65bp) A-T
Patient 5: Caribbean American, age of onset of DM:8y, HbA1C(diagnosis):16.8, HNF1A mutation: E1:c.74C>G
Patient 6: Caribbean American, age of onset of DM:3yo, HbA1C(diagnosis):14.1, HNF1A mutation: E1: c.166A>T, E7: c.1398C>T, c.1483G>A
Patient 7: Mixed Hispanic/Arab, age of onset of DM:7yo, HbA1C(diagnosis):5.7, HNF1A mutation: E7: c.1398C>T, c.1483G>A, E10: c.1830T>A
Other mutational analysis is pending.
Out of these 7 patients, 5 patients were switched to sulfonylurea therapy. On this therapy, HgbA1C improved in these patients from an average of 12 to 6.7. Glyburide was successful in spite of previous insulin therapy from 1-10y. Also, one patient out of these 7 presented with a phenotype seen in Oji-Cree DM with morbid obesity and severe insulin resistance.
Conclusions: MD is highly unappreciated in children. MD should be considered in cases of AD inherited DM in spite of pancreatic antibodies. According to our data, mutations in HNF1A are a highly prevalent in childhood. Therefore, children with AD inherited DM should be screened for MD and sulfonylurea treatment should be considered in these patients.

1. Hattersley AT, Pearson ER 2006 The Interaction of Therapeutic Response, B-Cell Physiology, and Genetics in Diabetes. Endocrinology 147:2657-2663

Nothing to Disclose: SG, LN, DT, SP, IP, SB, EJ-D, IK, FL, AB, ST

sort_order 2997
Pub # OR39-2
Session Information ORAL SESSION: CLINICAL - MODY & More (11:15 AM-12:45 PM)
Title Liver Adenomatosis in MODY 3 Diabetes Mellitus Families: Screening 174 Patients
Author String A Rod, C Bellanne-Chantelot, L Chiche, J-P Riveline, J-F Gautier, J Timsit, S Laboureau-Soares Barbosa, L Chaillous, R Valero, E Larger, F Moreau, J-M Wilhelm, M Popelier, P-J Guillausseau, C Thivolet, P Lecomte, P-Y Benhamou, Y Reznik
CHU C[ocirc]te de Nacre, Caen, France; H[ocirc]pital La Pitié Salpêtrière, Paris, France; CHU C[ocirc]te de Nacre, Caen, France; Centre Hospitalier Sud Francilien, Corbeil-Essonnes, France
H[ocirc]pital Saint-Louis, Paris, France; H[ocirc]pital Cochin, Paris, France; CHU H[ocirc]tel Dieu, Angers, France; CHU H[ocirc]tel Dieu, Nantes, France; H[ocirc]pital La Timone, Marseille, France; H[ocirc]pital Hotel Dieu, Paris, France; H[ocirc]pital Civil, Strasbourg, France; Centre Hospitalier Saint Morand, Altkirch, France; CH Rambouillet, Rambouillet, France; H[ocirc]pital Lariboisière, Paris, France; H[ocirc]pital Debrousse, Lyon, France; CHU Tours - H[ocirc]pital Bretonneau, Tours, France; CHU Grenoble, Grenoble, France
Body **Background and aims:** Liver adenomatosis is a rare disorder susceptible to hemorrhagic complication and rarely malignant transformation. Liver adenomatosis results from the biallelic inactivation of the HNF1A gene which encodes a transcriptional factor. The epidemiology of the disease is poorly documented. The aim of this study was to evaluate the frequency of liver adenomatosis in a population of MODY 3 patients carrying a HNF1A germinal mutation, and to describe the clinical course of the disease in the patients affected by the liver disease.
Materials and methods: 174 patients from 74 families MODY 3 were included in 13 French centres. Screening for liver adenomatosis was performed by systematic liver ultrasonography. When the disease was suspected, liver CT or MRI was performed for confirmation of the diagnosis. Histopathological analysis was performed when a surgery was mandatory.
Results: Among 137 patients carrying an HNF1A mutation, 9 cases of liver adenomatosis were identified in 7 different families. Mutations were spread all over the coding region of the HNF1A gene. Patients mean age was 32,8 years (11-56), the M/F sex ratio was 2/7, 7/9 patients had diabetes mellitus, the two remaining patients were children presently normoglycemic. Liver imaging showed adenomas of various sizes from less than ten mm (1/9), to larger lesions (8/9) up to 120 mm. Liver biology was near normal in all patients. One case of adenomatosis was revealed by two episodes of internal hemorrhage. Five women had ten pregnancies without any complication nor progression of the adenoma size. Histopathological confirmation of liver adenomatosis was available in five patients, and all adenomas were steatotic at variable degree.
Conclusion: The frequency of liver adenomatosis in this cohort of MODY 3 diabetic patients (6,5%) and the risk for hemorrhagic complication of the disease favours the systematic screening for liver adenomatosis in MODY 3 families.
Nothing to Disclose: AR, CB-C, LC, J-PR, J-FG, JT, SL-SB, LC, RV, EL, FM, J-MW, MP, P-JG, CT, PL, P-YB, YR

sort_order 2998
Pub # OR39-3
Session Information ORAL SESSION: CLINICAL - MODY & More (11:15 AM-12:45 PM)
Title Two Novel Mutations of the Hepatocyte Nuclear Factor-4 alpha in Maturity-Onset Diabetes of the Young 1 in Japan
Author String M Fujiwara, N Namba, K Miura, T Kitaoka, H Hirai, H Kondou, T Shimotsuji, C Numakura, K Ozono
Osaka University Graduate School of Medicine, Osaka, Japan; Minoh City Hospital, Osaka, Japan; Yamagata University School of Medicine, Yamagata, Japan
Body Maturity-onset diabetes of the young (MODY) is a subgroup of monogenic diabetes mellitus (DM) in youth characterized by autosomal dominant inheritance. Hepatocyte nuclear factor-4 alpha (HNF-4 α) is a ligand-activated transcription factor and mutations of the gene are known to cause MODY1. To date, about thirty to forty mutations in the *HNF4A* gene have been identified, but reports of novel mutations from East Asian countries including Japan have been fairly rare. Here we report two novel *HNF4A* mutations in two Japanese cases.
Case 1 is an 8-year-old girl, who tested positive for glucosuria at a school medical examination. Her height and weight were 135 cm and 32.5 kg respectively, and her body mass index (BMI) was 17.8. Laboratory tests revealed elevated serum fasting blood glucose (209 mg/dl), high HbA1c (11.5 % JDS), normal serum C-peptide, negative serum anti-GAD antibody, and negative urinary ketones. She is now on intensive insulin therapy. Her father and paternal aunt, who were not obese, were diagnosed as DM in their early thirties, and are now treated with insulin. Her paternal grandfather also suffers from DM. Direct sequencing of *HNF4A* from genomic DNA revealed a heterogeneous missense mutation of an adenine residue in exon 7, c.824A>G (p.Asn275Ser). This mutation was not found in 116 alleles of unrelated nondiabetic subjects or was not a known polymorphism. The same mutation was also detected in the father, but not in the mother who does not have DM.
Case 2 is a 14-year-old girl, who tested positive for glucosuria at a school medical examination. Her height and weight were 156.8 cm and 51.4 kg, respectively, and her BMI was 20.9. Laboratory tests revealed elevated serum fasting blood glucose (126 mg/dl), high HbA1c (9.0 % JDS) and negative serum anti-GAD antibody. Now she is well controlled by glibenclamide and metformin. Her mother, maternal grandfather, and two maternal great-uncles became diabetic in their twenties or thirties. Direct sequencing of *HNF4A* demonstrated a heterogeneous frame shift mutation in exon 6, c.692-695delAGGA (p.Lys231ThrfsX5). The same mutation was found in her mother and maternal grandfather, while the mutation was not detected in other family members who do not have DM.
Both of these mutations are in a domain that may play a role in HNF-4 α dimerization, and the amino acids where these mutations were detected are well conserved. We assume that these mutations are the cause of MODY1 in these patients.

Nothing to Disclose: MF, NN, KM, TK, HH, HK, TS, CN, KO

sort_order 2999
Pub # OR39-4
Session Information ORAL SESSION: CLINICAL - MODY & More (11:15 AM-12:45 PM)
Title Effects of Two 11 β -HSD1 Inhibitors on the Hypothalamo-Pituitary-Adrenal Axis of Male and Female Type 2 Diabetic Patients
Author String S Fuerst-Recktenwald, M Abt, W Arlt
F Hoffmann-La Roche Ltd, Basel, Switzerland; University of Birmingham, Birmingham, UK
Body **Background:** 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1) converts inactive cortisone (E) to active cortisol (F) thereby amplifying glucocorticoid action at local cellular level. 11 β -HSD1 inhibitors are assumed to have beneficial effects on the metabolic syndrome but might also exert effects on systemic F regulation. Therefore we assessed the effects of two different competitive inhibitors of 11 β -HSD1 (RO5027838 (RO838) and RO5093151 (RO151)) on the hypothalamo-pituitary-adrenal (HPA) axis of type 2 diabetic (T2DM) patients.
Methods: This was a randomized, double-blind, placebo controlled parallel group study in 110 patients with T2DM (56 male, 54 female). HPA axis function was assessed by a 24-hour serum profile, an ACTH stimulation test and 24-h urinary steroid metabolite profiling. 11 β -HSD1 and 11 β -HSD2 activity was assessed via urinary F over E metabolite ratios.
Results: Four weeks of treatment with both compounds showed significant selective inhibition of 11 β -HSD1 activity as assessed by urinary Tetrahydrocortisol (THF) + α -THF/THE ratio, max. inhibition was 69% and 88% for RO838 and RO151, respectively. In the 24-hour serum profile upregulation of the HPA axis was observed in the RO151 groups only, where treatment led to increases in AUC_{1-24h} for ACTH and E, however with individual levels still mostly within upper limits of normal (ULN), without significant changes in circulating F. This resulted in significant increases in adrenal androgen precursors (dehydroepiandrosterone only in females, androstenedione in both sexes). However sex hormone-binding globulin did not change and absolute values of testosterone were still mostly within ULN. There was no evidence of adrenal insufficiency with appropriate F responses to ACTH stimulation in all groups. The upregulation of the HPA axis in the RO151 groups resulted in a trend for higher response in adrenal F production at 60 and 90 minutes compared to placebo, suggesting an increasingly stimutable HPA axis. Both compounds were well tolerated with a safety profile similar to placebo.
Conclusions: Both compounds showed a clear inhibitory effect on human 11 β -HSD1 activity and did not induce adrenal insufficiency. The compounds differed in their effects on the HPA axis, which was only upregulated with RO151 that had also shown a more pronounced 11 β -HSD1 inhibition. The effects of long-term exposure to 11 β -HSD1 inhibition on HPA axis regulation remains to be examined.

Sources of Research Support: ROCHE.

Disclosures: SF-R: Clinical Researcher, Roche Pharmaceuticals. MA: Employee, Roche Pharmaceuticals. WA: Consultant, Roche Pharmaceuticals.

sort_order 3000
Pub # OR39-5
Session Information ORAL SESSION: CLINICAL - MODY & More (11:15 AM-12:45 PM)
Title IGF-I Bioactivity Decreases during Insulin Therapy in Type 2 Diabetic Patients: Comparison of High Doses of Insulin Glargine and NPH Insulin in the LANMET Study
Author String AJ Varewijck, JAMJL Janssen, M Vahatalo, SWJ Lamberts, H Yki-Jarvinen
Erasmus MC, Rotterdam, Netherlands; City of Turku Health Centre, Turku, Finland; University of Helsinki, Helsinki, Finland
Body
Aim Effects of chronic insulin therapy on circulating insulin-like growth factor-I (IGF-I) bioactivity are unknown. In the present study we compared IGF-I bioactivity in type 2 diabetic patients before and after 36 weeks of high dose treatment with either insulin glargine or NPH insulin.
Methods In the LANMET study, poorly controlled type 2 diabetic patients on metformin were randomized to receive either insulin glargine (G+MET group) or NPH insulin (NPH+MET group) for 36 weeks. In the present study, circulating IGF-I bioactivity was measured using an IGF-I kinase receptor activation (KIRA) bioassay and total IGF-I by immunoassay before and after 36 weeks of insulin therapy in patients who used higher than median insulin doses (>70 IU/day), (age: 54.6±1.0 yrs, BMI 34.3±0.8 kg/m², HbA_{1c} 9.5±0.25 %). The KIRA bioassay was also used to compare potencies of insulin glargine and NPH insulin to induce auto-phosphorylation of the IGF-I receptor *in vitro*, over a wide concentration range (100-100000 pmol/L).
Results *In vitro*, at concentrations <10000 pmol/L, insulin glargine and NPH insulin similarly activated the IGF-I receptor; at higher concentrations, insulin glargine was 1.6-3.7 fold more potent than NPH.
After 36 weeks of insulin therapy, total insulin doses were comparable in the G+MET (107±9 IU/day) and NPH+MET groups (105±8 IU/day) (p=0.90). Before insulin therapy, serum IGF-I bioactivity was similar in the G+MET (118±16 pmol/L) and NPH+MET (129±14 pmol/L) group. After 36 weeks, IGF-I bioactivity had decreased significantly (p=0.02) and did not differ between the G+MET (102±15 pmol/L) and NPH+MET (114±8 pmol/L) groups (p=0.49). Serum total IGF-I concentrations were comparable in both groups and did not change during insulin therapy.
Conclusion Insulin therapy decreases serum IGF-I bioactivity similarly in patients using insulin glargine and NPH insulin.

Sources of Research Support: The LANMET study was sponsored by sanofi-aventis but the present study was investigator-initiated and not supported by grants from the industry. Sanofi-aventis had no involvement in the study design nor in the collection, analysis, and interpretation of data. J.A.M.J.L. Janssen has received an unrestricted grant from Novo Nordisk A/S (Alphen aan de Rijn, the Netherlands).

Nothing to Disclose: AJV, JAMJLJ, MV, SWJL, HY-J

sort_order 3001
Pub # OR39-6
Session Information ORAL SESSION: CLINICAL - MODY & More (11:15 AM-12:45 PM)
Title Effects of Low- and High-Glycemic-Load Diets on Postprandial Plasma Incretins
Author String SS Runchey, ML Neuhouser, LM Valsta, X Song, Y Schwarz, JW Lampe
University of Washington, Seattle, WA; Fred Hutchinson Cancer Research Center, Seattle, WA; National Institute for Health and Welfare (THL), Helsinki, Finland
Body The incretin gut hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP), promote insulin release when released in response to ingested macronutrients (carbohydrate, fat and protein). Low glycemic load (GL) diets may lead to an improvement in postprandial hyperinsulinemia and may ultimately reduce risk of type II diabetes. Whether the incretin effect can explain metabolic benefits of low GL diets is unknown. We aimed to assess the effect of low- and high- GL experimental diets on post-prandial incretin measures after prescribed test meals and to evaluate for modification of the response by adiposity. We used a randomized, controlled, crossover feeding trial of two 28-day intervention periods of low- and high-GL diets in 16 healthy lean (body fat <25% for men or <32% for women), and overweight/obese participants (body fat [ge] 25% for men or [ge] 32% for women), aged 20-45 years. Blood samples were drawn at 8 time points over 4 hours following standardized test meals commensurate with participants' preceding low- or high- GL diet treatments. Test meals were isocaloric with equivalent carbohydrate, protein, and fat distributions; however, dietary fiber differed between the two meals (8.0 and 5.0 g/meal for low- and high- GL meals, respectively). Plasma GIP and GLP-1 (7-36 and 9-36) were measured by immunoassay. Following the 28-day controlled-diet intervention, the high- as compared to the low-GL test meal resulted in higher post-prandial GIP (mean \pm SD iAUC 60924 \pm 18192 vs. 44859 \pm 13930 pg/ml x 240 min, P = 0.009). This trend was seen in the 6 lean individuals (mean iAUC 61729 \pm 15810 vs. 37576 \pm 7449 pg/ml x 240 min, P = 0.011) and the 10 overweight/obese individuals (60441 \pm 20299 vs. 49228 \pm 15363 pg/ml x 240 min, P = 0.182). No difference was detected in post-prandial levels of GLP-1 between high and low GL treatments (469.8 \pm 267.3 vs. 550.1 \pm 287.7 pmol/l x 240 min). Further, as expected, fasting incretin concentrations were similar on both diets following the 28-day controlled diets. We conclude that the high GL test meals led to higher post-prandial GIP iAUC in healthy individuals. These results suggest that regular intake of a high GL diet may lead to chronically elevated post-prandial levels of GIP, which may contribute to subsequent hyperinsulinemia, and increased risk of obesity and insulin insensitivity.

Sources of Research Support: NIH grants U54 CA116847, R03 CA132158, and T32 HL007028.

Nothing to Disclose: SSR, MLN, LMV, XS, YS, JWJL

sort_order	3002
Pub #	CDW8-1
Session Information	CAREER DEVELOPMENT WORKSHOP: Career Development Workshop: Promotion, Tenure & Other Career Opportunities (11:15 AM - 11:45 AM)
Title	Promotion, Tenure & Other Career Opportunities
Author String	SJ Rhodes Indiana University School of Medicine, Indianapolis, IN
Body	Disclosure Incomplete: SJR

sort_order	3003
Pub #	CDW8-2
Session Information	CAREER DEVELOPMENT WORKSHOP: Career Development Workshop: Promotion, Tenure & Other Career Opportunities (11:15 AM - 11:45 AM)
Title	Promotion, Tenure & Other Career Opportunities
Author String	Camper University of Michigan Medical School, Ann Arbor, MI
Body	

sort_order	3004
Pub #	CDW8-3
Session Information	CAREER DEVELOPMENT WORKSHOP: Career Development Workshop: Promotion, Tenure & Other Career Opportunities (11:15 AM - 11:45 AM)
Title	Promotion, Tenure & Other Career Opportunities
Author String	Roberson Cornell University College of Veterinary Medicine, Ithaca, NY
Body	

sort_order	3005
Pub #	CP2
Session Information	CLINICAL PRACTICE GUIDELINE: CLINICAL - Hyperprolactinemia: An Endocrine Society Clinical Practice Guideline (11:15 AM - 12:00 PM)
Title	Moderator
Author String	Ho Princess Alexandra Hospital, Queensland, Australia
Body	

sort_order	3006
Pub #	Y4
Session Information	ENDOCRINE YEAR IN BASIC/CLINICAL SCIENCE SESSION: CLINICAL - The Year in Adrenal (12:15 PM - 1:00 PM)
Title	The Year in Adrenal
Author String	RM Carey University of Virginia Health System, Charlottesville, VA
Body	Session supported by: Corcept Therapeutics Nothing to Disclose: RMC

sort_order	3007
Pub #	CDW9
Session Information	CAREER DEVELOPMENT WORKSHOP: Career Development Workshop: Funding & National Institutes of Health Loan Repayment Opportunities (12:15 PM - 1:00 PM)
Title	NIH Funding & Training Opportunities
Author String	H Khachaturian National Institutes of Health, Bethesda, MD
Body	<p>Dr. Henry Khachaturian, NIH extramural program policy officer, will offer insight and an overview of the training, fellowship and career development opportunities available at the National Institutes of Health. In addition, he will also highlight the NIH Loan Repayment Programs, which annually offer researchers up to \$35,000 of student loan repayment. Researchers performing clinical, pediatric, health disparities or contraception and infertility research may be eligible for loan repayment. At the conclusion of this presentation, participants should be able to draft a career plan that includes multiple stages of NIH support and find NIH program officers who may counsel them on how to apply and receive NIH training support.</p> <p>Nothing to Disclose: HK</p>

sort_order	3008
Pub #	Y5
Session Information	ENDOCRINE YEAR IN BASIC/CLINICAL SCIENCE SESSION: BASIC - The Year in Endocrine Genetics (1:00 PM - 1:45 PM)
Title	The Year in Endocrine Genetics
Author String	WF Crowley Massachusetts General Hospital, Boston, MA
Body	This lecture will highlight the issues of mono- vs polygenic genetics as they relate to endocrine disorders. It will the use of human disease models to discover new genes that control endocrine systems and point to some of the year's major genetic advances, techniques, and tools and their potential biological impact on the field. Nothing to Disclose: WFC

sort_order	3009
Pub #	CMF13-1
Session Information	CASE MANAGEMENT FORUM: CLINICAL - Management of Subclinical Hyperthyroidism (1:00 PM - 1:45 PM)
Title	Management of Subclinical Hyperthyroidism
Author String	KD Burman Washington Hospital Center, Kensington, MD
Body	Disclosures: KDB: Consultant, Up To Date; Investigator, Exelixis, Inc., Amgen, Pfizer, Inc.

sort_order	3010
Pub #	CMF13-2
Session Information	CASE MANAGEMENT FORUM: CLINICAL - Management of Subclinical Hyperthyroidism (1:00 PM - 1:45 PM)
Title	Management of Subclinical Hyperthyroidism
Author String	GA Brent Veterans Affairs Greater Los Angeles Healthcare, Los Angeles, CA
Body	Nothing to Disclose: GAB

sort_order	3011
Pub #	CMF14-1
Session Information	CASE MANAGEMENT FORUM: CLINICAL - Medical Therapy of Cushing Disease: Safety & Efficacy (1:00 PM - 1:45 PM)
Title	Medical Therapy of Cushing Disease: Safety & Efficacy
Author String	XY Bertagna Hospital Cochin, Paris, France
Body	Session supported by: Corcept Therapeutics Nothing to Disclose: XYB

sort_order 3012
Pub # CMF14-2
Session Information CASE MANAGEMENT FORUM: CLINICAL - Medical Therapy of Cushing Disease: Safety & Efficacy (1:00 PM - 1:45 PM)
Title Medical Therapy of Cushing Disease: Safety & Efficacy
Author String LK Nieman
National Institute of Child Health and Human Development/National Institutes of Health, Bethesda, MD
Body Session supported by: Corcept Therapeutics
Disclosure Incomplete: LKN

sort_order	3013
Pub #	M40
Session Information	MEET-THE-PROFESSOR: CLINICAL - Clinical Management of Adrenocortical Carcinoma (1:00 PM - 1:45 PM)
Title	Clinical Management of Adrenocortical Carcinoma
Author String	MA Habra University of Texas MD Anderson Cancer Center, Houston, TX
Body	Session supported by: Corcept Therapeutics Nothing to Disclose: MAH

sort_order 3014
Pub # M41
Session Information MEET-THE-PROFESSOR: CLINICAL - Continuous Glucose Monitoring & Its Role in Diabetes Management (1:00 PM - 1:45 PM)
Title Continuous Glucose Monitoring & Its Role in Diabetes Management
Author String DL Trence
University of Washington Medical Center, Seattle, WA
Body Session supported by: Medtronic Diabetes
Disclosures: DLT: Stock Owner, Medtronic Minimed; Principal Investigator, Novo Nordisk.

sort_order	3015
Pub #	M42
Session Information	MEET-THE-PROFESSOR: CLINICAL - Key Issues in Managing the Perimenopause (1:00 PM - 1:45 PM)
Title	Key Issues in Managing the Perimenopause
Author String	MI Cedars University of California, San Francisco, CA
Body	Nothing to Disclose: MIC

sort_order	3016
Pub #	M43
Session Information	MEET-THE-PROFESSOR: CLINICAL - Klinefelter Syndrome from Cradle through Adolescence (1:00 PM - 1:45 PM)
Title	Klinefelter Syndrome from Cradle through Adolescence
Author String	I Fennoy Columbia University College of Physicians & Surgeons, New York, NY
Body	Nothing to Disclose: IF

sort_order	3017
Pub #	M45
Session Information	MEET-THE-PROFESSOR: CLINICAL - Renal Bone Disease for the Endocrinologist (1:00 PM - 1:45 PM)
Title	Renal Bone Disease for the Endocrinologist
Author String	MS Cooper University of Birmingham, Birmingham, UK
Body	Nothing to Disclose: MSC

sort_order	3018
Pub #	M46
Session Information	MEET-THE-PROFESSOR: CLINICAL - Who Needs MODY Screening? (1:00 PM - 1:45 PM)
Title	Who Needs MODY Screening?
Author String	L Philipson University of Chicago, Chicago, IL
Body	Disclosure Incomplete: LP

sort_order	3019
Pub #	M44
Session Information	MEET-THE-PROFESSOR: CLINICAL - Management of the Abnormal C's: Coronary Calcium Scores, CIMT, CRP & Other Cryptic Markers of Coronary Artery Disease (1:00 PM - 1:45 PM)
Title	Management of the Abnormal C's: Coronary Calcium Scores, CIMT, CRP & Other Cryptic Markers of Coronary Artery Disease
Author String	A Chait University of Washington, Seattle, WA
Body	Disclosure Incomplete: AC

sort_order 3020
Pub # OR40-1
Session Information ORAL SESSION: BASIC/TRANSLATIONAL - New Insights into the Coordinated Control of Glucose Balance & Lipid Homeostasis (2:00 PM-3:30 PM)
Title Insulin Signaling Plays a Central Role in the Response of the Sterol Regulatory Element Binding Proteins to Nutrients and Statin Treatment
Author String S Biddinger, J Haas, Y Wang, J Miao
UCSF, San Francisco, CA; Children's Hospital Boston, Boston, MA

Body Derangements in lipid metabolism drive much of the morbidity and mortality associated with diabetes, including dyslipidemia, atherosclerosis and fatty liver disease. The Sterol Regulatory Element Binding Proteins, SREBP-1c and SREBP-2, are transcription factors that play a central role in the control of hepatic lipid metabolism. They mediate the changes in lipid metabolism produced by diabetes, nutrients, and statin drugs, which are widely used to prevent cardiovascular disease. We have previously shown, using Liver Insulin Receptor Knockout (LIRKO) mice, that disruption of hepatic insulin signaling is sufficient to produce dyslipidemia and atherosclerosis (1). Here, we use LIRKO mice to dissect the specific role of hepatic insulin signaling in modulating the response of the SREBPs to nutrients and statins. Surprisingly, some aspects of nutrient regulation of lipid metabolism are preserved in LIRKO livers: SREBP levels are four to ten-fold higher in fed versus fasted LIRKO mice, and hepatic triglyceride levels are similar to controls. However, the ability of nutrients to induce SREBPs, either by re-feeding a high carbohydrate diet for six hours or feeding a high fructose diet for one week, is markedly compromised in LIRKO livers. Moreover, insulin signaling is necessary for the statin response. Although statins induce SREBP-2 and transcription of its target, the LDL receptor in control livers, statins decrease LDL receptor mRNA by 60% in LIRKO livers. Furthermore, statins increase serum markers of hepatotoxicity, such as alanine transaminase (ALT), by 800% in LIRKO but not control mice, suggesting that insulin is necessary for both the efficacy of statin therapy and the prevention of statin-induced liver toxicity. In conclusion, insulin plays a dominant role in the regulation of the SREBPs by nutrients and statins. This may have implications in the treatment of patients with Type 1 diabetes, an insulin-deficient state, versus Type 2 diabetes, a state of hyperinsulinemia and partial insulin resistance.

Sources of Research Support: R03 DK083697, Joslin Diabetes Center DERC; Pilot and Feasibility Program (SBB).

Nothing to Disclose: SB, JH, YW, JM

sort_order

3021

Pub #

OR40-2

Session Information

ORAL SESSION: BASIC/TRANSLATIONAL - New Insights into the Coordinated Control of Glucose Balance & Lipid Homeostasis (2:00 PM-3:30 PM)

Title

Reduction of the Sterol Sensor SCAP in the Brain of Diabetic Mice Alters Brain Cholesterol Metabolism and Function

Author String

HA Ferris, R Suzuki, CR Kahn
Joslin Diabetes Center, Boston, MA

Body

Insulin action in the brain modulates both memory and feeding behavior, although the mechanisms are unclear. The brain is the most cholesterol rich organ in the body, almost all of which comes from synthesis *in situ*. We recently demonstrated that in streptozotocin (STZ)-induced diabetic mice there is a broad reduction in the genes of the cholesterol biosynthetic pathway in the brain resulting in decreased synthesis of cholesterol and decreased expression of the major transcriptional regulator of this process, SREBP-2 (1). The sterol sensing protein SCAP, which plays a key role in the post-transcriptional regulation of SREBP-2, was also decreased by 50% in the brains of STZ-treated mice. Administration of insulin intracerebroventricularly to the STZ-diabetic mice partially rescued SCAP expression without effecting blood glucose. Similar decreases in SCAP protein were observed in the obese diabetic db/db mouse, whereas in the obese insulin resistant ob/ob mouse SCAP protein was mildly increased. Selective deletion of the *Scap* gene in the central nervous system was accomplished by breeding nestin-Cre transgenic mice with *Scap* floxed mice. Homozygous disruption of the *Scap* gene resulted in perinatal lethality with microcephaly, increased staining for glial fibrillary acidic protein (GFAP), and histological evidence of gliosis. Heterozygous (Het) SCAP KO mice showed a 50% reduction in brain SCAP and a 30% reduction in brain cholesterol synthesis, similar to what was seen in STZ-diabetic mice. Brains of these mice also had increased expression of GFAP, whereas expression of synaptophysin expression was decreased in SCAP Het mice suggesting impaired signaling between neurons. Het mice also showed impaired cognitive function in the novel-object recognition test. Metabolically, SCAP Het KO mice had increased *Agrp* expression with a small increase in nocturnal food consumption; however, this was balanced by an increase in activity and VO_2 . Thus, insulin deficient diabetes results in a reduction of SCAP expression which contributes to a reduction of cholesterol synthesis in the brain. This leads to cognitive dysfunction and disordered control of eating which may contribute to the pathology observed in insulin deficient diabetic states.

(1) Suzuki, R et al., Cell Metab 2010; 12(6):567.

Sources of Research Support: NIH Institutional Training Grant #T32DK007260 and NIH DERC Core Facilities #P30DK036836.

Nothing to Disclose: HAF, RS, CRK

sort_order 3022
Pub # OR40-3
Session Information ORAL SESSION: BASIC/TRANSLATIONAL - New Insights into the Coordinated Control of Glucose Balance & Lipid Homeostasis (2:00 PM-3:30 PM)
Title Humanin Acutely Increases Triglyceride Secretion from the Liver through the Hypothalamus
Author String K Su, L Cui, S Wang, L Klein, A Nemkal, P Kishore, R Muzumdar
Albert Einstein College of Medicine, Bronx, NY; Albert Einstein College of Medicine, Bronx, NY
Body Humanin (HN), an endogenous antiapoptotic peptide, suppresses Alzheimers disease related neurotoxicity and has broad cytoprotective effects in vitro. We recently demonstrated that HN and its analogs increase hepatic and peripheral insulin sensitivity via the hypothalamus. Since HN has important effects on hepatic insulin action, we hypothesized that HN may acutely regulate triglyceride (TG) secretion from the liver in vivo.
We infused a potent HN analog, HNG, into third ventricle (ICV) of awake, unstressed and chronically catheterized Sprague-Dawley rats and studied plasma TG levels following an injection of Tyloxapol (Triton WR1339, Sigma-Aldrich Corp, St. Louis, MO), an inhibitor of TG clearance. Control (artificial CSF, aCSF, n=5) and HNG-infused rats (1 ug over 4 hours, n=5) were matched for age (3 mo), body weight (300 ± 6.6 vs. 304 ± 8.5g), blood glucose levels (137 ± 3.2 vs. 139 ± 5.12 mg/dl) and serum triglycerides at baseline (0.20 ± 0.07 vs. 0.28 ± 0.08 mg/ml). HNG or aCSF was infused ICV for 120 min after an initial stabilization phase of 60 min. All animals received a bolus injection of tyloxapol (600 mg/kg) at 60 min. Blood samples for TG measurements were obtained just prior to tyloxapol administration and every 30 min thereafter for 120 min.
With infusion of tyloxapol, there was a steady linear increase in triglyceride levels in plasma in both groups from TG accumulation. Serum TG levels at 120 min were significantly higher in HNG as compared to control (HNG=5.50 ± 0.29 vs. aCSF=4.33 ± 0.33 mg/ml, p<0.05). The rate of TG secretion was calculated in the animals based on plasma triglyceride levels at 0 and 120 min time points using the following equation: secretion rate of TG/hr=(TG at 120 min- Tg at 0 min)/number of hours. The rate of TG secretion was significantly higher in HNG treated animals compared to controls (HNG= 2.6 ± 0.01 vs. aCSF= 2.1± 0.07, p<0.05).
We have demonstrated for the first time that a humanin analog, HNG, potently affects hepatic triglyceride secretion through the hypothalamus. Because insulin action in the liver increases TG secretion, this effect could be related to the increase in hepatic insulin sensitivity demonstrated with HN and its analogs. We conclude that humanin likely has potent centrally mediated effects on hepatic triglyceride secretion in vivo.
Nothing to Disclose: KS, LC, SW, LK, AN, PK, RM

sort_order 3023
Pub # OR40-4
Session Information ORAL SESSION: BASIC/TRANSLATIONAL - New Insights into the Coordinated Control of Glucose Balance & Lipid Homeostasis (2:00 PM-3:30 PM)
Title Effect of Aging and Resistance Exercise on AMPK and mTOR Signaling in Human Muscle
Author String M Li, LB Verdijk, K Sakamoto, LJC van Loon, N Musi
Audie L. Murphy Veterans Hospital, San Antonio, TX; University of Texas Health Science Center at San Antonio, San Antonio, TX; Texas Diabetes Institute, San Antonio, TX; NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Centre, Maastricht, Netherlands; University of Dundee, Dundee, UK; The Sam and Ann Barshop Institute for Longevity and Aging Studies, San Antonio, TX
Body Aging is associated with an increased incidence of type 2 diabetes (T2D). Alterations in glucose, lipid, and protein metabolism are thought to be responsible for the higher risk for developing T2D in the elderly. AMP-activated protein kinase (AMPK) is an energy/nutrient-sensitive Ser/Thr kinase whose activation enhances lipid oxidation in muscle by phosphorylating acetyl-CoA carboxylase (ACC) and promotes glucose uptake by increasing GLUT4 translocation through phosphorylation of TBC1D1/4. mTOR is another energy/nutrient-sensitive Ser/Thr kinase that plays a key role in controlling protein synthesis. Animal studies suggest that aging leads to altered signaling through AMPK-ACC and mTOR in muscle. These changes have been implicated in the metabolic abnormalities that with aging. Our goals were to determine whether: (1) aging leads to a downregulation of the AMPK-ACC and mTOR pathways in human muscle; and (2) resistance exercise training can restore aging-related alterations in AMPK-ACC and mTOR signaling. Measurements of AMPK-ACC and mTOR signaling were performed in vastus lateralis muscle samples from 32 healthy, elderly, nondiabetic, community-dwelling subjects [age=72±1 y, fasting plasma glucose (FPG)=104±1 mg/dl, hemoglobin A1c=5.9±0.1%] and 32 healthy, younger, nondiabetic subjects (age=25±1, FPG=92±1, A1c=5.4±0.1%). In older subjects, the muscle samples were obtained before and after 3 months of resistance training (3 sessions/week). RESULTS: Aging caused significant (P<0.05) decreases in AMPKα2 activity (by 25%), and in the phosphorylation of AMPK (by 48%), ACC (by 47%) and mTOR (by 70%). AMPKα1 activity and the protein content of LKB1, an upstream kinase for AMPK, were similar between groups. Resistance exercise caused an increase in AMPKα1 activity in older subjects by 1.4-fold (P<0.05). However, AMPKα2 activity, LKB1 protein content, and the phosphorylation of AMPK, ACC, and mTOR were not affected by resistance training. SUMMARY/CONCLUSIONS: (i) alterations in the AMPK-ACC and mTOR pathways could explain some of the changes in glucose, lipid, and protein metabolism that occur with aging; and (ii) resistance exercise causes an isoform-selective (α1) upregulation of AMPK activity, without affecting ACC and mTOR phosphorylation.
Sources of Research Support: National Institutes of Health (NIA and NIDDK); American Diabetes Association; American Federation for Aging Research.
Nothing to Disclose: ML, LBV, KS, LJCvL, NM

sort_order

3024

Pub #

OR40-5

Session Information

ORAL SESSION: BASIC/TRANSLATIONAL - New Insights into the Coordinated Control of Glucose Balance & Lipid Homeostasis (2:00 PM-3:30 PM)

Title

Resveratrol Improves Glucose Metabolism and Reduces Adipose Tissue Inflammation in Overweight Humans

Author String

SS Bursheh, D Mehta, K Zhang, W Li, D Athonvarangkul, S Kehlenbrink, M Hawkins, P Kishore
Albert Einstein College of Medicine, Bronx, NY

Body

Resveratrol (RES), a plant-derived polyphenol, has attracted extensive interest in the lay press based on favorable effects on insulin action, mitochondrial function and inflammation in rodent studies. We recently showed that RES improves insulin sensitivity and muscle mitochondrial function in overweight humans (1). Since RES can reduce macrophage activation, we hypothesized that effects on adipose tissue inflammation might contribute to the beneficial effects of RES on glucose metabolism.

These questions were examined in n=7 overweight, insulin resistant subjects (6M/1F, Age=48±3 yr, BMI=32.5±1.9 kg/m², HOMA-IR= 3.9±0.3), at baseline (B) and following 28 days of RES 2 g/day. Insulin action was evaluated during 6 hour stepped 'pancreatic clamp' studies with progressive increases in insulin infusion rates (15, 30, 80 [μU/m²/min), to optimally examine both hepatic and peripheral insulin sensitivity. Biopsies of skeletal muscle (vastus lateralis) and subcutaneous abdominal adipose tissue were obtained under basal insulin conditions.

RES was well tolerated with no adverse effects. Peripheral insulin-mediated glucose uptake improved significantly with RES (B= 5.93 ±0.95 vs. RES= 10.07 ±1.98 mg/kg/min; ~70% increase, P=0.014), but hepatic insulin sensitivity was not affected. Skeletal muscle mitochondrial density per area (by electron microscopy) increased by 147±40% with RES. As we previously observed, RES induced changes in skeletal muscle gene expression consistent with improved mitochondrial function. Additionally, RES reduced the gene expression of several inflammatory factors in adipose tissue, including PAI-1 (by 58%), TNF-α (by 28%), inducible nitric oxide synthase (iNOS; by 19%) and IL-6 (by 24%). Additionally, RES increased the gene expression of various anti-inflammatory factors in adipose tissue, including adiponectin (32% increase) and arginase-1, the marker of alternate (less inflammatory) activation of ATMs (2.2-fold increase).

In summary, a one month course of resveratrol 2 g/day improved insulin-mediated glucose uptake and skeletal muscle mitochondrial density in overweight, insulin resistant subjects, in concert with decreased markers of inflammation and increased anti-inflammatory factors in adipose tissue. These favorable effects on many features of the metabolic syndrome suggest that resveratrol may have therapeutic potential in overweight, insulin resistant individuals.

(1) Kehlenbrink S, Li W, Koppaka S, Zhang K, Tomuta N, Crandall J, Kishore P, Hawkins M. Resveratrol Improves Insulin Action and Muscle Mitochondrial Function in Overweight Humans. Diabetes, June 2010, Vol 59, Suppl 1; A83

Sources of Research Support: NIH PO1-AG021654, NIH K23RR023335.

Nothing to Disclose: SSB, DM, KZ, WL, DA, SK, MH, PK

sort_order

3025

Pub #

OR40-6

Session Information

ORAL SESSION: BASIC/TRANSLATIONAL - New Insights into the Coordinated Control of Glucose Balance & Lipid Homeostasis (2:00 PM-3:30 PM)

Title

Reduction in Plasma Concentrations of Endotoxin (LPS) and the Expression of Toll-like Receptor-4 (TLR-4) and TLR-2 after Roux-en-Y Gastric Bypass Surgery (RYGB) and Weight Loss

Author String

J Caruana, S Monte, H Ghanim, S Dhindsa, K Korzeniewski, J Schentag, P Dandona
State University of New York at Buffalo, Buffalo, NY; Sisters of Charity Hospital, Buffalo, NY; State University of New York at Buffalo, Buffalo, NY

Body

We have previously demonstrated that the intake of a high fat high carbohydrate (HFHC) meal acutely induces an increase in plasma concentrations of endotoxin (LPS), and the expression of TLR-4 and CD-14 in peripheral blood mononuclear cells (MNC). This is associated with a comprehensive oxidative and inflammatory stress response. Since LPS and TLR-4 may have a role in the pathogenesis of insulin resistance, obesity and atherogenesis, we have now investigated whether the caloric restriction and the weight loss associated with RYGB results in the reduction of these inflammatory indices. Fifteen type 2 diabetic patients with morbid obesity underwent RYGB following which their caloric intake diminished and they lost 38.5±2.9Kg in weight over 6 months. BMI fell from 54.4±3.1 to 40.5±2.9Kg/m². There was a significant fall in plasma concentrations of glucose (from 148±8 to 101±4mg/dl), insulin (from 18.5±2.2 to 8.6±1.0m[micro]U/ml) and HOMA-IR (from 7.1±1.1 to 2.1±0.3). There was a concomitant reduction in the plasma concentrations of LPS (from 0.567±0.033 to 0.443±0.022EU/ml, P<0.05). The mRNA expression in MNC of TLR-4 also fell by 25±9%, TLR-2 by 42±8% and CD14 by 27±10%. There was no significant change in MyD88 gene expression in MNC. In addition, there was a reduction in several pro-inflammatory mediators including CRP (from 10.7±1.6 to 5.8±1.0mg/L) and MMP-9 (from 492±42 to 356±26ng/ml). These data demonstrate that with the marked reduction in caloric and the weight loss that occur after RYGB there is marked reversal of the pro-inflammatory state which incorporates a comprehensive reduction in LPS and the facilitator receptor CD14 required for its ligation to its receptor, TLR-4. The reduction in the downstream signaling of LPS probably contributes to reversal of the inflammatory state and the restoration of insulin sensitivity as reflected in the reduction in plasma glucose and insulin concentrations and HOMA-IR.

Sources of Research Support: NIH Grants R01-DK075877 and R01-DK069805 awarded to PD; American diabetes Grant awarded to PD; American Diabetes Grant 10-JF-13 awarded to SD.

Disclosures: SD: Speaker, Abbott Laboratories. PD: Principal Investigator, GlaxoSmithKline; Clinical Researcher, Sanofi-Aventis; Speaker, Novartis Pharmaceuticals; Eli Lilly & Company; GlaxoSmithKline; Sanofi-Aventis. Nothing to Disclose: JC, SM, HG, KK, JS

sort_order 3026
Pub # OR41-1
Session Information ORAL SESSION: TRANSLATIONAL - Cell Signaling (2:00 PM-3:30 PM)
Title Temporal and Spatial Regulation of Site-Specific Somatostatin Receptor Phosphorylation
Author String M Ghosh, A Schonbrunn
University of Texas - Houston, School of Medicine, Houston, TX

Body G protein coupled receptors (GPCRs) are stringently regulated by phosphorylation of multiple Ser and Thr residues within their intracellular domains. Previous studies have shown that phosphorylation at different sites has distinct consequences for receptor activity, such that the functional state of a receptor is determined by the particular phosphorylated species that exist: a so-called phosphorylation bar code. The somatostatin 2A receptor (sst2A) mediates many of the neuromodulatory and neuroendocrine actions of somatostatin (SS) and is the target for the SS analogs used to treat neuroendocrine tumors. Not only does phosphorylation of different sites produce distinct effects on sst2A receptor internalization and uncoupling but different agonists produce specific patterns of sst2A receptor phosphorylation. To elucidate the spatial and temporal regulation of sst2A phosphorylation, we examined agonist-stimulated phosphorylation of multiple sites using phospho-site specific antibodies. SS increased sst2A receptor phosphorylation sequentially, first on S341/343 and then on T353/354. Phosphorylation of all residues preceded receptor internalization. Unexpectedly, reversal of receptor phosphorylation was determined by the duration of prior agonist exposure. In acutely stimulated cells, when most receptors remained on the cell surface, dephosphorylation occurred only on T353/354. In contrast, both S341/343 and T353/354 were rapidly dephosphorylated when cells were stimulated long enough to allow receptor internalization before agonist removal. Consistent with these results, dephosphorylation of T353/354 was not affected by agents that block receptor internalization whereas dephosphorylation of S341/343 was completely inhibited. Thus, receptor endocytosis is essential for full reactivation of sst2A receptors after agonist-induced phosphorylation. An okadaic acid sensitive phosphatase catalyzed dephosphorylation of T353/354 both intracellularly and at the cell surface. In contrast, dephosphorylation of S341/343 was insensitive to this inhibitor, showing that a different phosphatase was involved. Together, our results demonstrate that the phosphorylation and dephosphorylation of neighboring GRK sites in the sst2A receptor are subject to specific spatial, temporal, and enzymatic regulation. As a result, the pattern of sst2A receptor phosphorylation is determined by the duration of agonist stimulation and the subcellular localization of the receptor.

Sources of Research Support: NIH grant DK032234.

Nothing to Disclose: MG, AS

sort_order 3027
Pub # OR41-2
Session Information ORAL SESSION: TRANSLATIONAL - Cell Signaling (2:00 PM-3:30 PM)
Title Hormonal Synergy and Antagonism: A GnRH/Activin Integrative Site Mediates Oscillatory FSH β Transcription
Author String NA Ciccone, S Xu, RS Carroll, UB Kaiser
Brigham and Women's Hospital, Harvard Medical School, Boston, MA
Body GnRH and activin are mediators of FSH β transcription and act in synergy to augment FSH β gene expression. Herein we test the hypothesis that a GnRH-responsive element within the rat FSH β promoter acts in concert with an adjacent Pitx site to form a functional GnRH/activin integrative site. To explore the importance of Pitx in GnRH/activin synergy, L β T2 cells were transfected with an FSH β LUC reporter harboring either a wild type (WT) or a mutated Pitx binding site; this mutation abrogated both GnRH/activin synergy and preferential stimulation of FSH β transcription at low GnRH pulse frequency. To assess the physiological significance of this finding, we investigated the possibility that GnRH modulates activin function in a pulse frequency dependent manner. We hypothesized that low GnRH pulse frequency enhances activin activity by increasing activin A production and hence pSMAD3 levels, while high GnRH pulse frequency attenuates pSMAD3 activity by promoting increased SMAD3 interactions with repressors. Although not detected under basal conditions in L β T2 cells, we found that both inhibin β A mRNA and activin A protein are induced by GnRH stimulation and were associated with increased FSH β mRNA levels in response to both continuous and pulsatile GnRH. Bio-neutralization of endogenous activin A by a specific antibody reduced the GnRH stimulation of WT, but not a Pitx mutant, FSH β LUC reporter. To investigate how GnRH can attenuate activin function at high GnRH pulse frequencies, we measured the gene expression of two repressors of SMAD3 activity: PPM1A, a protein phosphatase and TGIF, a SMAD binding transcriptional repressor. By real time RT-qPCR, we found that both PPM1A and TGIF expression are increased to a greater extent at high, rather than low, GnRH pulse frequencies supporting a role for these candidates to attenuate activin function. As histone deacetylases (HDACs) are known to interact with both protein phosphatases and TGIF, we predicted that HDACs mediate the attenuation of FSH β transcription by reducing SMAD3 activity. To explore this possibility, we treated L β T2 cells in the presence or absence of the HDAC inhibitor, TSA. HDAC inhibition is associated with a significant increase in both GnRH-stimulated FSH β transcription and FSH β mRNA levels. In conclusion, GnRH pulse frequency-dependent FSH β transcription is mediated through both synergy and antagonism of GnRH action on activin function involving both SMAD3 phosphorylation and histone acetylation.

Nothing to Disclose: NAC, SX, RSC, UBK

sort_order 3028
Pub # OR41-3
Session Information ORAL SESSION: TRANSLATIONAL - Cell Signaling (2:00 PM-3:30 PM)
Title Generation of a Specific Activin Antagonist by Modification of the Activin A Propeptide
Author String Y Makanji, KL Walton, KL Chan, PG Gregorevic, DM Robertson, CA Harrison
Prince Henry's Institute of Medical Research, Clayton, Australia; Baker IDI Heart and Diabetes Institute, Melbourne, Australia
Body Elevated activin A levels in inhibin deficient mice promote the development of gonadal tumours and induce cachexia by reducing muscle, liver, stomach and fat mass. As activin A is an important regulator of tissue growth, inhibiting the actions of this TGF- β family ligand may halt or reverse pathology in diseased tissues. In this study, we modified the activin A propeptide to generate a specific activin antagonist. Propeptides mediate the synthesis and secretion of all TGF- β ligands and, for some family members (e.g. TGF- β 1), bind the mature growth factor with high enough affinity to confer latency. By linking the C-terminal region of the TGF- β 1 propeptide to the N-terminal region of the activin A propeptide, we generated a chimeric molecule (AT propeptide) with increased affinity for activin A. The AT propeptide was 30-fold more potent than the activin A propeptide at suppressing activin-induced FSH release by L β T2 pituitary gonadotrope cells. Binding of the AT propeptide to activin A shields the type II receptor binding site, thereby reducing Smad2 phosphorylation and downstream signalling. In comparison to the commonly utilised activin antagonists, follistatin (IC₅₀ 0.42 nM), soluble ActRIIA-Fc (IC₅₀ 0.47 nM) and soluble ActRIIB-Fc (IC₅₀ 0.91 nM), the AT propeptide (IC₅₀ 2.6 nM) was slightly less potent, however, it was more specific; inhibiting activin A and activin B (IC₅₀ 10.26 nM), but not the closely related ligands, myostatin and GDF-11. As such, the AT propeptide represents the first specific activin antagonist and it should be an effective reagent for blocking activin actions *in vivo*.

Sources of Research Support: Project (CH #494804) and Program Grants (DMR # 494802) from the National Health and Medical Research Council of Australia and the Victorian Government's Operational Infrastructure Support Program.

Nothing to Disclose: YM, KLW, KLC, PGG, DMR, CAH

sort_order 3029
Pub # OR41-4
Session Information ORAL SESSION: TRANSLATIONAL - Cell Signaling (2:00 PM-3:30 PM)
Title Roles of Follistatin-Like 3 (FSTL3) in Testicular Development and Function: A Proteomic Analysis
Author String A Mukherjee, J Seebacher, K Oldknow, J Villen, T Goswami, PJ O'Shaughnessy, SP Gygi, AL Schneyer
Royal Veterinary College, London, UK; Harvard Medical School, Boston, MA; University of Glasgow, Glasgow, UK; Pioneer Valley Life Sciences Institute, Springfield, MA
Body Follistatin-like 3 (FSTL3) is a secreted glycoprotein, structurally similar to follistatin, is known to act as an inhibitor of TGF β ligands such as activin, myostatin and GDF11. Like activin, FSTL3 is expressed strongly in the testis but the role FSTL3 plays in testis development and physiology is not clearly understood. We have shown that FSTL3 deletion in mice leads to an increase in testicular size in the adults. Moreover, unlike their WT counterparts testicular size does not regress by 16 months in FSTL3 KO mice. Importantly testicular functions of testosterone and sperm production are not altered in FSTL3 KO mice. We find that Sertoli cells and germ cell numbers are increased, whereas Leydig cell numbers are not affected by FSTL3 deletion. To identify and investigate molecular pathways contributing to increased Sertoli cell and germ cell production as well as the lack in age-dependent testicular regression, we undertook a combined in silico data mining and quantitative proteomics approach. From the data mining exercise we find that IGFBPs are acutely induced at a time when Sertoli cell expansion is curtailed suggesting a role for IGF, which acts via AKT activation, in Sertoli cell expansion. Tryptic digests of WT and FSTL3 KO testis proteins were mixed after chemically modifying FSTL3 KO digests and analysed by LC-MS/MS. Of 45572 peptides analysed, 1285 proteins were differentially expressed between WT and FSTL3 KO testes. Of these 12 are significantly upregulated and 8 significantly downregulated in FSTL3 KO mice. Our preliminary findings show increased AKT activation in FSTL3 KO mice. Among the substrates of AKT are GSK3 β and zyxin, both of which are identified as proteins differentially expressed in FSTL3 KO mice. AKT dependent phosphorylation negatively regulates GSK3 β function thus allowing β -catenin-dependent cell cycle events to progress. We find that indeed, GSK3 β is phosphorylated to a greater extent in FSTL3 KO mouse testis. In addition AKT dependent zyxin phosphorylation is known to allow zyxin-acinus interaction which reduces acinus-dependent apoptosis. Studies to confirm the zyxin in FSTL3 KO testis are currently in progress. Taken together, our findings suggest that the induction of AKT activation in FSTL3 KO mice is important for expansion of Sertoli cell numbers and that maintenance of zyxin in FSTL3 KO mice testes is essential to promote sustained spermatogenesis and thus reduced testicular regression in FSTL3 KO mice.

Nothing to Disclose: AM, JS, KO, JV, TG, PJO, SPG, ALS

sort_order 3030
Pub # OR41-5
Session Information ORAL SESSION: TRANSLATIONAL - Cell Signaling (2:00 PM-3:30 PM)
Title Paxillin Is a Critical Mediator of Cross-Talk between Cytoplasmic Kinase Signaling and Nuclear Transcription
Author String A Sen, SR Hammes
University of Rochester School of Medicine and Dentistry, Rochester, NY
Body Erk signaling plays a critical role in the modulation of transcription and subsequent downstream cellular processes such as cell proliferation. However, how Erk activation in the cytoplasm leads to transcriptional changes in the nucleus is poorly understood. Our studies in prostate cancer (PCa) cells show that paxillin, normally thought to be a cytoplasmic scaffolding protein that regulates multiple extranuclear signaling, mediates both Erk activation in the cytoplasm as well as Erk actions in the nucleus. Thus, we propose that, in PCa cells, paxillin serves as a liaison between Erk-mediated cytoplasmic signaling and nuclear transcription. We show that, while paxillin is required for receptor tyrosine kinase-mediated Erk activation, subsequent Erk-mediated phosphorylation of paxillin at serine (S83/126/130) residues is also required for Erk-mediated transcription and PCa cell proliferation. In fact, siRNA-mediated knockdown of paxillin in PC3 cells completely abrogates EGF-induced cyclin D1 expression and cell proliferation. Interestingly, under basal conditions, paxillin is primarily localized in the cytosol. However, in EGF-stimulated cells, Erk-mediated phospho-serine paxillin is almost exclusively localized in the nucleus, suggesting that phospho-serine paxillin might function inside the nucleus. Since activated Erk also translocates to the nucleus, we hypothesized that in PCa cells paxillin might mediate nuclear translocation and subsequent transcriptional activity of Erk. However, when Erk-mediated phosphorylation of paxillin is blocked by expressing paxillin lacking the target serine residues, activated Erk still translocates to the nucleus but Erk-mediated transcription does not occur. This suggests that in fact nuclear translocation of paxillin and Erk are independent of each other, but that paxillin may still be a required co-activator of Erk-mediated transcription. How paxillin co-activates Erk-mediated transcription is unclear, and further studies are under way to understand this mechanism. In summary, our studies indicate that paxillin is a critical regulator of PCa physiology, serving as a mediator of both Erk activation and Erk-mediated transcription. The physiological significance of paxillin in PCa is further evidenced by our observation that both paxillin and phospho-paxillin expression are significantly upregulated in PCa patient samples, suggesting that paxillin might be a potential diagnostic or therapeutic target for PCa.

Sources of Research Support: NIH Grant DK59913 to SRH.

Nothing to Disclose: AS, SRH

sort_order 3031
Pub # OR41-6
Session Information ORAL SESSION: TRANSLATIONAL - Cell Signaling (2:00 PM-3:30 PM)
Title Role of FGF21 in Undernutrition-Related Attenuation of Growth
Author String RA Kubicky, S Wu, A Kharitonov, F De Luca
St Christopher's Hospital for Children, Philadelphia, PA; Lilly Research Laboratories, Indianapolis, IN
Body
Background: Transgenic mice overexpressing FGF21 exhibit reduced growth. Undernutrition, often accompanied by growth retardation, is associated with increased FGF21 expression. Thus, we hypothesized that FGF21 is causally related to the growth reduction due to chronic undernutrition.
Results: We first compared tibial growth, body linear growth, and weight change between mice with a targeted deletion of FGF21 (KO, n=5) and wild-type (WT, n=6) mice fed *ad lib* with standard chow. After 4 weeks, we found no difference between the two groups relative to any of the above-listed parameters. We then exposed KO (n=23) and WT (n=23) mice to a food-restricted diet (50% of the amount of food consumed during the *ad lib* experiment). After 4 weeks of food restriction, FGF21 mRNA expression in the liver of WT mice was greater than that measured in WT mice at the end of the *ad lib* experiment ($p<0.001$), while FGF21 mRNA expression was undetectable in the KO mice at the end of both *food restriction* and *ad lib* experiments.
After 4 weeks of food restriction, KO mice' tibial growth was significantly greater ($9.3\pm 0.7\%$ vs. $4.5\pm 1.4\%$, $p<0.01$) than that of WT mice. In addition, KO's body length was preserved while that of WT mice was reduced (compared to the initial body length) ($0.6\pm 0.7\%$ vs. $-3.0\pm 0.7\%$, $p<0.01$). No difference in weight loss or food consumption was found between KO and WT mice. At the end of the study, IGF-1 mRNA expression in the liver of KO mice was greater than that of WT mice ($p<0.05$). In the two subgroups of mice injected with one dose of GH (5 [micro]g/g wt) (WT =6, KO =8) at the end of the 4 weeks of food restriction, liver Stat5 phosphorylation and IGF-1 mRNA and protein expression in KO mice were greater than those in WT mice ($p<0.05$). In another experiment, KO mice injected daily with recombinant FGF21 (rFGF21 5 mg/kg wt/day) for the 4 week-period of food restriction exhibited reduced tibial growth ($3.7\pm 0.6\%$ vs. $9.3\pm 0.7\%$, $p<0.01$) and body growth ($-3.5\pm 0.6\%$ vs. $0.6\pm 0.7\%$, $p<0.05$) compared to non-treated KO mice. In contrast, we found no difference for these two growth parameters comparing food-restricted KO mice treated with rFGF21 and untreated WT mice.
Conclusion: Our findings suggest that increased hepatic FGF21 expression in mice during calorie deprivation causes reduced bone growth. Such effect is associated with a FGF21-mediated impairment of hepatic GH action. Further studies are needed to explore any effect of FGF21 directly at the long bones' growth plate.
Nothing to Disclose: RAK, SW, AK, FDL

sort_order 3032
Pub # OR42-1
Session Information ORAL SESSION: TRANSLATIONAL - Pediatric Endocrinology: Growth & Adrenal (2:00 PM-3:30 PM)
Title A Novel Entity of Isolated Adrenal Insufficiency Caused by Partial Inactivation of P450 Side-Chain Cleavage (CYP11A1) Enzyme
Author String S Parajes, C Kamrath, I Rose, A Taylor, CF Mooij, V Dhir, J Grotzinger, W Arlt, N Krone
School of Clinical and Experimental Medicine, University of Birmingham, Birmingham, UK; Justus-Liebig-University, Giessen, Germany; Medical Faculty, Christian-Albrechts-University of Kiel, Kiel, Germany
Body Cytochrome P450 side-chain cleavage enzyme (CYP11A1) catalyses the first and rate-limiting step of steroidogenesis, the conversion of cholesterol to pregnenolone (Preg). Cholesterol is transported by steroidogenic acute regulatory protein (STAR) into the mitochondria and converted into 22R-hydroxycholesterol (22HC) by CYP11A1. CYP11A1 further converts 22HC into Preg by 20 α -hydroxylation and cleavage of the C20-C22 bond. To date only 9 patients with CYP11A1 deficiency have been described. All patients presented with adrenal insufficiency (AI) and disorder of sex development in 46,XY individuals. Here we describe two brothers (46,XY) presenting with AI and normal male genital phenotype. The older boy first presented with signs and symptoms suggestive of AI at the age of 2 years, but was only diagnosed at the age of 4.1 years during an adrenal crisis (salt-loss with high renin, high ACTH and low cortisol). His brother was diagnosed with AI at the age of 2.5 years being clinically asymptomatic. In contrast, he had only highly elevated ACTH and low cortisol, but renin and U&Es were normal. Of note, a maternal uncle had died at the age of 9 years during an episode of febrile seizures. Mutation analysis of *DAX1* and *Star* genes did not show mutations. Sequencing of *CYP11A1* revealed a novel homozygous mutation (c.1351C>T; R451W) in both brothers and in heterozygous state in the parents. *In vitro* enzyme assays were optimised for the conversion of cholesterol and 22HC to characterise the novel R451W mutation and five published missense mutations (L141W, L222P, R353W, A359V, V415E). COS7 cells were co-transfected with wild-type or mutant cDNA of *CYP11A1*, adrenodoxin and with or without *Star*. Preg synthesis was measured by liquid chromatography tandem-mass spectrometry (LC/MS). The R451W mutation partially reduced enzyme activity to 40% of wild-type activity, which is consistent with the *in silico* results. Mild inactivation of CYP11A1 by L141W, L222P, A359V and severe impairment by R353W and V415E were confirmed. Our study is the first to assess mutant CYP11A1 enzyme activity by assaying the conversion of the natural substrate cholesterol and intermediate product 22HC employing LC/MS. Importantly, we present a novel entity of isolated AI caused by a partial inactivation of CYP11A1. This entity needs to be added to the differential diagnosis in patients with isolated AI and could have been clinically mistaken for familial glucocorticoid deficiency in one of our patients.

Nothing to Disclose: SP, CK, IR, AT, CFM, VD, JG, WA, NK

sort_order 3033
Pub # OR42-2
Session Information ORAL SESSION: TRANSLATIONAL - Pediatric Endocrinology: Growth & Adrenal (2:00 PM-3:30 PM)
Title Establishment and Characterization of One Pediatric Adrenocortical Xenograft Model for the Preclinical Evaluation of New Therapies
Author String EM Pinto, RC Ribeiro, C Morton, GP Zambetti
St Jude Children's Research Hospital, Memphis, TN; St Jude Children's Research Hospital, Memphis, TN; University of Tennessee College of Medicine, Memphis, TN; St Jude Children's Research Hospital, Memphis, TN
Body
Purpose: New therapeutic regimens for pediatric adrenocortical tumors (ACT), which carry dismal prognosis, are urgently needed. Human pediatric ACT tumor xenograft models, which recapitulate the biology of human disease, are required to explore new potential effective compounds and their combination. Herein, we report the successful establishment and characterization of one xenograft model of human pediatric ACT and their response to selected chemotherapeutic agents.
Material and Methods: A fresh ACT tissue obtained from a patient eleven years old was subcutaneously transplanted into female CB17 *scid^{-/-}* mice. Once established as xenograft, further transplantations were from mouse to mouse and each tumor developed consistently in more than 95% of recipient mice. Histopathological, immunohistochemical, hormonal and molecular studies, including identification of *TP53* status, western blotting for p53 and IGF2 protein and Affymetrix U133v2 GeneChip to examine global gene expression profiles were performed in both tumors. Weekly, measurements of implanted tumor volume in animals treated with various therapeutic agents were compared with those of control animals receiving no treatment. The xenograft model was treated with CP751871, Rapamycin, Vincristine, Cyclophosphamide, Actinomycin D, Topotecan, Etoposide, Cisplatin, Doxorubicin and Taxol alone or in combination. **Results:** Primary and xenograft tumors had histological and immunophenotypic features characteristic of adrenocortical tumors. The xenograft tumor retained the same profile of steroids secretion and molecular findings to the primary adrenocortical carcinoma. Genomic DNA from both tumors harbors the G245C inactivating mutation located in DNA binding domain of p53 protein. Western blotting results revealed the high expression of full length p53 and IGF2 protein in both tumors and RNA expression profile show similar pattern between xenograft and primary tumor. Topotecan and Cisplatin were well tolerated and their use is responsible for the higher response and survival among chemotherapeutic agents used in these xenografts models. **Conclusions:** A xenograft model of human pediatric adrenocortical tumor has been developed. This model retained the morphological and biochemical features of the primary tumor and demonstrated comparable biological behavior in all transplanted mice. This model could be useful tools for developing new diagnostic and therapeutic strategies against pediatric adrenocortical tumors.

Nothing to Disclose: EMP, RCR, CM, GPZ

sort_order 3034
Pub # OR42-3
Session Information ORAL SESSION: TRANSLATIONAL - Pediatric Endocrinology: Growth & Adrenal (2:00 PM-3:30 PM)
Title Post-Receptor Growth Hormone Insensitivity (GHI) Associated with Severe Immune Dysfunction Caused by a Novel Bioinactive STAT5b
Author String P Scalia, AS Martinez, E Feigerlova, P Fang, L Bezrodnik, MI Gaillard, DD Giovanni, MG Ballerini, HG Jasper, JJ Heinrich, RG Rosenfeld, V Hwa, HM Domene Hospital de Niños Ricardo Gutiérrez [rdquo], Buenos Aires, Argentina; Oregon Health & Science University, Portland, OR; Hospital de Niños Ricardo Gutiérrez [rdquo], Buenos Aires, Argentina
Body
The mouse *Stat5b*^{-/-} knock-out model and rare human *STAT5B* gene mutations identified to date have demonstrated the critical involvement of STAT5b in both growth and immunity. Patients with STAT5b deficiency show GH insensitivity (GHI) and a variable degree of immune dysregulation which results in a broad spectrum of skin and respiratory infections.
Patient: We describe a girl, adopted at four days of age, with severe cutaneous eczema, who presented with several infections associated with failure to thrive since the first year of life. Immunological evaluation revealed T lymphopenia (low CD3/CD4, CD8 and Treg cell numbers), poor proliferative response after antigen stimulation, and normal B cell counts. The patient was also severely growth retarded, reaching an adult height of 122.7 cm (-6.14 SDS). Endocrine evaluations indicated GHI, which was confirmed by a normal GH response to provocative tests (GHmax: 27.1 ng/ml), low levels of serum IGF-I (16 ng/ml; -3.7 SDS) and IGFBP-3 (0.84 mg/L; -4.5 SDS) and a negative IGF-I/IGFBP-3 generation test. Prolactin levels were significantly elevated (83 ng/ml; reference values <25 ng/ml).
Results: The phenotype of the patient was consistent with STAT5b deficiency. Sequencing of the *STAT5B* gene was undertaken and revealed a novel homozygous T to C transition in exon 16, which resulted in a p.F646S missense mutation. F646, a highly conserved residue throughout the human STAT family of proteins, is within the critical SH2 domain, a region necessary for STAT5b to dock to activated receptors, to dimerize and to stabilize interactions with DNA. Preliminary reconstitution studies indicate that the regenerated N-terminally FLAG-tagged STAT5b:F646S, is readily over-expressed in HEK293(GHRII) cells, is immunodetectable and of normal size, although expression is considerably lower than that of wild-type FLAG-STAT5b. The expressed mutant FLAG-STAT5b:F646S cannot be phosphorylated or activated by GH.
Conclusion: A novel missense *STAT5B* mutation, p.F646S, has been identified in a patient who presented with a complex phenotype consistent with STAT5b deficiency. Only the second *STAT5B* missense mutation to be identified to date, the new mutation resulted in a bioinactive STAT5b variant that was not well expressed. The phenotype of our patient, together with previously described cases, confirms the crucial role of STAT5b in normal postnatal growth as well as normal immunity.

Sources of Research Support: In part, by a grant from the March of Dimes (RGR). EF is supported by a Fulbright Scholar Award.

Nothing to Disclose: PS, ASM, EF, PF, LB, MIG, DDG, MGB, HGJ, JJH, RGR, VH, HMD

sort_order 3035
Pub # OR42-4
Session Information ORAL SESSION: TRANSLATIONAL - Pediatric Endocrinology: Growth & Adrenal (2:00 PM-3:30 PM)
Title Skeletal Muscle Mitochondrial Function Predicts Longitudinal Growth Velocity in Children and Adolescents
Author String SE McCormack, M McCarthy, M Hrovat, D Systrom, SK Grinspoon, A Fleischman
Massachusetts General Hospital, Boston, MA; Children's Hospital Boston, Boston, MA; Massachusetts General Hospital, Boston, MA
Body **Background:** Periods of rapid growth require an increase in energy utilization and substrate formation. Mitochondrial function contributes to both of these, and therefore may be related to longitudinal growth velocity.
Methods: 29 children and adolescents ages 8 - 15 years were enrolled in a comprehensive longitudinal assessment of glucose homeostasis and mitochondrial function. (Initial observations from the baseline cohort have been published.)⁽¹⁾ Fasting laboratory studies and an estimate of mitochondrial function (as assessed by the time to phosphocreatine recovery after sub-maximal quadriceps exercise using ³¹P magnetic resonance spectroscopy) were obtained at baseline and one year later.
Results: Data were complete for 23 subjects. Subjects were 11.3 years old (\pm SD 1.9) at the beginning of the study; 61% of subjects were male. By design, 26% (6) were Tanner Stage I, 43% (10) were Tanner Stage II, and 30% (7) were Tanner Stage 3. Average annualized growth velocity at one year for boys was 7.2 cm/year (\pm SD 1.5) and for girls, 6.5 cm/year (\pm SD 1.7). Better mitochondrial function at baseline ($R^2=0.3$, $p=0.0072$) predicted faster growth velocity in the following year; this result persisted after controlling for age, sex, Tanner stage, height, weight, and BMI. Higher alkaline phosphatase ($R^2=0.39$, $p=0.0014$) was also associated with more rapid growth. Higher IGF-1 was associated with slower growth velocity, but this did not reach statistical significance ($R^2=0.12$, $p=0.12$); however, a rise in IGF-1 over the year did predict faster growth ($R^2=0.25$, $p=0.02$). A multivariate model confirms the independence of these effects.
Discussion: The association of better mitochondrial function with increased linear growth in healthy children is, to our knowledge, a novel finding. Mitochondrial function may reflect overall well-being, or indicate that the pubertal growth spurt requires increased fuel and substrate utilization and therefore more mitochondrial efficiency. High alkaline phosphatase, suggestive of high bone turnover, foretells rapid growth. Rising IGF-1, likely from increasing growth hormone secretion, coincides with faster growth, but an already relatively high level may signal that growth is about to slow.
Conclusions: We report a novel association between better skeletal muscle mitochondrial function and faster linear growth in healthy children; future studies are warranted.

(1) Fleischman A, Kron M, Systrom DM, Hrovat M, Grinspoon SK. Mitochondrial function and insulin resistance in overweight and normal-weight children. *J Clin Endocrinol Metab.* 2009;94(12):4923-30.

Sources of Research Support: NIH Grant 5K23DK80658 awarded to AF.

Disclosures: SKG: Investigator, Theratechnologies; Consultant, Serono; Theratechnologies. Nothing to Disclose: SEM, MM, MH, DS, AF

sort_order 3036
Pub # OR42-5
Session Information ORAL SESSION: TRANSLATIONAL - Pediatric Endocrinology: Growth & Adrenal (2:00 PM-3:30 PM)
Title The Correlation of Clinical Response to Growth Hormone with mRNA Expression Profiles in Turner Syndrome
Author String A Stevens, S Tajbakhsh, A Whatmore, M Westwood, P Clayton
University of Manchester, Manchester, UK
Body Recombinant human growth hormone (rhGH) is used to treat girls with Turner syndrome (TS) to improve their adult height but the gain is variable (0-20cm). Only ~46% of the variability in the first year response to rhGH can be accounted for by current prediction models, implying that genetic profiling could provide data that improve prediction. The aim of this study was to use an ex-vivo fibroblast model to explore mRNA expression profiles in response to rhGH and associate mRNA expression profiles with biological pathways.
Three fibroblast cell lines were used, C10 - control; T1 - from a TS patient responding well to rhGH (Height SDS at start = -4.9 with a change in height SDS over 4 years of + 1.8) and T5 - from a poor responder to rhGH (Height SDS at start = -2.5 with a change in height SDS over 4 years of - 0.3). Gene expression was measured using Affymetrix HG-U133 plus 2.0 arrays (four replicates per cell line), differential gene expression was analysed using ANOVA and Ingenuity Pathway Analysis software (IPA) was used to assess the biological function of genes.
Comparison of C10 to both TS lines showed variability in gene expression clustered in pathways associated with development of reproductive, cardiac, nervous and skeletal systems and muscular function (16, 10, 50, 26 and 26 genes out of 301 differentially expressed genes respectively, $p < 0.05$). The Wnt signalling pathway also showed significant change with 8 out of 169 pathway members showing altered expression ($p < 0.01$). The *IGFBP5* gene, associated with muscular function, showed the greatest individual change in expression in TS (upregulated 670 fold).
When the T1 and T5 cell lines were compared, 6 out of 25 differentially expressed genes were associated with general development ($p < 0.05$); 4 genes with muscular function ($p < 0.05$) and 3 genes with cardiac development ($p < 0.05$). Two key developmental genes *HOXD10* and *TBX5* were downregulated in the T1 good responder line (43 fold and 125 fold relative to T5 respectively), while Wnt pathway members, Secreted Frizzled-Related Protein 4 (*SFRP4*) and Frizzled Homolog 10 (*FZD10*), both membrane proteins associated with cell growth, were upregulated in T1 (52 fold and 33 fold respectively), implying that these genes may contribute to the clinical response to GH in TS.
This work is an important step towards the identification of novel biomarkers for clinical response to rhGH in Turner Syndrome.

Nothing to Disclose: AS, ST, AW, MW, PC

sort_order

3037

Pub #

OR42-6

Session Information

ORAL SESSION: TRANSLATIONAL - Pediatric Endocrinology: Growth & Adrenal (2:00 PM-3:30 PM)

Title

Patient Satisfaction and Evaluation of Height Gains after Growth Hormone Treatment in Turner Syndrome: A Population-Based Study

Author String

D Regnard, E Ecosse, J Coste, J-C Carel, on Behalf of StaTur Study Group
AP-HP Robert Debré Hospital and University Paris 7 Denis Diderot, Paris, France; Groupe Hospitalier Cochin - Saint Vincent de Paul, Paris, France

Body

Growth hormone is widely used in Turner syndrome and other non-GHD conditions. Little is known of how the patients themselves evaluate treatments effects.

As part of the STaTur population based cohort study, we asked the patients to subjectively rate the effects of treatment and to quantify the influence of treatment on their adult height. Patients were also asked to provide the minimal height gain that they thought would warrant the use of GH in Turner syndrome. Patients statements were compared to the measured height gain induced by GH as the difference between adult height and pre-treatment projected height using Turner syndrome normative data. 568 of the 818 (69%) patients who received the questionnaire responded at a mean age of 22.6 ± 2.6 years, 6 years after the end of GH treatment.

Patients satisfaction with treatment effect was rated as positive by a vast majority of patients (very positive, 36%; positive 52%), neutral by 9% and negative or very negative by 3%. Patients estimated the height gain induced by treatment to 13.6 ± 7.9 cm (median 12), a mean of 4.7 ± 7.6 cm (median 3.5) over the measured height gain. Although 71% of patients overestimated the height gain, there was a strong correlation between the estimated and measured height gain ($r = 0.826$). The minimal GH-induced height gain to warrant treatment ("if I had to do it again") was 11.1 ± 7.5 cm (median 10), a mean of 2.1 ± 8.8 cm over the measured height gain. This minimal height gain to warrant treatment was higher than the measured height gain for 55% of patients and was not correlated to the measured height gain, to adult height itself, to self esteem or psychological distress scores.

We conclude that there is a discrepancy between subjective appreciation and objective estimates of treatment effects in patients with Turner syndrome. These data have implications for patients and family counseling on GH treatments in Turner syndrome and other non-GH deficient conditions.

Disclosures: J-CC: Investigator, Lilly USA, LLC; Scientific Board Member, Pfizer Global R&D. Nothing to Disclose: DR, EE, JC

sort_order 3038
Pub # OR43-1
Session Information ORAL SESSION: TRANSLATIONAL - Thyroid Cancer (2:00 PM-3:30 PM)
Title Establishment of a Mouse Model of Thyroid Cancer Expressing the PAX8-PPAR γ Fusion Protein (PPFP) and Its Response to Pioglitazone
Author String ME Dobson, E Diallo-Krou, V Grachtchouk, J Yu, LA Colby, JE Wilkinson, T Giordano, RJ Koenig
University of Michigan, Ann Arbor, MI; Methodist Hospital Research Institute, Houston, TX; University of Michigan, Ann Arbor, MI; University of Michigan, Ann Arbor, MI
Body About 30% of follicular thyroid cancers harbor a chromosomal translocation that results in the expression of PPFP, a fusion protein consisting of the majority of PAX8 followed by the nuclear hormone receptor PPAR γ 1. Transfection studies demonstrate that PPFP causes cellular proliferation and colony formation in soft agar, and inhibits apoptosis. These effects, as well as the oncogenic action of PPFP, are thought to result from inhibition of PPAR γ transcriptional activity. However, this hypothesis appears to conflict with the observation that PPFP thyroid cancers display increased expression of PPAR γ target genes (e.g. ANGPTL4 and AQP7), and this PPAR γ -like activity can be replicated by luciferase reporter assays in PPFP transfected thyroid cells. To better understand PPFP's biological function, we generated a transgenic mouse model of thyroid cancer that combines Cre-dependent PPFP expression (PPFP;Cre) with homozygous deletion of floxed Pten (Pten^{FF};Cre), both of which are thyroid-specific. Though neither PPFP;Cre mice nor Pten^{FF};Cre mice develop thyroid tumors, the combined PPFP;Pten^{FF};Cre mice develop thyroid cancer. The cancers invade the trachea and local vasculature, and distant metastases occur in the lungs and soft tissues. RT-qPCR analysis showed ~5-fold induction of Angptl4 and a borderline ~2-fold induction of Aqp7 in the PPFP;Pten^{FF};Cre thyroids, providing further evidence that PPFP can induce PPAR γ target genes in vivo. These data led us to test the effects of the PPAR γ agonist pioglitazone (Pio) on gene expression and thyroid cancer progression. Two month old PPFP;Pten^{FF};Cre mice, along with a Pten^{FF};Cre control group, were fed \pm Pio for 10 weeks. Pio had no effect on thyroid size or histology in Pten^{FF};Cre mice. In contrast, the thyroids in Pio-fed PPFP;Pten^{FF};Cre mice decreased to 15% the size of the control diet group. Metastases were present in 58% PPFP;Pten^{FF};Cre mice on the control diet, but none were found in the mice fed Pio. Remarkably, Pio caused an adipogenic response in the PPFP;Pten^{FF};Cre thyroids as evidenced by the development of lipid droplets and induction of many adipocyte PPAR γ target genes. In the absence of Pio, the PPFP;Pten^{FF};Cre thyroids showed induction of some of these genes but repression of others. These data suggest a more complex mechanism for PPAR γ -specific gene regulation by PPFP than has been previously described, and predict that Pio may be therapeutic in PPFP positive cancer patients.

Nothing to Disclose: MED, ED-K, VG, JY, LAC, JEW, TG, RJK

sort_order 3039
Pub # OR43-2
Session Information ORAL SESSION: TRANSLATIONAL - Thyroid Cancer (2:00 PM-3:30 PM)
Title Combination Vitamin D Receptor (VDR) Activation and Mitogen Activated Protein Kinase (MAPK) Inhibition in Thyroid Cancer
Author String ZD Crees, V Sharma, JP Klopper
University of Colorado Denver School of Medicine, Aurora, CO; University of Colorado Cancer Center, Aurora, CO
Body Radioiodine resistant thyroid cancers account for the majority of thyroid cancer deaths but have no approved effective therapy. The VDR represents a novel therapeutic target for these cancers. Two PTCs (TPC1 and BCPAP) and five ATCs (C643, HTh74, HTh7, SW1736 and 8505C) were shown to express vitamin D receptor (VDR) protein, but have a variable response to vitamin D (VD - calcitriol) in terms of decreased cell proliferation after 100nM VD for 6 days (drug/media replenished at 3 days). TPC1 was the most sensitive; C643, HTh74 and 8505C were modestly sensitive and the rest were resistant. A possible mechanism of VD resistance is constitutive MAPK signaling, present in >70% of thyroid cancers and shown to decrease VDR transactivation by preventing co-activator recruitment to the RXR:VDR heterodimer complex in a model of RAS transformed keratinocytes. All cells were treated for 6 days alone and in combination with a dose titration of VD (1 nM, 10nM, 100nM) and the selective MEK1/2 inhibitor selumetinib (ARRY-142886, AZD6244) (0.1uM, 0.5uM, 1.0uM, 2.5uM, 5.0uM) with assessment of proliferation by the sulforhodamine (SRB) assay. The combinational drug effect was determined using both the Bliss Independence and the Loewe Additivity criteria which define drug synergy by both the effect (Bliss) and the dose (Loewe) and thus are distinct yet complimentary calculations. All intermediate dose combinations were calculated to be synergistic by both methods. The dose of selumetinib in combination with 100nM VD required to decrease the proliferation greater than 50% relative to control was evaluated (data presented is % proliferation relative to control for VD, selumetinib (dose) and combination): TPC1 - 39%, 62% (0.1uM), 14%, C643 - 89%, 48% (5uM), 44%, HTh74 - 80%, 76% (2.5uM), 50%, 8505C - 88%, 69% (0.5uM), 48%, HTh7 - 122%, 41% (0.5uM), 35%; SW1736 - 112%, 43% (0.1uM), 32%; BCPAP - 108%, 42% (0.5uM), 35%. In summary, combination VD and selumetinib treatment provides a synergistic decrease in thyroid cancer cell proliferation. The most VD sensitive cells gain significant antiproliferative synergistic effect with selumetinib. The antiproliferative effect in the other cell lines is driven largely by MEK inhibition, but the combination with VD decreases cell growth more than either drug alone. Therefore, combination VD and selumetinib therapy may allow for therapeutic efficacy at lower individual drug doses in patients with advanced thyroid cancer.

Sources of Research Support: American Cancer Society MRSG-06-193-01-TBE - JPK; R25GM083333 (Initiative for Maximizing Student Diversity) from the National Institute of General Medical Sciences - ZDC; AstraZeneca.

Nothing to Disclose: ZDC, VS, JPK

sort_order 3040
Pub # OR43-3
Session Information ORAL SESSION: TRANSLATIONAL - Thyroid Cancer (2:00 PM-3:30 PM)
Title Aberrant Expression of Enzymes Involved in the Glycolysis Pathway Is Associated with the *BRAF* Mutation and Aggressive Tumor Features in Thyroid Cancer
Author String H Guan, Y Gao, W Zhang, Z Shan, W Teng
The First Affiliated Hospital of China Medical University, Shenyang, China
Body
Objectives: A variety of solid tumors prefer to anaerobic glycolysis rather than the Krebs cycle for energy production even under normoxia. It remains to be investigated whether enzymes involved in glycolysis pathway are aberrantly expressed in thyroid cancer and whether their expression are related to the *BRAF* mutation, a major mutation in thyroid cancer, as well as aggressiveness of cancer cells.
Methods: Expression of pyruvate kinase M2 (PKM2), lactate dehydrogenase (LDH) subunits LDHA and LDHB were examined in human thyroid tissues of 120 papillary thyroid cancer (PTC), 60 PTC-matched normal thyroid and 40 nodular goiter. Expression of these enzymes in relation to clinicopathologic characteristics and the *BRAF* mutation was analyzed. The three enzymes were also examined in undifferentiated thyroid cancer cell lines 8505C, 8305C, MB-1, PTC cell lines IHH-4, BCPAP, medullary thyroid cancer cell line TT, follicular thyroid cancer cell lines ML-1, FTC-133, and normal thyroid cell line Nthy-ori 3-1. Thyroid cell lines 8505C and BCPAP were used to assess glycolysis process, growth and invasion of tumor cells *in vitro*.
Result: Aberrant over-expression of PKM2 and LDHA were detected in 95% (114/120) and 91% (109/120) of PTC specimens. There expression was found to be associated with poor clinicopathological features including high T stages, advanced tumor stages and lymph nodes metastasis. PTCs harboring the *BRAF* mutation were detected more intensive immunostaining of PKM2 and LDHA than those without the mutation. Aberrant expression of PKM2 and LDHA was also found in all thyroid cancer cell lines, but not in the normal thyroid cell line. Specific siRNA of either *PKM2* or *LDHA* gene in 8505C and BCPAP cells led to reduced lactate and ATP production, and glucose consumption. Knockdown also suppressed tumor cell growth and invasion *in vitro*, decreased the colony-forming capability in agarose of the cells.
Conclusion: PKM2 and LDHA provide a selective growth and invasion advantage for thyroid cancer cells through activating glycolysis process. Aberrant PKM2 and LDHA expression may serve as a useful biomarker as well as a potential treatment target for thyroid cancer. The *BRAF* mutation may lead to tumor aggressiveness through, at least in part, changing the expression of enzymes involved in glycolysis such as PKM2 and LDHA.

Nothing to Disclose: HG, YG, WZ, ZS, WT

sort_order 3041
Pub # OR43-4
Session Information ORAL SESSION: TRANSLATIONAL - Thyroid Cancer (2:00 PM-3:30 PM)
Title The Importance of Fibroblast Growth Factor Receptor 2 Heteroisoforms in Thyroid Cancer Progression
Author String M Guo, W Liu, S Serra, S Asa, S Ezzat
Ontario Cancer Institute/University Health Network, Toronto, Canada; Ontario Cancer Institute/University Health Network, Toronto, Canada
Body **Background:** The importance of tumor-stromal interactions has become increasingly evident. The fibroblast growth factor receptor 2 (FGFR2) gene affords a unique opportunity as it encodes a protein whose extracellular third Ig-like domain is alternatively spliced. The FGFR2-IIIb isoform is characteristically noted in epithelial cells whereas FGFR2-IIIc is typically expressed in mesenchymal cells. We recently reported that FGFR2 was down-regulated through extensive DNA promoter methylation in thyroid epithelial cancer cells and that re-expression of FGFR2-IIIb interrupted disease progression. We identified the melanoma-associated antigen-A (MAGE-A) as a nuclear target of FGFR2-IIIb signaling governing cell cycle control and metastasis development.
Objective: We aimed to investigate the role of the FGFR2 alternatively spliced variants in modulating thyroid cancer behavior.
Methods and Results: We stably introduced the two FGFR2 isoforms in thyroid carcinoma WRO cells and in mouse fibroblast 3T3 cells. Both isoforms resulted in reduced fibronectin, MAGE-A3, and MMP9, and increased p21 leading to enhanced Rb dephosphorylation. Consistent with these results, FGFR2-IIIb as well as FGFR2-IIIc reduced cell invasion and colony formation in soft agar when expressed independently. Orthotopic mouse xenografts showed that FGFR2-IIIb as well as FGFR2-IIIc significantly reduce tumor growth when introduced alone. In marked contrast, heterologous xenografts revealed that FGFR2-IIIc fibroblasts support the most efficient thyroid tumor growth when epithelial cells expressed FGFR2-IIIb but not FGFR2-IIIc. Conversely, FGFR2-IIIb epithelial cells supported the most efficient neoplastic growth when associated fibroblasts expressed FGFR2-IIIc, but not FGFR2-IIIb.
Conclusion: Our findings highlight the importance of cellular context in assigning growth promoting or suppressive functions to FGFR2 isoforms. Further, they emphasize the role of heteromeric vs. homodimeric receptor interactions in governing epithelial-stromal cross-talk in promoting thyroid cancer progression.

Sources of Research Support: Canadian Institutes of Health Research.

Nothing to Disclose: MG, WL, SS, SA, SE

sort_order

3042

Pub #

OR43-5

Session Information

ORAL SESSION: TRANSLATIONAL - Thyroid Cancer (2:00 PM-3:30 PM)

Title

PBF Binds Directly to p53 and Abrogates Its Tumor Suppressive Role in Thyroid Cancer

Author String

R Seed, M Read, N Sharma, J Fong, G Lewy, V Smith, P Kwan, G Ryan, K Boelaert, J Franklyn, C McCabe
University of Birmingham, Birmingham, UK

Body

PTTG is a multifunctional proto-oncogene overexpressed in thyroid cancers, which binds to p53 and modulates its function. PBF, a binding partner of PTTG, is also overexpressed in thyroid cancer and can transform cells independently of PTTG. Moreover, subcutaneous expression of PBF elicits tumors in nude mice. Given the established role of ionising radiation in thyroid tumorigenesis, we investigated the relationship between PBF and the tumor suppressor protein p53. PBF repressed p53-mediated gene regulation through HDM2 promoter assays in p53-null H1299 cells. PBF failed to influence promoter activity directly, but when co-expressed with p53 significantly repressed p53-mediated HDM2 promoter activity by approximately 30% ($p < 0.0001$). Exposure of wild-type mouse thyrocytes to gamma-irradiation resulted in a significant increase in PBF protein expression after 24 hrs (1.88 ± 0.09 -fold, $P < 0.017$). Co-immunoprecipitation assays revealed direct binding of PBF and p53 in TPC-1 human thyroid papillary carcinoma cells, with a marked increase in binding after treatment with gamma-irradiation. Furthermore, transient overexpression of PBF in TPC-1 cells resulted in a significant decrease in p53 protein levels compared to controls ($75 \pm 2.5\%$ decrease after 90 minutes, $p < 0.028$, $n=4$). Additionally, in MTT proliferation assays, we observed a significant reduction of cell viability in mock-transfected TPC-1 cells after treatment with gamma-irradiation compared to untreated controls ($17.9 \pm 0.008\%$ decrease, $p < 0.016$, $n=4$). Critically, overexpression of PBF abrogated this observed decrease of cell viability ($0.2 \pm 0.007\%$ decrease, $p=NS$, $n=4$). To investigate this mechanistically, we examined the effect of PBF overexpression on 88 p53-mediated genes in focused microarrays. Our preliminary data implicate repression of the pro-apoptotic genes FASL and APAF-1 in the maintenance of cell viability by PBF. Taken together these data highlight a novel potential mechanism of thyroid tumorigenesis, whereby PBF stabilizes in response to DNA damage, binds directly to p53 and inhibits its function.

Nothing to Disclose: RS, MR, NS, JF, GL, VS, PK, GR, KB, JF, CM

sort_order 3043
Pub # OR43-6
Session Information ORAL SESSION: TRANSLATIONAL - Thyroid Cancer (2:00 PM-3:30 PM)
Title Identification of Thyroid Cancer Stem Cells
Author String F Frasca, F Giani, V Vella, ML Nicolosi, R Masucci, M Manusia, R Vigneri
University of Catania, School of Medicine, Catania, Italy; Garibaldi Nesima Hospital, Catania, Italy; Garibaldi Nesima Hospital, Catania, Italy
Body Background. Cancer stem cells (CSCs) are cells within tumors with stem cell like properties, representing the driving force of tumor-growth, responsible for tumor chemo-resistance, de-differentiation and relapse. Poorly differentiated thyroid carcinomas are chemo-resistant and often lethal. It is important to isolate CSC population in thyroid carcinomas, where these cells may influence tumor behavior and prognosis. As stem cells may grow in vitro as floating spheres, we tried to isolate and characterize both normal and cancer thyrospheres. Results. Surgical normal and malignant thyroid tissue was digested by collagenase IV. Cells were seeded in serum-free stem cell medium with the addition of growth factors. Thyrospheres appeared after 7 days of cultures (n=528±78/gram of tissue) Compared to normal thyrospheres, cancer thyrospheres displayed an irregular shape and a higher clonogenic potential after replating at single cell suspension. FACS analysis revealed that cancer thyrospheres underwent symmetric division at higher rate than normal thyrospheres. TaqMan Real time PCR revealed that compared to normal thyrospheres, the expression of stem cell markers Oct-4, ABCG2 and HTERT was higher in cancer thyrospheres (Oct-4: 2.8±0.6 fold, p<0.05; ABCG2: 22.4±6.2 fold p<0.001; HTERT: 3.7±0.3, p<0.01), while they expressed Tg, TPO, and TSH-R at lower levels. Moreover, Real Time PCR indicated that, compared to normal, cancer thyrospheres displayed a reduced increase in thyroid specific markers expression in response to differentiating medium containing TSH. cAMP assay indicated that TSH stimulation elicited a reduced cAMP production in cancer thyrospheres (60± 25 pmol/L) compared to normal thyrospheres (180±35 pmol/L). qRT-PCR array indicated that several genes were selectively up-regulated in cancer thyrospheres including COL9A1, ABCG2, DVL1, FRAT1, WNT1 and KRT15. In contrast, APC, IGF1, NCAM1, ALDH1A1 and CD8B genes were selectively up-regulated in normal thyrospheres. Conclusions. These results indicate that thyroid cancers contain thyrosphere-forming cells that are less differentiated more prone to symmetric division and expressing several sets of genes involved in cancer progression and epithelial-mesenchymal transition. Perspectives. These thyroid cancer stem cells may be a suitable model for testing novel therapies for poorly differentiated thyroid carcinomas.

Sources of Research Support: Italian Association for Cancer Research (AIRC).

Nothing to Disclose: FF, FG, VV, MLN, RM, MM, RV

sort_order 3044
Pub # OR44-1
Session Information ORAL SESSION: CLINICAL - Calcium Kinetics & Metabolic Bone Disease (2:00 PM-3:30 PM)
Title Extremely Elevated Calcium Absorption in Idiopathic Infantile Hypercalcemia Using Calcium Isotopic Measurement
Author String A Dauber, JN Hirschhorn, SA Abrams
Children's Hospital Boston, Boston, MA; Broad Institute, Cambridge, MA; Harvard/MIT Health Sciences and Technology - Beth Israel Deaconess Medical Center, in Collaboration with Pfizer Inc and Merck & Co, Boston, MA; Harvard Medical School, Boston, MA; Baylor College of Medicine, Houston, TX
Body Background: Idiopathic Infantile Hypercalcemia (IIH) is a rare entity in childhood whose pathophysiology is not well understood. There have been reports of elevated Vitamin D levels in these patients (1) but this is not a consistent finding. Other studies have suggested that the hypercalcemia is due to increased absorption of calcium from the intestines(2-4). The only two studies to look directly at calcium absorption were done in the 1950s and 1960s and did not exclude Williams' Syndrome, hyperparathyroidism or Vitamin D intoxication(2,4). We measured the calcium (Ca) absorption in an infant with severe IIH using stable Ca isotopes(5).
Clinical Case: The subject initially presented at age 10 months with failure to thrive after failing to gain any weight in the preceding 4 months. His laboratory studies showed: Ca level 16.3 mg/dl (normal 8-10.5), PTH <3 pg/ml (10-65), 25OHD 43 ng/ml (30-80), 1,25OHD 33 pg/ml (15-75), undetectable PTHrP, and urine Ca:Cr ratio 1.26. FISH for Williams' Syndrome was negative and both parents serum and urine calcium levels were normal. The subject had severe bilateral nephrocalcinosis. He was placed on a low Ca diet and his Ca levels and hypercalciuria gradually improved.
The subject was admitted to the inpatient clinical research center at the age of 17 months while on a low Ca diet. Fasting labs were obtained. 20 micrograms of ⁴⁶Ca was given IV immediately prior to the first morning feeding which contained 1 mg of ⁴⁸Ca mixed in 90 ml of Calcilo formula. For the second feeding, 1.5 mg of ⁴²Ca was given mixed in 30 ml of whole milk. Urine was collected for 24 hours following the second feeding and then twice daily for the subsequent four days. Calcium isotope ratios were measured using thermal ionization magnetic sector mass spectrometry following purification by oxalate precipitation(5). Fractional calcium absorption was calculated from the relative recovery of oral and IV calcium isotopes in the 24-h urine collection(6).
Baseline labs included: Ca 10.7 mg/dl, PTH 10.6 pg/ml, 25OHD 13 ng/ml, 1,25OHD 83 pg/ml, and urine Ca:Cr ratio 0.04. He absorbed ~95% of the calcium from the low calcium feed (normal ~65% (7)) and ~85% from the normal calcium feed (normal ~45%(8)).
Conclusions: We report the use of stable calcium isotopes to measure calcium absorption in IIH. Calcium absorption was extremely elevated in an infant with IIH confirming increased absorption as the underlying pathophysiological process in this disorder.

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(3) Martin ND, Snodgrass GJ, Cohen RD. Idiopathic infantile hypercalcaemia--a continuing enigma. *Archives of disease in childhood* 1984;59:605-13.
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(5) Abrams SA. Using stable isotopes to assess mineral absorption and utilization by children. *The American journal of clinical nutrition* 1999;70:955-64.
(6) Abrams SA, Griffin IJ, Hicks PD, Gunn SK. Pubertal girls only partially adapt to low dietary calcium intakes. *J Bone Miner Res* 2004;19:759-63.
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(8) Lynch MF, Griffin IJ, Hawthorne KM, Chen Z, Hamzo M, Abrams SA. Calcium balance in 1-4-y-old children. *Am J Clin Nutr* 2007;85:750-4.

Sources of Research Support: USDA/ARS Children's Nutrition Research Center, Houston TX; Harvard Catalyst | The Harvard Clinical and Translational Science Center (NIH Award #UL1 RR 025751 and financial contributions from Harvard University and its affiliated academic health care centers).

Nothing to Disclose: AD, JNH, SAA

sort_order 3045
Pub # OR44-2
Session Information ORAL SESSION: CLINICAL - Calcium Kinetics & Metabolic Bone Disease (2:00 PM-3:30 PM)
Title Calcium Absorption, Kinetics, Bone Density and Bone Structure in Hereditary Vitamin D-Resistant Rickets Patients
Author String D Tiosano, S Hadad, Z Chen, A Nemirovsky, V Gepstein, D Militianu, Y Weisman, S Abrams
Rambam Health Care Campus, Haifa, Israel; Rambam Health Care Campus, Haifa, Israel; Baylor College of Medicine, Houston, TX; Rambam Health Care Campus, Haifa, Israel; Meyer Children's Hospital, Haifa, Israel; Tel Aviv University, Tel Aviv, Israel
Body Background: Hereditary 1,25-dihydroxyvitamin D-resistant rickets (HVDRR) is caused by mutations in the Vitamin D Receptor gene. During infancy and childhood HVDRR patients suffer from severe hypocalcemia and rickets that are treatable with huge calcium supplement, whereas after puberty spontaneous recovery in calcium metabolism appears without calcium supplement.
Aims: We aimed to elucidate the spontaneous recovery in calcium metabolism in HVDRR patients.
Methods: We used stable calcium isotopes, DXA and micro-MRI analysis in 17 HVDRR patients, ages 1.5 to 37 years and controls.
Results: Fractional calcium absorption rate (FCAR) in patients age 1.5 to 17 years was $45.6 \pm 10.7\%$ less than controls, $p < 0.00004$, whereas, in patients ages 18 to 26 years FCAR was $48 \pm 22\%$ higher than controls, $p < 0.001$. FCAR in patients older than 28 years was comparable to controls. Patients' 18 to 29 years had significantly higher bone calcium accretion rates (V_{o+}) than controls, $p < 0.02$. Patients younger than 18 and older than 29 years had comparable V_{o+} to controls. Femoral neck BMD significantly increased from -2.38 ± 0.30 Z-score in patients ages 12 to 17 years to 0.28 ± 0.87 Z-score in patients age 18 to 37 years ($p < 0.0001$). No significant differences were found in bone structure parameters between adult HVDRR patients and controls.
Conclusion: HVDRR patients have a unique calcium absorption profile. From infancy to the end of puberty and after the age of 28 years their FCAR is very low, whereas after puberty there is a unique period of recovery in FCAR and bone calcium accretion leads to normalization of BMD and bone structure.
Nothing to Disclose: DT, SH, ZC, AN, VG, DM, YW, SA

sort_order 3046
Pub # OR44-3
Session Information ORAL SESSION: CLINICAL - Calcium Kinetics & Metabolic Bone Disease (2:00 PM-3:30 PM)
Title The Use of Sodium Thiosulfate in the Treatment of Familial Tumoral Calcinosis: A Novel Application
Author String NM Yalla, H Mawad
University of Kentucky, Lexington, KY; University of Kentucky, Lexington, KY
Body
INTRODUCTION
Familial Tumoral Calcinosis (FTC) is a rare genetic disorder characterized by ectopic calcifications. We present a case of normo-phosphatemic FTC with extensive peripheral vascular calcifications treated with sodium thiosulfate infusions (STS) over 2 years. There was stabilization of the peri-articular and arterial calcifications and marked improvement in the patient's symptoms.
CLINICAL CASE
A 54 year old Caucasian female presented with a history of advanced PVD, peri-articular and soft tissue calcifications attributed to FTC. The patient's 4 siblings, who were the product of a consanguineous marriage between 3rd degree relatives, share her diagnosis.
A full metabolic workup was initiated: normal baseline renal function, total Ca 9.6 (8.7-9.9mg/dl), albumin 3.6g/dl, ionized calcium 4.9 (4.6-5.1 mg/dl), PTH (total) 39 (14-66 pg/ml), serum phosphorus 4.1 (2.7-4.8 mg/dl), Vit D 25 OH 30 (<57ng/ml), 1,25(OH) VIT D 72 (15-75pg/ml), FGF 23 (<=180 RU/ml).
An auto-immune work up was negative. Bone survey revealed juxta-articular calcifications at multiple anatomic sites and marked calcification in the lower extremity vasculature. Arterial duplex and MR angiogram of peripheral arteries confirmed severe PVD. Coronary CT Angiography was normal with a calcium score of 0.
The patient was diagnosed with normo-phosphatemic tumoral calcinosis. Given its properties as a calcium chelator and proven benefit in patients with tumoral calcinosis secondary to renal failure, we initiated the patient on STS. The patient was loaded with 12.5mg IV thrice a week for 1 month, then 12.5mg IV once a week for 2 months. The dose was gradually increased to 25mg IV once a week for 2 years. The patient noted significant improvement in her lower extremity claudicating pain and her baseline walking distance. Interestingly these gains have persisted after the discontinuation of infusions. Comparison of plain x-rays showed no obvious reduction in peri-articular and arterial calcification. However, neither was there progression in the 2 year period.
CLINICAL LESSON
Few treatment modalities are available for the management of normo-phosphatemic FTC. The therapeutic effects of STS are attributed to the high solubility of Ca thiosulfate salts which inhibit the precipitation of Ca salts and promote the dissolution and mobilization of calcium deposits.^[1,2,3,4] This is the first case report to suggest benefit from STS in the treatment of the familial form of tumoral calcinosis.

(1) Cicone J, Petronis J, Embert C., et al. Successful treatment of calciphylaxis with intravenous sodium thiosulfate.
(2) Kyriakopoulos G, Kontogianni K. Sodium thiosulfate treatment of tumoral calcinosis in patients with end stage renal disease. Renal Failure 1990;12:213-9.
(3) Yatzidis H, Agroyannis B. Sodium thiosulfate treatment of soft tissue calcifications in patients with end stage renal disease. Peritoneal Dial Bull 1987;7:250-2.
(4) Papadakis JT, Patrikarea A, Digenis GE, et al. Sodium Thiosulfate in the treatment of tumoral calcifications in a hemodialysis patient without hyperparathyroidism. Nephron 1996;72:308-12.
Abstract
Nothing to Disclose: NMY, HM

sort_order 3047
Pub # OR44-4
Session Information ORAL SESSION: CLINICAL - Calcium Kinetics & Metabolic Bone Disease (2:00 PM-3:30 PM)
Title The Impact of Vitamin D Status on Osseous Healing Outcomes after Oral Surgery
Author String JD Bashutski, RM Eber, JS Kinney, E Benavides, S Maitra, TM Braun, WV Giannobile, LK McCauley
University of Michigan, Ann Arbor, MI; University of Michigan, Ann Arbor, MI; University of Michigan, Ann Arbor, MI; University of Michigan, Ann Arbor, MI
Body
Background
Periodontal disease is the most widespread bone resorptive disease and is mediated by the host immune response to bacterial insult. Parathyroid hormone stimulates conversion of vitamin D to its active form. Because vitamin D plays a crucial role in bone maintenance and immunity, there is biologic rationale to suspect that a vitamin D deficiency could negatively affect bone regeneration. While vitamin D deficiency has been associated with periodontitis, there is little information regarding its effect on oral periodontal surgery outcomes. This study addressed whether the outcomes of periodontal surgery differed in patients with initial vitamin D deficiency versus sufficiency as well as the effect of teriparatide administration.
Methods
Forty patients with severe chronic periodontitis received periodontal surgery along with 1000 mg calcium and 800 IU of Vitamin D for 6 weeks. Patients also received daily self-administered injections of parathyroid hormone 1-34 (teriparatide) or placebo beginning 3d prior to surgery and continuing for 6wks to correspond with periodontal osseous healing time. Serum 25(OH)D was evaluated at baseline, 6wks, and 6mos post-surgery. Clinical and radiographic outcomes were evaluated for 1 year.
Results
Control patients with baseline vitamin D deficiency (serum 25(OH)D <20ng/mL) had significantly less post-surgical clinical attachment level (CAL) gain and probing depth (PPD) reduction (both measures of periodontal healing) than vitamin D sufficient patients. Patients with baseline vitamin D deficiency had poorer surgical outcomes than vitamin D sufficient patients for clinical attachment gain (-0.43 mm vs. 0.92 mm, p<0.01) and probing depth reduction (0.43 mm vs. 1.83 mm, p<0.01). Patients taking teriparatide, however, had similar CAL (1.75 mm vs. 1.54 mm, NS) and PPD improvements (1.88 mm vs. 2.57 mm, NS) at 1 year regardless of vitamin D levels. In contrast, radiographic intrabony linear defect resolution in teriparatide patients was greater in the vitamin D sufficient subjects (2.05 mm vs. 0.87 mm, p=0.03).
Conclusions
These data suggest that vitamin D deficiency at the time of periodontal surgery negatively affects treatment outcomes for up to 1 year, despite a 6 wk post-surgical supplementation. Teriparatide administration diminishes these effects. Since vitamin D deficiency is highly prevalent, assuring adequate vitamin D levels prior to periodontal surgery may improve surgical outcomes.
Sources of Research Support: In part, by Eli Lilly through an investigator-initiated study, the American Academy of Periodontology Foundation Tarrson Regeneration Scholarship, and the University of Michigan Clinical Research Unit NIH/NCRRL UL1RR024986.
Nothing to Disclose: JDB, RME, JSK, EB, SM, TMB, WVG, LKM

sort_order 3048
Pub # OR44-5
Session Information ORAL SESSION: CLINICAL - Calcium Kinetics & Metabolic Bone Disease (2:00 PM-3:30 PM)
Title Fracture Risk after Bariatric Surgery
Author String KM Nakamura, EGC Haglund, JA Clowes, SJ Achenbach, EJ Atkinson, LJ Melton, KA Kennel
Mayo Clinic, Rochester, MN; Mayo Clinic, Rochester, MN; Mayo Clinic, Rochester, MN; Guthrie Clinic, Sayre, PA; HealthEast Care System, St Paul, MN
Body
Introduction: Bariatric surgery is an increasingly common treatment for medically complicated obesity. Adverse changes in multiple parameters of bone health after bariatric surgery have been reported, but the clinical importance of these observations remains unknown. We hypothesized that bariatric surgery patients are at increased risk of fracture.
Methods: Utilizing the resources of the Rochester Epidemiology Project, we conducted a retrospective study of fracture incidence in the 277 SE Minnesota residents who underwent a first bariatric surgery between 1985-2004 at Mayo Clinic Rochester. Fracture data were expressed as standardized incidence ratios (SIR), comparing the number of observed fractures to the number of expected by skeletal site. Expected numbers of fractures were derived by applying age- and sex-specific incidence rates from the local population to the age- and sex-specific person-years of follow-up. Potential risk factors were evaluated by hazard ratios (HR) from regression models.
Results: The mean (\pm SD) age at bariatric surgery was 43.7 ± 9.9 yrs with 83% (229) females. Gastric bypass surgery was performed in 94% of cases. Following bariatric surgery, 82 subjects experienced 138 fractures. Mean time to first fracture was 5.9 years (range, 0.2 to 18.6) with mean duration of follow-up of 9 years (range, 0.02 to 25.2). The SIR for any fracture was 2.1 (CI, 1.7 to 2.7). The SIR for a first fracture at hip, wrist, spine or humerus was 1.9 (CI, 1.2 to 2.8) and was 2.3 (CI, 1.8 to 2.9) for a first fracture at all other sites; notable were fractures of the foot (SIR, 3.0; CI, 2.0 to 4.3), leg (SIR, 2.2; CI, 1.3 to 3.4), and hand (SIR, 3.1; CI, 1.8 to 4.9) fractures. After adjustment for age, better activity status before surgery was associated with a lower risk (HR, 0.43; CI, 0.23 to 0.81), but history of fracture prior to bariatric surgery was not associated with subsequent fracture risk.
Conclusion: This study demonstrates an increased rate of fracture following bariatric surgery which suggests that structural and biochemical changes in bone observed after bariatric surgery are clinically important. Clinicians should discuss bone health with patients who have undergone or are considering bariatric surgery. Further prospective studies are needed to identify strategies that optimize bone health in these patients.

Nothing to Disclose: KMN, EGCH, JAC, SJA, EJA, LJM, KAK

sort_order 3049
Pub # OR44-6
Session Information ORAL SESSION: CLINICAL - Calcium Kinetics & Metabolic Bone Disease (2:00 PM-3:30 PM)
Title Impacts of Serum Calcium and Phosphate on Coronary Atherosclerosis Detected by Cardiac Computed Tomography
Author String KJ Kim, S-K Lim, S Shin, H-J Chang, KM Kim, Y Rhee, YJ Kim
Severance Hospital, Yonsei University College of Medicine, Seoul, Korea; Cardiovascular Center, Yonsei University College of Medicine, Seoul, Korea; Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
Body
Background
It is well-known that high serum calcium (Ca), inorganic phosphate (P), and calcium phosphate product (CPP) levels are associated with high rates of cardiovascular disease (CVD) in patients with advanced chronic kidney disease (CKD). So far, whether this relationship persists among individuals with normal kidney function has not been elucidated. This study aims to explore the relationship of serum Ca, P and CPP with coronary atherosclerosis evidenced by cardiac computed tomography (CT) in subjects with near-normal kidney function.
Methods
We consecutively enrolled 7,553 subjects (52 ± 10 years, male 57 %) who underwent cardiac CT for the evaluation of suspected coronary artery disease (CAD) and had near normal kidney function (estimated glomerular filtration rate (eGFR): $>60\text{ml}/\text{min}/1.73\text{m}^2$). Subjects were compared across quartiles of serum Ca, P and CPP using analysis of variance, and multiple logistic regression analyses for coronary atherosclerosis (coronary artery calcium score (CACS) >100 ; the presence of CAD: any plaque on coronary CT angiography (cCTA); $>50\%$ CAD: $>50\%$ diameter stenosis on cCTA) were also performed.
Results
Higher level of serum Ca and CPP was significantly associated with CACS >100 , the presence of CAD, and $>50\%$ CAD in a continuous fashion ([Ca] adjusted odd ratio [OR] (per mg/dl): 1.21, $p=0.026$; OR: 1.15, $p=0.004$; OR=1.53, $p<0.001$, [CPP] OR=1.03, $p<0.001$; OR=1.01, $p=0.048$; OR=1.02, $p=0.003$, respectively). Serum P was an independent risk factor only for CACS >100 (OR 1.29, $p<0.001$).
Ca was a risk factor for the presence of CAD and $>50\%$ CAD in both genders ([male] OR: 1.15, $p=0.032$; OR: 1.52, $p<0.001$, [female] OR: 1.16, $p=0.048$; OR: 1.68, $p<0.001$, respectively), but was a risk factor for CACS >100 only in male (OR 1.23, $p=0.047$). In male, P was a risk factor for CACS >100 , but in female, such an association was not found (OR 1.11, $p=0.446$). CPP was associated with CACS >100 , the presence of CAD, and $>50\%$ CAD (OR: 1.04, $p<0.001$; OR: 1.01, $p=0.145$; OR 1.02, $p=0.005$) only in male.
Conclusion
High serum Ca was consistently associated with coronary atherosclerosis in subjects with near normal kidney function. The effects of Ca, P, and CPP on coronary atherosclerosis are different depending on gender, which may reflect the differential impact.

Nothing to Disclose: KJK, S-KL, SS, H-JC, KMK, YR, YJK

sort_order 3050
Pub # OR45-1
Session Information ORAL SESSION: CLINICAL - Polycystic Ovary Syndrome & Other Female Androgenic Disorders (2:00 PM-3:30 PM)
Title Early Metformin Treatment (Age 8[en dash]12) in Girls with Precocious Pubarche to Prevent Polycystic Ovary Syndrome (PCOS) in Adolescence: A Randomized Study over 7 Years
Author String L Ibanez, A Lopez-Bermejo, M Diaz, MV Marcos, F de Zegher
Hospital Sant Joan de Déu, University of Barcelona, Esplugues, Spain; Hospital Dr Josep Trueta and Girona Institute for Biomedical Research, Girona, Spain; Hospital de Terrassa, Terrassa, Spain; University of Leuven, Leuven, Belgium
Body
Context
Among the girls with precocious pubarche (PP), those with a low birthweight (LBW) are known to be at the highest risk for developing PCOS by adolescence [1]. In LBW-PP girls, we studied the effects of early/prolonged versus late/brief metformin treatment on the prevalence of PCOS in adolescence.
Study Design
Open-label, randomized study over 7 yr.
Patients
38 LBW-PP girls.
Intervention
At age 8 yr, LBW-PP girls were randomized into two subgroups: [ldquo]early metformin[rdquo] girls (N=19) received metformin for 4 yr [2] and remained then untreated for 3 yr; [ldquo]late metformin[rdquo] girls (N=19) remained untreated for 5 yr [3], received then metformin for 1 yr, and remained thereafter untreated for 1 yr.
Main Outcomes
Height; menstrual cyclicality; endocrine-metabolic screening (blood; fasting state; follicular phase); body composition by absorptiometry; abdominal fat (subcutaneous vs visceral) and hepatic adiposity by MRI.
Results
At age 15 yr, [ldquo]early metformin[rdquo] girls were 4 cm taller on average, had less visceral and less hepatic fat, and had a lower neutrophil count than [ldquo]late metformin[rdquo] girls. The prevalence of PCOS (by NIH criteria) was 7-fold higher in [ldquo]late metformin[rdquo] girls (PCOS in 7 of 19) than in [ldquo]early metformin[rdquo] girls (1 of 19).
Conclusion
In LBW-PP girls, early metformin therapy (8-12 yr) was associated with a lower prevalence of adolescent PCOS. Metformin, when given across the potentially critical window of puberty, may have the capacity to reprogram metabolism toward less visceral and hepatic adiposity, toward a less pro-inflammatory state, and thus away from PCOS.

[1] Ibañeta et al. J Clin Endocrinol Metab 1998;83:3558-3562.
[2] Ibañeta et al. J Clin Endocrinol Metab 2008;93:1841-1845.
[3] Ibañeta et al. J Pediatr 2010;156:98-102.

Nothing to Disclose: LI, AL-B, MD, MVM, FdZ

sort_order 3051
Pub # OR45-2
Session Information ORAL SESSION: CLINICAL - Polycystic Ovary Syndrome & Other Female Androgenic Disorders (2:00 PM-3:30 PM)
Title Polycystic Ovarian Morphology (PCOM) in Adolescents with Regular Menstrual Cycles Is Associated with Elevated Anti-Müllerian Hormone (AMH): Impact of Different Diagnostic Criteria
Author String C Villarroel, P Lopez, PM Merino, G Iniguez, E Codner
University of Chile, Santiago, Chile; Servicio de Salud Metropolitano Centro, Santiago, Chile; University of Chile, Santiago, Chile
Body
Context: The significance of polycystic ovarian morphology (PCOM) during adolescence is not clear and different ultrasonographic criteria of PCOM have been utilized during this stage of life.
Objective: To determine whether PCOM during adolescence is associated with elevated anti-Müllerian hormone (AMH) levels and to evaluate which of three previously reported diagnostic criteria of PCOM for adolescents correlate better with AMH levels.
Method: We studied ovarian function in non-obese adolescents with regular menstrual cycles, who did not exhibit clinical signs of hyperandrogenism. Steroids, gonadotropin, AMH and Inhibin B levels were measured during the follicular phase. Transabdominal gynecological ultrasound (TA-US) was performed by a single observer (CV). PCOM was defined by Rotterdam criteria (RC), ovarian volume > 10.8 ml (OV10.8) and ovarian volume > 7.82 ml (OV7.82). Multifollicular ovaries were defined by the presence of 6 to 11 follicles between 4 and 10 mm and an ovarian volume less than 10 ml.
Results: PCOM according to the RC, OV10.8 and OV7.82 was present in 33.8, 13.5 and 43.2% of the girls, respectively. Girls with PCOM had higher AMH levels than girls without PCOM (using RC: 72.5 ± 6.1 ; using OV10.8 ml: 80.5 ± 11.7 ; using OV7.82 ml: 53.4 ± 6.5 ; and without PCOM: 34.6 ± 3.1 pmol/L; $P < 0.001$). Lower FSH levels were observed in girls with PCOM diagnosed with the three classifications compared to girls without PCOM.
AMH levels above 50.25 pmol/L had a sensitivity and specificity of 84.0 and 83.7%, respectively, to diagnose PCOM according to the RC (AUC= 0.873). A lower level of accuracy was observed for the other two sets of diagnostic criteria (AUC for OV10.8 and OV7.82 of 0.81 and 0.587, respectively). AMH levels correlated with the number of 2- to 5-mm, but not 6-9 mm follicles. Similar levels of inhibin B, androgens, and LH were observed in girls with and without PCOM. Girls with multifollicular ovaries had AMH levels (34.4 ± 3.8 pmol/L) similar to those of girls without this ovarian pattern (32.1 ± 3.6 pmol/L).
Conclusions: The elevated AMH and decreased FSH levels, without elevated androgen levels, observed in non-hyperandrogenic girls with regular menstrual cycles and PCOM suggest that this ovarian pattern is secondary to a larger number of small, growing follicles. Multifollicular ovaries were associated with normal AMH levels. AMH can be used as a surrogate marker for PCOM diagnosed during adolescence using the Rotterdam criteria.

Sources of Research Support: Fondecyt Grant 1100123.

Nothing to Disclose: CV, PL, PMM, GI, EC

sort_order 3052
Pub # OR45-3
Session Information ORAL SESSION: CLINICAL - Polycystic Ovary Syndrome & Other Female Androgenic Disorders (2:00 PM-3:30 PM)
Title Parent-of-Origin Effects on Glucose Homeostasis in Polycystic Ovary Syndrome
Author String K Kobaly, A Cooper, M Urbanek, RS Legro, A Dunaif
Feinberg School of Medicine, Northwestern University, Chicago, IL; Pennsylvania State University College of Medicine, Hershey, PA
Body **Introduction:** Polycystic ovary syndrome (PCOS), a common endocrine disorder affecting reproductive aged women, is associated with metabolic abnormalities including an increased risk of type 2 diabetes mellitus (T2D). PCOS is a complex genetic disease. We performed this study to test the hypothesis that women with PCOS may have a higher propensity for glucose intolerance based on parent-of-origin.
Methods: The families of 540 women with PCOS were studied (n=429 fathers [F], n=500 mothers [M]). The probability of a PCOS proband having dysglycemia (fasting glucose >100 mg/dL or known T2D) based on whether their parents were dysglycemic was examined. We analyzed whether the fibrillin-3 PCOS susceptibility variant (D19S884 Allele 8) was associated with an increased risk of dysglycemia in these families.
Results: BMI did not differ between F and M (30.0 ± 5.5 F vs 30.6 ± 6.9 M, $p=0.414$). F were older than M (58 ± 8 F vs 55 ± 8 M, $p<0.0001$), however, ANCOVA adjusting for age and BMI did not change the significant results so unadjusted results are reported. F had a significantly higher fasting glucose than M (109 ± 39 F mg/dL vs 101 ± 33 M mg/dL, $p<0.0001$). F had significantly higher proinsulin:insulin molar ratios than M, a marker of beta-cell dysfunction (0.19 ± 0.14 F vs 0.15 ± 0.10 M, $p<0.0001$). F also had a slight but significant increase in HOMA-IR (2.25 ± 1.42 F vs 2.10 ± 1.54 M, $p=0.0257$), suggesting modest decreases in insulin action compared to M. Dysglycemia in PCOS probands was associated with M dysglycemia (odds ratio [OR] 1.80, confidence interval [CI] 1.11-2.92, $p=0.0168$), but not F dysglycemia (OR 1.19 CI, 0.73- 1.95, $p=0.494$). Odds ratios were increased when both parents were affected (OR 2.54 CI 1.33 to 4.85, $p=0.0046$). There was no difference in rates of dysglycemia between carriers and non-carriers of D19S884 A8 in probands or their parents.
Conclusions: Our findings suggest that there are parent-of-origin effects on glucose homeostasis in PCOS. M dysglycemia is a stronger predictor of dysglycemia in PCOS probands suggesting that the intrauterine environment contributes to metabolic defects associated with the syndrome. There are sex-specific changes in metabolic defects as F have evidence for beta-cell dysfunction and insulin resistance. This study provides evidence that both genes and environment play a role in the pathogenesis of dysglycemia in PCOS.
Nothing to Disclose: KK, AC, MU, RSL, AD

sort_order 3053
Pub # OR45-4
Session Information ORAL SESSION: CLINICAL - Polycystic Ovary Syndrome & Other Female Androgenic Disorders (2:00 PM-3:30 PM)
Title Adrenal Contribution to Hyperandrogenemia in Peripubertal Girls with Obesity
Author String CM Burt Solorzano, J Collins, JP Beller, MY Abshire, CR McCartney, JC Marshall
University of Virginia, Charlottesville, VA; University of Virginia, Charlottesville, VA; University of Virginia, Charlottesville, VA
Body
Hyperandrogenemia (HA) in adolescence is a forerunner to adult polycystic ovary syndrome (PCOS), yet androgen sources in peripubertal girls remain unclear. Our data suggest that ~70% of obese girls have HA, including pre- and early pubertal girls (1-3). The primary source of HA in PCOS women is thought to be ovarian, although some patients have adrenal HA as well. Since ovarian activity is thought to be limited prior to thelarche, we propose that the adrenal gland is a major contributor to HA in obese pre- and early pubertal girls. Our previous studies suggest that testosterone (T) secretion in normal early pubertal girls (Tanner 1-2, n=8) follows a diurnal rhythm with overnight levels nearly doubling by early morning (4). The explanation for this is unclear, but the similarity of timing to diurnal changes of cortisol suggests an adrenal origin in response to increased morning ACTH secretion. This study examines adrenal steroid production in normal (NW) and overweight (OW) girls throughout puberty.
We have complete data for overnight dexamethasone (DEX) suppression (1mg po, 2200h) and ACTH stimulation (250[μg] IV, 0700h next day) tests in 4 NW (BMI<85%) and 17 OW (BMI[ge]85% girls ages 7-18. In contrast to control subjects not receiving DEX (n=71), who exhibited overnight free T increases of 20-75% (4), girls receiving DEX had complete suppression of this overnight T production, with free T decreases of 15-24%, regardless of pubertal stage or weight status. This suggests an adrenal contribution to the normal overnight T rise during puberty. Despite free T decreases overnight in all groups after DEX, free T levels remained >5-fold higher in OW late pubertal (Tanner 3-5) girls after DEX compared to NW counterparts after DEX, suggesting a possible ovarian contribution to HA later in puberty.
ACTH administration resulted in greater free T responses in OW girls compared to NW girls. Specifically, OW early pubertal girls showed free T responses 10-fold higher than NW counterparts (increases over baseline=2.4±0.9 vs 0.2±0.2 pmol/L). OW late pubertal girls had >2-fold higher free T responses to ACTH compared to NW counterparts (8.5±1.6 vs 3.8±0.9 pmol/L), suggesting continued adrenal HA during late puberty.
These data suggest that, in OW girls, the adrenal is the main source of HA in early puberty and contributes to HA in late puberty. Ovarian steroid biosynthesis may contribute to late pubertal HA, but its role in early puberty requires further examination.

(1) McCartney CR et al., J Clin Endocrinol Metab 2006; 91:1714
(2) McCartney CR et al., J Clin Endocrinol Metab 2007; 92:430
(3) Knudsen KL et al., Obesity 2010; 18:2118
(4) McCartney CR et al., J Clin Endocrinol Metab 2009; 94:56

Sources of Research Support: Eunice Kennedy Shriver National Institute of Child Health and Human Development/National Institute of Health through cooperative agreement U544 HD28934 as part of the Specialized Cooperative Centers Program in Reproduction and Infertility Research (CRM, JCM, CBS, MA); F32 HD066855 (JC); General Clinical Research Center Grant M01 RR00847.

Nothing to Disclose: CMBS, JC, JPB, MYA, CRM, JCM

sort_order 3054
Pub # OR45-5
Session Information ORAL SESSION: CLINICAL - Polycystic Ovary Syndrome & Other Female Androgenic Disorders (2:00 PM-3:30 PM)
Title LH Pulsatility and Secretion Are Tightly Associated with Hormonal Control in CAH Patients
Author String A Bachelot, Z Chakhtoura, G Plu-Bureau, C Coussieu, Y Badachi, J Dulon, B Charbit, P Touraine
Pitié-Salpêtrière Hospital, Paris, France; Hotel-Dieu Hospital, Paris, France; Pitié-Salpêtrière Hospital, Paris, France; Pitié-Salpêtrière Hospital, Paris, France
Body Fertility in women with classical congenital adrenal hyperplasia (CAH) has been reported low. This has been attributed to several factors including gender dysphoria, post-surgical difficulties with intercourse, anovulation, and the effect of progesterone hypersecretion on endometrial receptivity. Some authors have also suggested that congenital adrenal virilization determines the hypothalamic-pituitary axis for hypersecretion of LH at puberty. Our aim was to evaluate LH pulsatility patterns in women with CAH, and to determine factor(s) that could account for the potential abnormality of LH pulsatility. Sixteen CAH women (10 with salt wasting form of CAH, 6 with simple virilizing form of CAH), aged from 18 to 40 years, with FSH levels under 15 UI/L, and 16 age-matched women, with regular cycles and FSH levels under 15 UI/L, were included in our study. Body mass index did not differ between the two groups (25.9 ± 1.6 kg/m² in the CAH group, 22.9 ± 0.5 kg/m² in the control group). In the CAH group, 8 patients had regular menstrual cycles, 3 presented oligomenorrhea and 5 amenorrhea. Patients and controls underwent frequent blood sampling study (every 10 min for 6 h) to determine endogenous LH pulse patterns. Seven CAH women had normal LH pulsatility patterns, with mean plasma LH level (6.9 ± 0.7 UI/L versus 5.9 ± 0.7 UI/L, ns), LH pulse number (4.0 ± 1.7 versus 3.9 ± 1.0 , ns) and amplitude (7.4 ± 2.2 versus 6.3 ± 2.4 UI/L) that did not differ from control women. On the contrary, in the remaining nine CAH women, mean plasma LH level (2.7 ± 1.1 UI/L versus 5.9 ± 0.7 UI/L, $p < 0.01$), LH pulse number (0.9 ± 0.8 versus 3.9 ± 1.0 , $p < 0.001$) and amplitude (2.8 ± 2.1 versus 6.3 ± 2.4 , $p < 0.001$) were dramatically low compared to controls. This group of CAH women represents the patients with poor hormonal control under treatment (mean 17OH progesterone levels 129.2 ± 54.1 ng/ml, mean progesterone levels 9.7 ± 3.3 ng/ml and mean testosterone levels 1.3 ± 0.5 ng/ml), especially with high progesterone levels, that could account for reduced LH pulses frequency and amplitude. In conclusion, LH pulsatility and secretion could be normal in CAH women with good hormonal control of their disease. Optimized glucocorticoid and mineralocorticoid regimes during fertility monitoring should then be an important concern in CAH women and suppression of serum progesterone concentrations during the follicular phase of the menstrual cycle should be a major objective tool in these patients.

Nothing to Disclose: AB, ZC, GP-B, CC, YB, JD, BC, PT

sort_order 3055
Pub # OR45-6
Session Information ORAL SESSION: CLINICAL - Polycystic Ovary Syndrome & Other Female Androgenic Disorders (2:00 PM-3:30 PM)
Title Measurement of Salivary Testosterone in Female Samples Using a Highly Sensitive LC-MS/MS Assay
Author String B Keevil, P MacDonald, L Owen, W Medowell, F Wu
University Hospital of South Manchester, Manchester, UK; London School of Hygiene & Tropical Medicine, London, UK; Manchester Royal Infirmary, Manchester, UK
Body
Direct measurement of salivary testosterone offers an attractive alternative to calculated free testosterone as it is thought to reflect circulating free testosterone. Previous methods for salivary testosterone have used immunoassay which is prone to specificity problems. LC-MS/MS methods have been used for male samples because of their better specificity but measurement in the female range has proved difficult due to the low concentrations present. We have developed a highly sensitive LC-MS assay in an attempt to improve the assay of salivary testosterone and include measurement in female samples.
Saliva (200 [micro]L), calibrators or QC was mixed with 10 [micro]L working internal standard (0.1[micro]g/L) and 1 mL of methyl tert-butyl ether (MTBE). Vortex mixed for 4 minutes and frozen at -80[deg]C (1hr). Unfrozen organic layer was transferred to a glass tube and evaporated. The residue was reconstituted with 100 [micro]L of 50:50 mobile, vortex mixed and transferred to a 96-well microtitre plate.
Liquid chromatography was performed using a Waters Acquity[trade] UPLC system. Extract (30 [micro]L) was injected directly from the microtitre plate onto a C18 Acquity 1.8[micro]m HSS T3 analytical column (2.1 x 50 mm). A solvent gradient was used to elute testosterone and D5 Testosterone from the column. TMS was performed on a Waters Quattro Xevo TQ-S in positive ionization mode. Multiple reaction monitoring transitions for testosterone were m/z 289.2>108.8 (quantifier) and m/z 289.2>96.8 (qualifier) and for D5-testosterone internal standard was m/z 294.1>99.8. Lower limit of quantitation was 2 pmol/L (0.06ng/dL), recovery was 98-109%. Interbatch precision (CV) was 4.4%, 6.0% and 2.8% at 17 (0.49), 100 (2.9) and 154(4.4) pmol/L (ng/dL) respectively. The median female range (n=96) was 10-15 pmol/L (0.29-0.43 ng/dL) and the median male range (n=96) was 100-150 pmol/L (2.9-4.3 ng/dL). Although cross validation of calibrators was performed to eliminate any calibration issues/bias we still found the LC-MS method gave 25% lower values than the RIA method in males and 400% lower in females.
Using a highly sensitive mass spectrometer we have developed an assay for salivary testosterone with greatly improved detection limits and confirmed that RIA was unsuitable for measuring salivary testosterone especially in female samples. We established reference ranges in saliva samples and found good demarcation between the male and female reference ranges.

Nothing to Disclose: BK, PM, LO, WM, FW

sort_order	3056
Pub #	CS1
Session Information	CLARK T SAWIN MEMORIAL LECTURE: TRANSLATIONAL - The History of the Endocrinology of Vitamin D (2:00 PM - 2:45 PM)
Title	The History of the Endocrinology of Vitamin D
Author String	MF Holick Boston University School of Medicine, Boston, MA
Body	Nothing to Disclose: MFH

sort_order	3057
Pub #	M48
Session Information	MEET-THE-PROFESSOR: CLINICAL - Management of Congenital Adrenal Hyperplasia in the Adult & Child (2:45 PM - 3:30 PM)
Title	Management of Congenital Adrenal Hyperplasia in the Adult & Child
Author String	ME Geffner Children's Hospital of Los Angeles, Los Angeles, CA
Body	Nothing to Disclose: MEG

sort_order	3058
Pub #	CMF15-1
Session Information	CASE MANAGEMENT FORUM: CLINICAL - Lipid Management Cases: By the Guidelines or by Common Sense? (2:45 PM - 3:30 PM)
Title	Lipid Management Cases by the Guidelines or by Common Sense?
Author String	K Feingold Veterans Affairs Medical Center, San Francisco, CA
Body	Disclosures: KF: Speaker, Abbott Laboratories, Merck & Co., Takeda; Principal Investigator, Merck & Co.

sort_order	3059
Pub #	CMF15-2
Session Information	CASE MANAGEMENT FORUM: CLINICAL - Lipid Management Cases: By the Guidelines or by Common Sense? (2:45 PM - 3:30 PM)
Title	Lipid Management Cases by the Guidelines or by Common Sense?
Author String	LR Tannock University of Kentucky, Lexington, KY
Body	Nothing to Disclose: LRT

sort_order	3060
Pub #	CMF16-1
Session Information	CASE MANAGEMENT FORUM: CLINICAL - Non-Insulin Treatment of Diabetes Mellitus in Children & Adolescents (2:45 PM - 3:30 PM)
Title	Non-Insulin Treatment of Diabetes Mellitus in Children & Adolescents
Author String	MD DeBoer University of Virginia, Charlottesville, VA
Body	Nothing to Disclose: MDD

sort_order	3061
Pub #	CMF16-2
Session Information	CASE MANAGEMENT FORUM: CLINICAL - Non-Insulin Treatment of Diabetes Mellitus in Children & Adolescents (2:45 PM - 3:30 PM)
Title	Non-Insulin Treatment of Diabetes Mellitus in Children & Adolescents
Author String	PS Zeidler Children's Hospital, Aurora, CO
Body	Disclosures: PSZ: Consultant, Astra Zeneca, Daichii-Sankyo, Bristol-Myers Squibb; Coinvestigator, Merck & Co.

sort_order	3062
Pub #	M47
Session Information	MEET-THE-PROFESSOR: CLINICAL - Erectile Dysfunction: Who, When, What Treatment? (2:45 PM - 3:30 PM)
Title	Erectile Dysfunction: Who, When, What Treatment?
Author String	JB Redmon University of Minnesota Medical School, Minneapolis, MN
Body	Nothing to Disclose: JBR

sort_order	3063
Pub #	M49
Session Information	MEET-THE-PROFESSOR: CLINICAL - Management of Mild Primary Hyperparathyroidism (2:45 PM - 3:30 PM)
Title	Management of Mild Primary Hyperparathyroidism
Author String	SJ Silverberg Columbia University College of Physicians & Surgeons, New York, NY
Body	Nothing to Disclose: SJS

sort_order	3064
Pub #	M50
Session Information	MEET-THE-PROFESSOR: CLINICAL - Management of Subtle & Overt Thyroid Dysfunction from Infancy through Puberty (2:45 PM - 3:30 PM)
Title	Management of Subtle & Overt Thyroid Dysfunction from Infancy through Puberty
Author String	RS Brown Children's Hospital Boston, Boston, MA
Body	Nothing to Disclose: RSB

sort_order 3065
Pub # M51
Session Information MEET-THE-PROFESSOR: CLINICAL - Pregnancy & Management of Diabetes: Before, during & after (2:45 PM - 3:30 PM)
Title Pregnancy & Management of Diabetes: Before, during & after
Author String SE Kirk
University of Virginia, Charlottesville, VA
Body Session supported by: Medtronic Diabetes
Nothing to Disclose: SEK

sort_order	3066
Pub #	M52
Session Information	MEET-THE-PROFESSOR: CLINICAL - The Benefits & Risks of Calcium Intake (2:45 PM - 3:30 PM)
Title	The Benefits & Risks of Calcium Intake
Author String	RS Bockman Hospital for Special Surgery, New York, NY
Body	Nothing to Disclose: RSB

sort_order	3067
Pub #	M53
Session Information	MEET-THE-PROFESSOR: CLINICAL - An Endocrinologist's Use of Vasopressin Antagonists (2:45 PM - 3:30 PM)
Title	An Endocrinologist's Use of Vasopressin Antagonists
Author String	JG Verbalis Georgetown University, Washington, DC
Body	Disclosures: JGV: Consultant, Astellas, Cardiokine, Otsuka, Sanofi-Aventis.

sort_order 3068
Pub # S72-1
Session Information SYMPOSIUM SESSION: BASIC - Programming & Plasticity in the Adrenal (3:45 PM - 5:15 PM)
Title In Search of Adrenocortical Stem & Progenitor Cells
Author String GD Hammer
University of Michigan, Ann Arbor, MI
Body Laboratory focuses on the molecular underpinnings of adrenocortical growth in development and cancer. Our goals are to characterize adrenocortical stem/progenitor cell population and elucidate how altered regulation of these cells contributes to adrenocortical disease. Classic molecular approaches to signaling and transcription are combined with whole animal biology to examine adrenal development and function as it pertains to disease. Lab Work has shown that the orphan nuclear receptor SF-1 is required for proliferation of the adrenocortical stem/progenitor cells while the orphan receptor Dax-1 serves to maintain the multipotency of these cells in vivo. Moreover, studies have provided a novel paradigm by which self-renewal pathways (WNT, NOTCH, SHH and IGF2) regulate the stem/progenitor pools of the adrenal cortex. Targeted loss- and gain-of-function of these pathways results in loss and expansion of adrenocortical stem/progenitor cells and variable adrenal failure and adrenal cancer. Ongoing molecular studies detail the mechanisms by which a variety of signals mediate SF-1 transcription and activation - predicting a unique layer of regulatory control common to multiple classes of transcription factors. Work on inhibin null mice has unraveled a unique role of inhibin as a gatekeeper of adrenal versus gonadal differentiation in the adrenal gland. In the absence of adrenal inhibin, unopposed TGF β 2/Smad3 signaling in the adrenocortical stem/progenitor cell results in uncontrolled stem/progenitor cell expansion and ultimate differentiation into ovarian tissue. The positional cloning of the mutation responsible for adrenocortical dysplasia in mice has provided clues to the role of telomere maintenance in these cells. Because the above signaling pathways and telomere biology are intimately involved in stem/progenitor cell biology, the lab's current efforts are heavily weighted towards understanding the signaling and transcriptional mechanisms involved in the regulation of adrenocortical stem/progenitor cells in development and cancer. With U-M collaborators, we are investigating how gene profiles can be used to diagnose adrenal cancer or predict how well a patient will respond to treatment. We aim to use new targeted biological-based therapies designed against these stem/progenitor signatures to treat cancer cells while sparing normal tissue. Targeted therapies against IGF1R receptor are currently active in national and international trials for adrenal cancer.

Disclosures: GDH: Ad Hoc Consultant & Study Investigator, OSI; Ad Hoc Consultant, Orphagen, HRA Pharma; Study Investigator, Concept.

sort_order 3069
Pub # S72-2
Session Information SYMPOSIUM SESSION: BASIC - Programming & Plasticity in the Adrenal (3:45 PM - 5:15 PM)
Title Transcriptional Regulation of Adrenal Development in Humans
Author String JC Achermann
University College of London Institute of Child Health, London, UK
Body Although several transcription factors and transcriptional co-regulators have been implicated in adrenal development from studies of transgenic mice (e.g., *Wt1*, *Cited2*, *Pbx1*, *Foxd2*, *Osr1*, *Pod1*, *Gli3*, *Sall1*), the role of these factors in human adrenal development is currently less clear. The human adrenal gland develops from around 4 weeks post-conception and undergoes a series of distinct morphological and functional changes throughout pre- and post-natal life. Two key transcriptional regulators of adrenal development that are implicated in human disease are the nuclear receptors DAX-1 (NR0B1) and steroidogenic factor-1 (SF-1, NR5A1, Ad4BP). Defects in DAX-1 cause X-linked adrenal hypoplasia congenita (AHC), but the molecular etiology of this condition remains poorly understood. The adrenal glands tend to be small and contain large cytomegalic cells resembling fetal adrenal cells, but relatively few biological samples have been studied in detail. Several reports have shown that DAX-1 can paradoxically act as a transcriptional repressor, although more recently several examples of DAX-1-dependent activation have emerged. In addition, DAX-1 may have a critical role in maintaining a pool of progenitor cells in the adrenal gland and preventing differentiation. Loss of DAX-1 function could result in accelerated differentiation without appropriate expansion, resulting in a gland that ultimately becomes hypoplastic. The related nuclear receptor SF-1 regulates many key genes involved in adrenal development and function. Several patients with adrenal failure due to SF-1 mutations are reported, though human SF-1 changes are more often associated with gonadal dysfunction. SF-1 plays an important role in supporting cellular differentiation and growth in the adrenal gland. Through ChIP-based approaches, manipulation of SF-1 in cell lines, and a yeast-two hybrid screen we have identified novel targets and co-regulators of SF-1 in early human adrenal development. We have recently focussed on angiotensin 2 and angiogenic networks as targets of SF-1 in adrenal development and tumorigenesis and explored an interaction with RING1 in modulating transcriptional activity. Finally, detailed studies of the adrenal gland during early human development are revealing new transcriptional networks that may be relevant to human adrenal function and disease.

Sources of Research Support: The Wellcome Trust (079666).

Nothing to Disclose: JCA

sort_order 3070
Pub # S72-3
Session Information SYMPOSIUM SESSION: BASIC - Programming & Plasticity in the Adrenal (3:45 PM - 5:15 PM)
Title Molecular Mechanisms of Adrenal Tumorigenesis
Author String CA Stratakis
National Institute of Child Health & Human Development/National Institutes of Health, Rockville, MD
Body There are different molecular pathways that control benign and malignant adrenocortical tumorigenesis. Molecularly, the overwhelming majority of benign lesions of the adrenal cortex leading to Cushing syndrome (CS) are linked to one or another abnormality of the cyclic (c) AMP signaling pathway. A small number of both massive macronodular adrenocortical disease (MMAD) and cortisol producing adenomas (CPAs) harbor somatic GNAS (Gsa) mutations. Micro-hyperplasias are either pigmented (the classic form being that of primary pigmented nodular adrenocortical disease or PPNAD) or non-pigmented (NP-MAH) and isolated (i) or in the context of other syndromes (Carney complex - CNC). Both CNC and iPPNAD are caused by germline *PRKARIA* mutations; somatic mutations of this gene that regulates cAMP-dependent protein kinase (PKA) are also found in 10-20% of all CPAs and abnormalities of PKA are present in most MMADs. NP-MAH forms of adrenal hyperplasia and some CPAs are associated with phosphodiesterase (PDE)-11A and PDE-8B sequence defects. Mouse models of *PRKARIA* and *PDE8B* deficiency also show that increased cAMP signaling leads to tumors in adrenal cortex and other tissues. Micro-RNA studies identified the Wnt-signaling pathway as the main culprit of PKA-induced tumor formation. We investigated *Prkar1a*^{+/-} mice when bred within the *Rb1*^{+/-} or *Trp53*^{+/-} backgrounds. All double heterozygous mice had significantly reduced life-spans and developed more tumors when compared with their single-heterozygous counterparts. Whole-genome transcriptome profiling of tumors produced by all models identified Wnt signaling as the main pathway activated by abnormal cAMP signaling, along with cell cycle abnormalities. Thus, it appears that *Prkar1a* haploinsufficiency is a generic but relatively weak tumorigenic signal. A *Prkar1a*^{+/-} *Prkaca*^{+/-} mouse model developed a variety of skeletal lesions that led to the identification of specific population of bone stromal cells. Thus cAMP signaling aberrations are essential in the pathogenesis of benign cortisol-producing lesions of the adrenal cortex; Wnt-signaling emerges as the main downstream effector of cAMP/PKA. We also review briefly new developments in aldosterone-producing tumors (*KCNJ5* gene) and adrenomedullary tumors (defects of the mitochondrial oxidation pathway) and how they may link with adrenocortical tumors, in conditions such as Carney Triad and others.

Nothing to Disclose: CAS

sort_order 3071
Pub # S73-1
Session Information SYMPOSIUM SESSION: BASIC - Prolactin, Jack of All Trades (3:45 PM - 5:15 PM)
Title Prolactin Actions in Mammary Development
Author String CJ Ormandy
Garvan Institute of Medical Research, Darlinghurst Sydney, Australia
Body Prolactin is a key regulator of the vast number of physiological adaptations required for lactation. Best described are the developmental events within the mammary gland, but prolactin also regulates many processes that accompany or are required for successful rearing of mammalian neonates, such as maternal behavior and metabolic regulation, with many many more physiological changes due to pregnancy and lactation attributable to prolactin action. Prolactin also acts in disease. High serum prolactin is associated with increased risk of breast cancer and prolactin has pro proliferative and survival actions on breast cancer cells. A key regulator of prolactin action in the mammary gland is the ets transcription factor E1F5, known as ESE2B in humans, which is capable of rescuing the failure of alveolar morphogenesis observed in prolactin receptor knockout mice when forcibly re expressed. E1F5 acts to specify the differentiation of a mammary progenitor cell toward the alveolar milk-producing lineage. We have constructed inducible expression and knock down models of ESE2B in breast cancer cell lines and in mouse tumours to study the potential roles of E1F5 in breast and mammary cancer. Forced expression of ESE2B resulted in reduced proliferation in the luminal breast cancer cell lines T47D and MCF7 due to delayed G1 to S phase cell cycle progression. This effect was also seen in anchorage independent culture and when the cells were grown as xenografts in mice. Knockdown of ESE2B produced little effect. An additional effect of reduced cell attachment was observed, accompanied by reduced beta1 integrin expression and signaling via focal adhesion kinase. Increased rates of apoptosis were seen. Forced expression of E1F5 in mice produced slower proliferation rates of the luminal-type tumours induced by the PyMT oncogene. A combination of genome-wide expression analysis and whole-genome chromatin immunoprecipitation and sequencing allowed us to identify the direct and indirect transcriptional targets of ESE2B, providing a mechanistic explanation of the effects above and affording further insight regarding the role of ESE2B in the specification of the phenotype of breast cancers.

Sources of Research Support: National Health and Medical Research Council of Australia, New South Wales Cancer Council, Cancer Institute New South Wales, RT Hall Trust, BNP Paribas Australia and the Australian Cancer Research Foundation.

Nothing to Disclose: CJO

sort_order 3072
Pub # S73-2
Session Information SYMPOSIUM SESSION: BASIC - Prolactin, Jack of All Trades (3:45 PM - 5:15 PM)
Title The Role of Prolactin in Peripartum Cardiomyopathy
Author String E Podewski
Hannover Medical School, Hannover, Germany
Body Peripartum cardiomyopathy (PPCM) is a serious, potentially life-threatening heart disease of unknown etiology in previously healthy women. It is characterized by a sudden onset of heart failure in association to pregnancy and child birth. Recent data showed that unbalanced peri/postpartum oxidative stress is linked to proteolytic cleavage of the nursing hormone prolactin (23-25kDa) into a potent anti-angiogenic, pro-apoptotic and pro-inflammatory factor (N-terminal 16kDa prolactin fragment). These observations strongly suggest that prolactin cleavage can operate as a specific pathomechanism for the development of PPCM. Consistent with these findings inhibition of prolactin secretion by bromocriptine, a dopamine D2 receptor agonist, prevented the development of PPCM in an animal model of PPCM. First clinical experience showed that bromocriptine prevented onset of PPCM in women with a high risk for the disease due to a PPCM in a previous pregnancy. Randomized trials in South Africa, the findings in the Hanover PPCM-register, and several case reports suggest that bromocriptine may be beneficial in acute PPCM. Thus, inhibition of prolactin release may represent a novel specific therapeutic approach to either prevent or treat patients with acute PPCM.
Nothing to Disclose: EP

sort_order 3073
Pub # S73-3
Session Information SYMPOSIUM SESSION: BASIC - Prolactin, Jack of All Trades (3:45 PM - 5:15 PM)
Title Prolactin & Vasoinhibins: Endogenous Players in Diabetic Retinopathy
Author String C Clapp
University Nacional Autonoma de Mexico, Queretaro, Mexico
Body Disruption of the quiescent state of blood vessels in the retina leads to aberrant vasopermeability, vasodilation, and angiogenesis, which are the major causes of vision loss in diabetic retinopathy. Prolactin expressed in the retina, or incorporated into the eye from the systemic circulation, is proteolytically cleaved to vasoinhibins, a family of peptides with potent antiangiogenic, vasoconstrictive, and antivasopermeability actions. Ocular vasoinhibins exert an essential suppression of blood vessel growth, dilation, and remodeling under normal conditions. Moreover, vasoinhibins have been shown to prevent retinal angiogenesis and vasopermeability associated with diabetic retinopathy, and inactivation of endothelial nitric oxide synthase is one of several mechanisms mediating their actions. Notably, the circulating levels of PRL increase in diabetes and are higher in patients with no retinopathy than in those with severe retinopathy. Hyperprolactinemia leads to vasoinhibin accumulation within the retina and reduces the increase in retinal vasopermeability induced by vascular endothelial growth factor and diabetes. These findings support the role of PRL and vasoinhibins both in the maintenance of normal retinal vasculature and in the cause and prevention of diabetic retinopathy.

Arnold E, Ramirez M, Lemini M, Arredondo-Zamarripa D, Diaz-Lezama N, Macotela Y, Martinez de la Escalera G, Thebault S. Instituto de Neurobiologia, Universidad Nacional Autonoma de Mexico (UNAM), Queretaro, Mexico.

Sources of Research Support: National Council of Science and Technology (CONACYT) grant SALUD-2008-CO1-87015.

Nothing to Disclose: CC

sort_order	3074
Pub #	S74-1
Session Information	SYMPOSIUM SESSION: TRANSLATIONAL - Estrogen Receptors in Cancer (3:45 PM - 5:15 PM)
Title	Receptor Modifications & Breast Cancer
Author String	SA Fuqua Baylor College of Medicine, Houston, TX
Body	Nothing to Disclose: SAF

sort_order 3075
Pub # S74-2
Session Information SYMPOSIUM SESSION: TRANSLATIONAL - Estrogen Receptors in Cancer (3:45 PM - 5:15 PM)
Title NF[κ]B & Estrogen Receptor Cross-Talk in Breast Cancer
Author String JM Frasor
University of Illinois at Chicago, Chicago, IL
Body In many tissues, estrogen is known to have an anti-inflammatory effect through its capacity to repress NF[κ]B transcriptional activity. However, in breast cancer we find that the estrogen receptor (ER) and NF[κ]B can also work together to synergistically up-regulate transcription of a unique set of target genes. These genes are highly enriched in the Luminal B subtype of ER positive breast tumors, which are known to be more aggressive and have a worse outcome than the Luminal A subtype, and can distinguish patients with a poor response to tamoxifen from those with a good one. The genes in this subset include ABCG2, a transporter associated with the development of drug resistance in breast cancer, BIRC3, an important cell survival factor in breast cancer cells, and PTGES, a key enzyme in prostaglandin production. Understanding the mechanisms by which ER and NF[κ]B work together to up-regulate expression of these genes is a major focus of our work. Although each gene we have examined so far appears to be regulated in a unique manner, we find that cooperativity between ER and the NF[κ]B family member, p65, at specific DNA sites is a common regulatory mechanism for all three genes. For example, we find that ER is recruited to an ERE located upstream of two NF[κ]B response elements of the BIRC3 gene only when NF[κ]B is active. Our data indicate that NF[κ]B-directed histone acetylation and changes in chromatin organization appear to play an important role in mediating accessibility of the ERE. Our findings also indicate that ER can not only repress NF[κ]B activity in breast cancer cells at known target genes, such as IL-8 and TNF α , but can also stabilize NF[κ]B interaction with DNA and enhance its activity at other newly identified targets, such as the drug transporter ABCG2. Thus, by modulating each others interaction with DNA, ER and NF[κ]B can work together in a cooperative manner to synergistically up-regulate specific target genes. Taken together, our findings suggest that local inflammation in the breast tumor microenvironment or constitutive activation of NF[κ]B within breast tumor cells may play an important role in promoting aggressiveness and attenuating drug responsiveness of ER positive breast tumors.

Nothing to Disclose: JMF

sort_order	3076
Pub #	S74-3
Session Information	SYMPOSIUM SESSION: TRANSLATIONAL - Estrogen Receptors in Cancer (3:45 PM - 5:15 PM)
Title	Estrogen Receptor-Beta & Epithelial-Mesenchymal Transition in Prostate Cancer
Author String	AM Mercurio University of Massachusetts Medical Center, Worcester, MA
Body	Nothing to Disclose: AMM

sort_order

3077

Pub #

S75-1

Session Information

SYMPOSIUM SESSION: TRANSLATIONAL - Organizational Effects of Estrogen across the Lifespan (3:45 PM - 5:15 PM)

Title

Sex Steroid Regulation of Kisspeptin Reproductive Circuits during Postnatal Development & Early Adulthood

Author String

AS Kauffman
University of California, San Diego, La Jolla, CA

Body

The status of the neuroendocrine reproductive axis differs dramatically between various life stages, including early perinatal development and puberty, as well as early and late adulthood. Several aspects of reproductive physiology also differ between the sexes, including timing of pubertal onset and the ability to generate a preovulatory gonadotropin surge. The reproductive axis is controlled by various hormonal and neural pathways that converge upon forebrain gonadotropin-releasing hormone (GnRH) neurons, and many of the developmental and sex differences in reproductive status likely reflect differences in the afferent circuits and factors that regulate GnRH neurons. Recently, the neuropeptide kisspeptin, encoded by the *Kiss1* gene, has been implicated as an important [rdquo] upstream[rdquo] regulator of GnRH neurons. *Kiss1* neurons are located in several discrete brain regions, including the anteroventral periventricular nucleus (AVPV) and arcuate nucleus (ARC) of the hypothalamus, as well as the amygdala. Accumulating evidence supports a critical role for *Kiss1* neurons as key stimulators of the reproductive axis at different life stages, including puberty and adulthood. Studies have now begun to examine how the neural *Kiss1* system is itself regulated at different life stages. In adult rodents, *Kiss1* neurons coexpress sex steroid receptors and are robustly regulated by sex steroids, primarily estradiol acting via estrogen receptor α . Intriguingly, the manner in which sex steroids regulate *Kiss1* neurons (stimulatory or inhibitory) is region-specific within the brain, a finding which may illuminate the cellular mechanism of hormone-mediated positive and negative feedback regulation of GnRH secretion. Recent findings also indicate that all *Kiss1* neural populations are sexually dimorphic in either their gene expression or regulation, and that sexual differentiation and development of *Kiss1* populations is regulated by estradiol signaling during critical periods of early postnatal (and perhaps pubertal) development. In addition, evidence now suggests that the timing of puberty onset is dependent, at least in part, on estradiol-mediated regulation of *Kiss1* neurons. These findings indicate that sex steroids, primarily estradiol, have striking effects on both the development and activity of kisspeptin circuits, though in many cases the specific mechanisms underlying estradiol's actions on *Kiss1* neurons remain to be elucidated.

Sources of Research Support: NIH grants R00 HD056157, R01 HD065856, U54 HD012303, and NSF grant IOS-1025893.

Nothing to Disclose: ASK

sort_order 3078
Pub # S75-2
Session Information SYMPOSIUM SESSION: TRANSLATIONAL - Organizational Effects of Estrogen across the Lifespan (3:45 PM - 5:15 PM)
Title Hypothalamic Changes with Aging/Menopause
Author String GS Neal-Perry
Albert Einstein College of Medicine, Bronx, NY
Body Female reproductive senescence is heralded by ovarian failure, hypogonadism, and a markedly increased risk for a number of age-related health problems that include, but are not limited to osteoporosis and cognitive dysfunction. Improved nutrition and enhanced access to medical care have increased the average lifespan for women in developed countries, and many will spend more than one third of their life in a post-menopausal state, thereby increasing the number of women at risk for menopause related morbidities and a reduced quality of life. Epidemiological studies indicate that a delayed natural menopause decelerates the appearance of much age-related morbidity, suggesting that development of treatments that delay natural menopause might reduce morbidity and significantly improve health for aging women. For many years it was assumed that the vast majority of neuroendocrine changes associated with the transition into reproductive senescence were a direct consequence of ovarian failure. However, recent studies in middle-aged humans and rodents suggest that aberrant responsiveness of the hypothalamic-pituitary axis to estradiol (E₂) feedback results in abnormal luteinizing hormone (LH) surges and elevated follicle-stimulating hormone, which may accelerate ovarian follicular depletion. We and others now have convincing evidence that long before overt ovarian failure there is an age-related suppression of responsiveness of the neuroendocrine axis to E₂ positive feedback. We use young and middle-aged rats to investigate the effect of advancing reproductive age on the ability of E₂ positive feedback conditions and insulin-like growth factor one (IGF-1) to modulate hypothalamic gonadotropin releasing hormone (GnRH) neuronal activation and GnRH-LH release. We demonstrate that age-related changes in the LH surge reflect, in part, reduced IGF-1 signaling, attenuated excitatory (glutamate and kisspeptin) and increased inhibitory (GABA) neurotransmission within the hypothalamus under E₂ positive feedback conditions. Our work also demonstrates that GnRH neurons retain responsiveness to excitatory inputs, suggesting that it may be possible to develop treatments that attenuate GnRH neuron dysfunction and delay natural menopause.

Nothing to Disclose: GSN-P

sort_order 3079
Pub # S75-3
Session Information SYMPOSIUM SESSION: TRANSLATIONAL - Organizational Effects of Estrogen across the Lifespan (3:45 PM - 5:15 PM)
Title Neuroendocrine Effects of Estrogens during Embryonic Development
Author String SA Tobet
Colorado State University, Fort Collins, CO
Body Evidence of sexual differentiation of the brain can be seen from the perspective of a number of characteristics. Although a majority of sexual dimorphisms are characterized in mature animals, mechanisms for their generation often operate during critical perinatal periods. Both genetic and hormonal factors likely contribute synergistically to physiological mechanisms that lead to the ontogeny of sexual dimorphisms in brain. Relevant mechanisms may include neurogenesis, cell migration, cell differentiation, cell death, axon guidance and synaptogenesis. On a molecular level, there are several ways to categorize factors that drive brain development. These range from the actions of transcription factors in cell nuclei that regulate the expression of genes controlling cell development and differentiation, to effector molecules that directly signal from one cell to another. In addition, several peptides or proteins in these and other categories might be referred to as 'biomarkers' of sexual differentiation with undetermined functions in development or adulthood. Although a majority of sex differences are revealed as a direct consequence of hormone actions, some may only be revealed after genetic or environmental disruption. In rodents, the bulk of experimental evidence points to estrogens as a major hormonal influence. Sex differences in cell positions in the developing hypothalamus, and estradiol influences on cell movements in vitro, suggest that cell migration may be one target for early molecular actions that impact the development of brain regions that control neuroendocrine functions.

Sources of Research Support: NIH Grant MH61376 awarded to SAT.

Nothing to Disclose: SAT

sort_order	3080
Pub #	S76-1
Session Information	SYMPOSIUM SESSION: TRANSLATIONAL - Transforming Growth Factor-beta Receptor Superfamily I, II & III (3:45 PM - 5:15 PM)
Title	Transforming Growth Factor-Beta Receptor 1 & Colon Cancer
Author String	B Pasche University of Alabama, Birmingham, AL
Body	Nothing to Disclose: BP

sort_order 3081
Pub # S76-2
Session Information SYMPOSIUM SESSION: TRANSLATIONAL - Transforming Growth Factor-beta Receptor Superfamily I, II & III (3:45 PM - 5:15 PM)
Title Inhibition of Activin Receptor II Signaling (by Follistatin)
Author String LM Bilezikjian
Salk Institute, La Jolla, CA
Body Activins are members of the TGF- β superfamily known to exert control over a diverse array of cellular processes during embryogenesis and in adult tissues. Activin signaling is initiated upon binding to type I and type II serine/threonine kinase receptors followed by phosphorylation of type I by type II receptors and activation of the SMAD signaling pathway. Given the ubiquitous expression and the plethora of activin actions, it is not surprising that ligand availability and actions are tightly regulated by a variety of mechanisms including extracellular binding proteins, cell surface co-receptors as well as intracellular modulators of SMAD actions. Follistatins are ubiquitous glycoproteins that display high affinity for activins and serve an important function as potent extracellular modulators of ligand bioavailability. Activins and follistatins act locally in many tissues to regulate processes that are tissue specific. Studies of a wide variety of cell types have shown that follistatin itself is a downstream target of activin and that the local control of follistatin expression is achieved through cell-type specific actions of activin. Activins and follistatins are produced in the pituitary and a local activin/follistatin network is critical for the control of pituitary differentiation and function. Activin effects on pituitary gonadotropes are critical for promoting differential FSH production. Studies on anterior pituitary cells have highlighted the existence of cell-type specific mechanisms and led to the identification of a cell-type specific factor that promotes activin-dependent induction of follistatin in gonadotropes. This factor is FOXL2, a member of the forkhead transcription factor family. Experiments have shown that FOXL2 is an obligatory partner of SMAD3 and permissive for activin-dependent activation of follistatin transcription in gonadotropes. Interestingly, pituitaries from Foxl2 mutant mice, compared to wildtype littermates, are dysmorphic, express lower follistatin mRNA levels and display alterations in pituitary hormone expression, including FSH β , a well established gonadotrope-specific target of activin. Whether analogous mechanisms that control differential activin-dependent, follistatin-modulated responses also dictate the local function of the activin/follistatin system in other tissues remains to be determined.

Sources of Research Support: In part by NICHD grant HD046941 and by the Clayton Medical Research Foundation, Inc.

Nothing to Disclose: LMB

sort_order 3082
Pub # S76-3
Session Information SYMPOSIUM SESSION: TRANSLATIONAL - Transforming Growth Factor-beta Receptor Superfamily I, II & III (3:45 PM - 5:15 PM)
Title The Type III Transforming Growth Factor- β Receptor & Cancer Progression
Author String GC Blobe
Duke University Medical Center, Durham, NC
Body Transforming growth factor- β (TGF- β) superfamily ligands have important roles in regulating cellular homeostasis, embryonic development and many aspects of cancer biology including proliferation differentiation, apoptosis, motility, immune surveillance and angiogenesis in a cell type and context specific manner. TGF- β superfamily signaling pathways also have diverse roles in human cancer, functioning to suppress cancer initiation, while promoting cancer progression. The TGF- β superfamily co-receptor, the type III TGF- β receptor (T β RIII, also known as betaglycan) mediates TGF- β superfamily ligand dependent as well as ligand independent signaling to both Smad and non-Smad signaling pathways. T β RIII also undergoes ectodomain shedding, with the balance of soluble to membrane bound T β RIII regulating TGF- β superfamily responses. Loss of T β RIII expression during cancer progression had been demonstrated in multiple human cancers, including cancers of the breast, ovary, prostate and uterus, with loss of expression occurring through loss of heterozygosity, epigenetic silencing and transcriptional downregulation. Loss of T β RIII expression correlates with increased disease stage, grade and with a poorer patient prognosis. T β RIII has direct effects on regulating cell adhesion, migration, invasion, proliferation, and angiogenesis, supporting a role for T β RIII as a suppressor of cancer progression and/or as a metastasis suppressor. T β RIII functions to mediate these effects both through regulating Smad signaling as well as through regulation of interacting receptor trafficking to regulate non-Smad signaling pathways. Defining the physiological function and mechanism of T β RIII action and alterations in T β RIII function during cancer progression should enable more effective targeting of T β RIII and T β RIII mediated functions for the diagnosis and treatment of human cancer.
Sources of Research Support: National Institutes of Health/National Cancer Institute Grants CA135006 and CA136786 awarded to GCB.
Nothing to Disclose: GCB

sort_order	3083
Pub #	S77-1
Session Information	SYMPOSIUM SESSION: CLINICAL - Clinical Decision-Making in Thyroid Nodules & Cancer: Time for Molecular Profiling? (3:45 PM - 5:15 PM)
Title	Molecular Diagnosis of Thyroid Nodules
Author String	MA Zeiger Johns Hopkins University, Baltimore, MD
Body	Disclosures: MAZ: Investigator, Veracyte, Inc.

sort_order	3084
Pub #	S77-2
Session Information	SYMPOSIUM SESSION: CLINICAL - Clinical Decision-Making in Thyroid Nodules & Cancer: Time for Molecular Profiling? (3:45 PM - 5:15 PM)
Title	Molecularly-Driven Initial Thyroid Cancer Management
Author String	JA Sipos Ohio State University, Columbus, OH
Body	Nothing to Disclose: JAS

sort_order 3085
Pub # S77-3
Session Information SYMPOSIUM SESSION: CLINICAL - Clinical Decision-Making in Thyroid Nodules & Cancer: Time for Molecular Profiling? (3:45 PM - 5:15 PM)
Title Individualizing Therapy for Advanced Thyroid Cancer: Role of Molecular Testing
Author String KC Bible
Mayo Clinic, Rochester, MN
Body Historically, cytotoxic chemotherapy has proven ineffective in advanced differentiated thyroid cancers (DTCs), and of only marginal palliative value in advanced medullary and anaplastic thyroid cancers (MTC and ATC). Based upon recent advances, however, there is emerging evidence that improved understanding of candidate therapeutic molecular targets in thyroid cancers can lead to individualized novel therapeutic approaches with potential to improve patient outcomes. In particular, the groundbreaking discovery that the RET proto-oncogene is constitutively activated and affects proliferation in familial MTC has led to Phase II and III clinical trials of the RET kinase inhibitor vandetanib, demonstrating the ability of vandetanib to induce disease regression and also improve progression-free survival in MTC patients. The targeting of yet additional signaling pathways known to be contributory to thyroid cancer pathogenesis has also led to promising outcomes in patients afflicted not only with MTC, but also with DTCs. For example, multiple small molecule VEGF-R inhibitors including sorafenib, sunitinib, axitinib and pazopanib have now demonstrated promising single agent clinical activity of in MTC and DTCs. Moreover, an increasing number of assayable and targetable additional signaling pathways (e.g. BRAF, EGFR, MEK, c-Met, PTEN, aurora kinases, p53) have also emerged as contributory to thyroid cancer phenotypes - raising the possibility that the evaluation of molecular derangements in individual tumors might eventually provide the basis for individualized therapeutics in these cancers. In this presentation we review the past, the present and the (anticipated) future directions of molecular testing as a guide to individualization of thyroid cancer therapies.
Nothing to Disclose: KCB

sort_order	3086
Pub #	S78-1
Session Information	SYMPOSIUM SESSION: CLINICAL - Recognition & Management of Atypical Forms of Diabetes (3:45 PM - 5:15 PM)
Title	Monogenic Forms of Diabetes
Author String	SAW Greeley University of Chicago, Chicago, IL
Body	Session supported by: Lilly USA, LLC Nothing to Disclose: SAWG

sort_order	3087
Pub #	S78-2
Session Information	SYMPOSIUM SESSION: CLINICAL - Recognition & Management of Atypical Forms of Diabetes (3:45 PM - 5:15 PM)
Title	Latent Autoimmune Diabetes in the Adult
Author String	SC Clement Georgetown University, Washington, DC
Body	Session supported by: Lilly USA, LLC

sort_order 3088
Pub # S78-3
Session Information SYMPOSIUM SESSION: CLINICAL - Recognition & Management of Atypical Forms of Diabetes (3:45 PM - 5:15 PM)
Title Cystic Fibrosis-Related Diabetes
Author String SJ Casella
Dartmouth Hitchcock Medical Center, Lebanon, NH
Body
Cystic Fibrosis Related Diabetes (CFRD) is a common co-morbidity that increases in incidence with age. The dramatic improvements in long term survival of cystic fibrosis (CF) have been accompanied by a rise in the prevalence of CFRD, with rates as high as 40-50% in adult cohorts. CFRD has many features of type 1 diabetes (T1DM), and we will compare and contrast the two illnesses in this presentation. The multicenter Cystic Fibrosis Related Diabetes Treatment Trial recently confirmed that insulin therapy is beneficial in CFRD patients, even before fasting hyperglycemia has developed. Clinical Practice guidelines for CFRD were recently updated based on a systematic, evidenced based review. The new guidelines will be discussed, including recommendations for screening, diagnosis, and the early use of insulin therapy.
Macrovascular complications are rare in patients with CFRD, and microvascular complications are also less common than in patients with T1DM. The diagnosis of CFRD has a major impact on the CF patient, however, because it is associated with decreased pulmonary function, poor nutritional status, and increased pulmonary exacerbations, leading to decreased long term survival. Recent reports indicate that mortality rates can be improved with more effective treatment of the illness. Though HgbA1c values are lower in CF (likely due to decreased red cell survival), higher levels indicate poor control and are associated with decreased pulmonary function.
A query of the CF Registry indicates that there is significant variation in CFRD care among CF Treatment Centers. Screening rates remain low in many centers and monitoring of patients with CFRD is suboptimal. The data also reveal significant variation in median HgbA1c among the various CF Treatment centers. Taken together, there appears to be ample opportunity for quality improvement in CFRD screening, monitoring, and outcomes. The CF Foundation, in collaboration with the Pediatric Endocrine Society, has arranged a national Learning and Leadership Collaborative dedicated to CFRD. Six pediatric and 4 adult CF treatment teams are participating in the year long project. Using the Clinical Microsystems quality improvement method, we are implementing best practices at each center, and tracking outcomes through the CF Registry. Proven change concepts will then be spread to other CF Treatment Centers to insure that all patients with CFRD have access to optimal care.

Session supported by: Lilly USA, LLC

Disclosures: SJC: Study Investigator, Eli Lilly & Company, Novo Nordisk, Pfizer, Inc.

sort_order	3089
Pub #	L8-1
Session Information	PLENARY: TRANSLATIONAL - microRNAs & Their Targets in Pregnancy & Labor (5:30 PM - 6:30 PM)
Title	microRNAs & Their Targets in Pregnancy & Labor
Author String	CR Mendelson University of Texas Southwestern Medical Center, Dallas, TX
Body	Nothing to Disclose: CRM

sort_order 3090
Pub # L8-2
Session Information PLENARY: TRANSLATIONAL - Extra-Nuclear Steroid Receptor Functions (5:30 PM - 6:30 PM)
Title Extra-Nuclear Steroid Receptor Functions
Author String ER Levin
University of California, Irvine/Long Beach Veterans Affairs Medical Center, Long Beach, CA
Body Classical sex steroid receptors traffic to the plasma membrane after palmitoylation by recently identified acyltransferase and facilitator proteins. Membrane-localized receptors engage small G proteins to cause calcium flux and cyclic nucleotide generation in seconds, and kinase cascade activation in several minutes. Estrogen (ER), progesterone, and androgen receptors traffic to the plasma membrane of hormone responsive-cancer cells, rapidly signaling to proliferation and survival. Gene transcription resulting from nuclear steroid receptor action often depends upon membrane-localized receptors rapidly signaling through ERK and other kinase pathways to cause epigenetic modifications. Mitochondrial ER β prevents apoptosis in lung and breast cancer, also mediating the response or resistance to tamoxifen in breast cancer cells. Extra-nuclear steroid receptors play important roles in cardiovascular, central nervous, and bone systems. ER functions include preventing cardiac hypertrophy, fibrosis, and acute vascular injury, stabilizing osteoblasts and preventing osteoclast formation, and consolidating memory while stimulating dendritic spine formation in the brain. Using a mouse created to express only membrane-localized, E domain of ER α while lacking nuclear ER α , estrogen rapid signaling impacts cell metabolism in the absence of the nuclear steroid receptor.
Nothing to Disclose: ERL