Cellular Pathology of Insulin Resistance in Lipodystrophy

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E1328. A comprehensive review of muscle lipid metabolism and the effects of specific lipid metabolites on insulin action.

**Current Thinking About the Diagnosis and Treatment of the Insulin-Resistant State: How to Use Insulin Therapy**

Irl B. Hirsch, MD

Bota VM, Hirsch IB. Insulin glargine or neutral protamine Hagedorn in patients with severe insulin resistance: is there a benefit? *Endocr Pract.* 2012;18:e49-e51. NPH insulin might be superior to the long-acting analogue glargine in cases of severe insulin resistance, but randomized studies are needed to confirm these findings and clarify mechanisms.

Chukwu JF, Hirsch IB, Trence D. Use of liraglutide in severely insulin resistant patients with type 2 diabetes. Presented at the ENDO 2012, the 94th annual meeting of the Endocrine Society, Houston, Texas, June 2012. A case report of benefits with the use of the GLP-1 analogue liraglutide in severely insulin-resistant patients.

de la Peña A, Riddle M, Morrow LA, et al. Pharmacokinetics and pharmacodynamics of high-dose human regular U-500 insulin versus human regular U-100 insulin in healthy obese subjects. *Diabetes Care.* 2011;34:2496-2501. A study showing that overall exposure to and action of U-500 regular insulin after subcutaneous injection are no different from those of U-100 regular insulin. However, for U-500, peaks of concentration and action profiles are blunted and the effect after the peak is prolonged.


conversion of appropriately selected patients from high-dose U-100 insulin to U-500 regular insulin therapy may potentially result in improved glycemic control and lower cost.


Saryusz-Wolska M, Szymańska-Garbacz E, Pawłowski M, Loba J, Czupryniak L. Splitting high dose of insulin and injecting it in two sites improves blood glucose control [Abstract 109]. Presented at the 47th annual meeting of the European Association for the Study of Diabetes, Lisbon, Portugal, 2011. Large depots of NPH insulin appear to be more efficacious when split into two depots.

Thewjitcharoen Y. Attempted suicide by massive insulin injection: a case report and review of the literature. *J Med Assoc Thai*. 2008;91:1920-1924. A case study in which a man who attempted suicide by injecting 10,000 units of human regular insulin and 6,000 units of NPH insulin required intravenous dextrose for 13 days to maintain a safe glucose level.

Wang Z, Hedrington MS, Gogitidze JN, et al. Dose-response effects of insulin glargine in type 2 diabetes. *Diabetes Care*. 2010;33:1555-1560. A study showing that, although it is possible that duration of insulin action is prolonged with increasing doses of glargine, there is no difference in insulin action for the 24 hours after injection once the dose is >1.0 unit/kg.

**Adipose Physiology and Metabolism**

Kevin Niswender, MD, PhD

Banerji MA, Faridi N, Atluri R, Chaiken RL, Lebovitz HE. Body composition, visceral fat, leptin, and insulin resistance in Asian Indian men. *J Clin Endocrinol Metab*. 1999;84:137-144. A study showing that increased visceral fat, which is related to dyslipidemia and increased frequency of insulin resistance, may account for the increased prevalence of diabetes and cardiovascular disease in Asian Indians.


Kern PA, Ranganathan S, Li C, Wood L, Ranganathan G. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. *Am J Physiol Endocrinol Metab*. 2001;280:E745-751. A study showing that tumor necrosis factor and interleukin-6, which may cause obesity-related insulin resistance, are expressed by adipose tissue at higher levels in subjects with obesity-related insulin resistance.


comparing fat distribution in subgroups of subjects with differing ages, BMIs, and levels of insulin sensitivity.


Roth J, Oiang X, Marbán SL, Redelt H, Lowell BC. The obesity pandemic: where have we been and where are we going? *Obes Res*. 2004;12(suppl 2)88S-101S. A discussion of advances in understanding of the pathophysiology and consequences of obesity.

Scherer PE. Adipose tissue: from lipid storage compartment to endocrine organ. *Diabetes*. 2006;1537-1545. A review of molecular aspects of the key constituent of adipose tissue, the adipocyte, which not only stores and releases lipids, but also plays a role in intracellular signaling and uses numerous protein factors to communicate with other organ systems.

Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG. Central nervous system control of food intake. *Nature*. 2000;404:661-671. A discussion of energy homeostasis, including a model that delineates the roles of individual hormonal and neuropeptide signaling pathways in the control of food intake and the ways in which obesity can arise from inherited or acquired defects in their functioning.


findings regarding its mechanism of action and offering a summary of the key epidemiological data that helped establish it as a biomarker for insulin sensitivity, cardiovascular disease, and other diseases.

**Genetic Basis of Lipodystrophies**

Abhimanyu Garg, MD


Agarwal AK, Xing C, DeMartino GN, et al. PSMB8 encoding the β5i proteasome subunit is mutated in joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy syndrome. *Am J Hum Genet*. 2010;87:866-872. The first report of mutation in
the proteasome subunit beta type 8 (PSMB8) gene in patients with joint contractures, microcytic anemia, and panniculitis-induced (JMP) syndrome.


Simha V, Garg A. Phenotypic heterogeneity in body fat distribution in patients with congenital generalized lipodystrophy due to mutations in the AGPAT2 or Seipin genes. *J Clin Endocrinol Metab.* 2003;88:5433-5437. An article reporting different patterns of body fat loss in patients with CGL types 1 and 2 using whole-body MRI.

Szymanski KM, Binns D, Bartz R, et al. The lipodystrophy protein seipin is found at endoplasmic reticulum lipid droplet junctions and is important for droplet morphology. *Proc Natl Acad Sci U S A.* 2007;104:20890-20895. An article showing the role of seipin in LD formation.


**Lipodystrophy Diagnosis and Clinical Presentation**

Elif A. Oral, MD

Agarwal AK, Simha V, Oral EA, et al. Phenotypic and genetic heterogeneity in congenital
generalized lipodystrophy. *J Clin Endocrinol Metab*. 2003;88:4840-4847. This article shows phenotypic heterogeneity between the two major types of CGL, type 1 and type 2.

Bingham A, Mamyrova G, Rother KI, et al. Predictors of acquired lipodystrophy in juvenile-onset dermatomyositis and a gradient of severity. *Medicine (Baltimore)*. 2008;87:70-86. This article describes the clinical features of 28 patients with juvenile dermatomyositis and 1 patient with adult-onset dermatomyositis, all of whom developed lipodystrophy.


Haque WA, Oral EA, Dietz K, Bowcock AM, Agarwal AK, Garg A. Risk factors for diabetes in familial partial lipodystrophy, Dunnigan variety. *Diabetes Care*. 2003;26:1350-1355. A study showing that increased adiposity as indicated by excess subcutaneous fat in the chin region and parity may predispose women with familial partial lipodystrophy, Dunnigan variety, to
develop diabetes.

Javor ED, Ghany MG, Cochran EK, et al. Leptin reverses nonalcoholic steatohepatitis in patients with severe lipodystrophy. *Hepatology*. 2005;41:753-760. A study finding that leptin therapy in patients with nonalcoholic steatohepatitis significantly reduced triglycerides, transaminases, hepatomegaly, and liver fat content and that these reductions were associated with significant reductions in steatosis and the hepatocellular ballooning injury seen in this condition.


Ji H, Weatherall P, Adams-Huet B, Garg A. Increased skeletal muscle volume in women with familial partial lipodystrophy, Dunnigan variety. *J Clin Endocrinol Metab*. Electronically published ahead of print on June 19, 2013. A study showing that female patients with familial partial lipodystrophy, Dunnigan variety, have increased skeletal muscle volume and mass compared to normal women.

Lungu AO, Zadeh ES, Goodling A, Cochran E, Gorden P. Insulin resistance is a sufficient basis for hyperandrogenism in lipodystrophic women with polycystic ovarian syndrome. *J Clin Endocrinol Metab*. 2012;97:563-567. A study showing that the endocrine features associated with lipodystrophy, which may be a model for polycystic ovarian syndrome, are corrected by leptin therapy, which reduces insulin resistance.


McDuffie JR, Riggs PA, Calis KA, et al. Effects of exogenous leptin on satiety and satiation in patients with lipodystrophy and leptin insufficiency. *J Clin Endocrinol Metab*. 2004;89:4258-4263. A study showing that increased leptin in patients with lipodystrophy results in less caloric, shorter, more satiating meals and longer-lived satiety, supporting the hypothesis
that leptin plays an important role in human appetite regulation.


Nelson MD, Victor RG, Szczepaniak EW, Simha V, Garg A, Szczepaniak LS. Cardiac steatosis and left ventricular hypertrophy in patients with generalized lipodystrophy as determined by magnetic resonance spectroscopy and imaging. Am J Cardiol. Electronically published ahead of print on June 22, 2013 (doi:pii: S0002-9149(13)01234-4. 10.1016/j.amjcard.2013.05.036). The findings of this study, which involved cardiac magnetic resonance imaging in patients with generalized lipodystrophy, support the theory that the concentric left ventricular hypertrophy characteristic of this condition may be caused by "lipotoxic cardiomyopathy," or excessive myocyte accumulation of triglyceride leading to adverse hypertrophic signaling.


Park JY, Chong AY, Cochran EK, et al. Type 1 diabetes associated with acquired generalized lipodystrophy and insulin resistance: the effect of long-term leptin therapy. *J Clin Endocrinol Metab.* 2008;93:26-31. A study showing that long-term recombinant leptin therapy is effective in treating the insulin resistance of patients with the unusual combination of type 1 diabetes and acquired generalized lipodystrophy.


Savage DB, Semple RK, Clatworthy MR, et al. Complement abnormalities in acquired lipodystrophy revisited. *J Clin Endocrinol Metab.* 2009;94:10-16. One well-studied form of acquired lipodystrophy is characterized by activation of the alternative complement pathway by C3 nephritic factor, low complement factor C3, and mesangiocapillary glomerulonephritis. This article describes an immunologically distinct form of acquired generalized lipodystrophy, with evidence of activation of the classical complement pathway (low C4) and autoimmune hepatitis.
Practical Use of Metreleptin in the Treatment of Lipodystrophy

Rebecca Brown, MD, MHSc

Chan JL, Lutz K, Cochran E, et al. Clinical effects of long-term metreleptin treatment in patients with lipodystrophy. *Endocr Pract.* 2011;17:922-932. This article summarizes the effects of leptin in the largest cohort of lipodystrophy patients (*n* = 72) and shows how more severely affected patients have greater metabolic improvements.


Javor ED, Moran SA, Young JR, et al. Proteinuric nephropathy in acquired and congenital generalized lipodystrophy: baseline characteristics and course during recombinant leptin therapy. *J Clin Endocrinol Metab.* 2004;89:3199-3207. This article summarizes the effects of leptin on kidney disease in lipodystrophy.

