Hormones and Aging: An Endocrine Society Scientific Statement

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Abstract

Multiple changes occur across various endocrine systems as an individual ages. Understanding of the factors that cause age-related changes and how they should be managed clinically is evolving. This statement reviews the current state of research in the growth hormone, adrenal, ovarian, testicular, and thyroid axes, as well as in osteoporosis, vitamin D, type 2 diabetes, and water metabolism, with a specific focus on older individuals. Each section describes the natural history and observational data in older individuals, available therapies, clinical trial data on efficacy and safety in older individuals, key points, and scientific gaps. The goal of this statement is to inform future research that refines prevention and treatment strategies in age-associated endocrine conditions, with the goal of improving the health of older individuals.

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Hormones regulate and coordinate multiple physiologic functions. With increasing age, declines in physical and cognitive function occur. The extent to which age-associated changes in hormonal regulation and increases in prevalence of specific endocrine diseases contribute to declines in physical and cognitive function is incompletely understood. This area will only expand in importance as the number of older individuals increases worldwide. Current projections show an increase in those aged 65 years and older from 703 million (1 in 11 people) to 1.5 billion in 2050 (1 in 6 people) (1).

This Scientific Statement was developed to provide a high-level summary of the current state of research across multiple hormonal axes in aging and to identify areas in need of future research. Each section describes the natural history and observational data in older individuals, available therapies, clinical trial data on efficacy and safety in older individuals, key points, and scientific gaps. The extent to which hormonal changes with age are deemed "normal aging" vs. "endocrine disease" can be arbitrary and depends in part on whether treatment is currently indicated. Four hypothalamic-pituitary axes are presented --growth hormone, adrenal, gonadal (divided into ovarian and testicular), and thyroid. These are followed by osteoporosis, vitamin D deficiency, diabetes, and water metabolism topics. Geroscience has emerged as a research approach examining biological mechanisms of aging and their interplay with comorbid disease. In the conclusion, cross-cutting themes of research areas in need of further investigation and the need for geroscience approaches are summarized.

GROWTH HORMONE AXIS

Natural history/observational data in older individuals

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Growth hormone is secreted in a pulsatile fashion. Peak GH secretion occurs at mid puberty (2), subsequently declining by 50% every 7-10 years. By the time the eighth decade is reached, GH levels are similar to those of GH-deficient young adults (3). Pulse frequency is similar across age, with approximately 18 secretory episodes of GH per 24 hours in children, adults, and older individuals (4). The decline in GH with aging is primarily seen in the amplitude of the secretory episodes, although interpulse levels also decline (Figure 1) (5). A reduction of serum IGF-1 levels occurs in parallel with the decline in average GH secretion in aging.

In premenopausal women, GH peak levels are higher than in men (6). This is likely due to reduced GH receptor sensitivity at the liver, and thus higher levels of GH are required to maintain normal serum IGF-1 levels. After menopause, GH levels are similar between women and similarly aged men (6). Oral estrogen supplementation inhibits hepatic IGF-1 synthesis and increases GH secretion through reduced feedback inhibition, whereas IGF-1 levels increase and GH secretion is unchanged when estrogen is administered by transdermal patch (7-9).

The decline in GH synthesis and secretion with aging is well-documented in all mammalian species. In humans as well as other species, decreased output by the GH/IGF-1 axis is correlated with increased percentage of total body and visceral fat, decreased muscle mass, decreased physical fitness, decreased immune function, and physiological declines in estrogen and androgen concentrations. Whether this decline in GH secretion is causative or only correlative is controversial. In children and adults with GH deficiency, GH replacement has demonstrated benefits on body composition, serum lipids, fitness, and bone density; it also increases growth velocity in children. However, potential adverse effects of GH stimulation on malignancy, senescence, and telomere shortening are concerns of GH therapy in older individuals.

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Controversy of whether GH deficiency extends life span

Caloric restriction and genetic alterations that reduce function in the growth hormone/IGF-1/insulin pathways have been shown in experimental invertebrate and vertebrate animal models to extend life span. Mouse models of mutants that lack GH release (GHRH receptor, GHRH, Prop1 and Pouf1) and that are GH insensitive (GHR) live significantly longer, and overexpression of GH reduces lifespan (bovine GH transgenic)(10). Whether this translates to humans is unclear. However, these are life-long experiments and are likely not applicable to aging in humans in the western world. This has also been recently reviewed in the context of humans with isolated GH deficiency (IGHD) type 1B, owing to a mutation of the growth hormone-releasing hormone (GHRH) receptor gene, in Itabaianinha County, Brazil. Individuals with IGHD are characterized by proportional short stature, doll facies, high-pitched voices, and central obesity. They have delayed puberty but are fertile and generally healthy. Moreover, these IGHD individuals are partially protected from cancer and some of the common effects of aging and can attain extreme longevity (10). In contrast, dwarfism associated with GH deficiency in patients with GH1 mutations is reported to significantly shorten median lifespan (11). There are studies which suggest that individuals with lower serum IGF-I levels have longer lives, potentially due to GH receptor exon 3 deletions (12), and that individuals with other GHR variants have major reductions in cancer and diabetes incidence without effects on lifespan (13). IGF-I receptor mutations have also been associated with longevity. In the Leiden Longevity Study, evidence has been presented that GH secretion is more tightly controlled in the offspring of long-lived families than in their partners, who served as age-matched controls (14).

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Age, gender, percentage body fat, body fat mass, aerobic fitness, IGF-1 and gonadal steroid concentrations are all related to 24-h GH release in adults. A major question is whether the decline of GH is due only to age or whether other factors are at play. It is well established that obesity, particularly increased visceral fat, is associated with reduced GH levels (15). In a study of highly and homogeneously active older male (n = 84) and female (n = 41) cyclists aged 55–79 years, it was shown that serum IGF-1 declined with age while testosterone in men did not. The authors suggest that the hormonal changes of aging involve not only the aging process but also inactivity (16).

Available therapies

There are no approved therapies for reversing the age-associated decline of GH secretion. Recombinant human GH (rhGH) is approved in pediatric patients with disorders of growth failure or short stature and in adults with growth hormone deficiency or with HIV/AIDS wasting and cachexia. Both GHRH and GH secretagogues exist but are not approved for use as anti-aging agents.

Clinical trial data on efficacy and safety in older individuals

In 2007, Liu et al published a systematic review of clinical trials of rhGH vs placebo, with or without lifestyle interventions (17). A total of 220 healthy older participants were enrolled and followed for a combined 107 patient years. Mean treatment was 27 weeks at a mean dose of 14 ug/kg day. Small changes in body composition (reduction in fat mass (-2.1 kg [95% CI, -2.8 to -1.35 kg]) and increase in lean body mass (2.1 kg [CI, 1.3 to 2.9 kg]), greater in men than in women) were found, at the expense of an increased rate of adverse events. These included soft

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tissue edema, arthralgias, carpal tunnel syndrome, and gynecomastia and a higher onset of diabetes mellitus and impaired fasting glucose. The conclusion of this review was that rhGH cannot be recommended as an anti-aging therapy.

Two randomized, placebo-controlled studies of the GH secretagogues MK-677 and capromorelin in older individuals demonstrated that these oral agents increase GH levels by enhancing the amplitude of GH pulses to levels reported in young individuals (4,18). These compounds also have the advantage that they cannot be overdosed, due to IGF-1 feedback. The major difference between the two studies was in the selection of participants. In the MK-0677 study, healthy individuals were studied, whereas in the capromorelin study, participants had mild functional impairment.

Sixty-five healthy adults ranging from 60 to 81 years of age were randomized to the GH secretagogue receptor agonist MK-677 to determine whether MK-677, an oral ghrelin mimetic, increases growth hormone secretion into the young-adult range without serious adverse effects, prevents the decline of fat-free mass, and decreases abdominal visceral fat compared with placebo (4). Over 12 months, MK-677 enhanced pulsatile growth hormone secretion and significantly increased fat-free mass vs placebo (1.1 kg [CI, 0.7 to 1.5 kg] vs -0.5 kg [95% CI, -1.1 to 0.2 kg]), but did not affect abdominal visceral fat, total fat mass, strength, or physical function. Body weight increased with an increase in appetite, mild lower-extremity edema, and muscle pain, along with small increases in fasting glucose and cortisol and a decrease in insulin sensitivity. Further development of this compound was not pursued.

Capromorelin is another GH secretagogue agonist, and a randomized trial was conducted in 395 adults aged 65 to 84 years of age with mild functional limitation to investigate the hormonal, body composition, and physical performance effects and the safety of 4 dosing groups

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of capromorelin vs placebo (18). Although the study was terminated early due to failure to meet predetermined treatment effect criteria, a sustained, dose-related rise in IGF-I concentrations occurred in all active treatment groups. At 6 months, body weight increased 1.4 kg in participants receiving capromorelin and decreased 0.2 kg in those receiving placebo (P = 0.006). Lean body mass increased 1.4 vs. 0.3 kg (P = 0.001), and tandem walk improved by 0.9 sec (P = 0.02) in the pooled treatment vs. placebo groups. By 12 months, stair climb also improved (P = 0.04). Adverse events included fatigue, insomnia, and small increases in fasting glucose, glycosylated hemoglobin, and indices of insulin resistance. No additional studies are planned for this compound.

Key Points

- At present, no therapy to increase GH secretion or action is approved as an anti-aging intervention.
- Studies with rhGH and GH secretagogues failed to demonstrate benefits that outweigh risks. However, it is possible that benefit could be maximized with the use of lower doses, in study populations with worse physical function, and in combination with exercise and adequate nutrition, without the adverse effects seen in previous studies.

Gaps in the Research

Studies in invertebrate and vertebrate models are important but may not be translatable to humans. Most animal studies have investigated lifelong interventions of over or under active somatotroph function. Intervening at different stages of the life cycle may help explain the

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conflicting data on whether too little or too much somatotroph function may be beneficial to extending life span.

The changes in GH secretion across the life cycle make the interpretation of animal studies and their translation to humans problematic. The objective should be to improve healthspan rather than lifespan. Thus, further studies of increasing or decreasing somatotrope function at different stages of the life cycle will be important, particularly to evaluate whether restoring pulsatile GH secretion as seen in 20-30 year old individuals would help prevent development of frailty and sarcopenia without increasing risks. It is clear that hormonal treatment alone will not be sufficient, so future trials will require evaluation of lower doses of GH/GH secretagogues with consideration of combination with exercise, nutrition interventions, and/or co-supplementation of other hormones (e.g. testosterone). Targeting the right population, such as those who have developed, or are at high risk for, frailty and sarcopenia, will also be vital. Further studies will need to be carried out for several years or longer.

ADRENAL AXIS

Natural history/observational data in older individuals

The adrenal glands produce several classes of hormones from different cell types or zones. The adrenal cortex synthesizes steroid hormones and hormone precursors, primarily the mineralocorticoid aldosterone from the zona glomerulosa, the glucocorticoid cortisol from the zona fasciculata, and the androgen precursors dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) from the zona reticularis (19) (Figure 2). DHEAS is largely a storage form and excreted product, with conversion to DHEA in a few tissues. The adrenal medulla is an extension of the sympathetic nervous system, which secretes epinephrine.

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Infants produce large amounts of aldosterone to compensate for the resistance of the neonatal kidney to mineralocorticoids and the low sodium content of human milk. Over time, the sodium content of the diet increases, and the need for aldosterone decreases; most American adults consume over 150 meq of sodium daily. Rather than having a uniform, continuous zona glomerulosa as seen in children and young adults, adrenal glands from adults in Western countries become increasingly discontinuous after age 40. Immunohistochemistry studies reveal pockets of cells that express the aldosterone synthase enzyme (CYP11B2) beneath the adrenal capsule (20), initially termed aldosterone-producing cell clusters and now called aldosterone-producing micronodules (APMs). APM cells commonly harbor somatic mutations in genes encoding subunits of ion channels that regulate aldosterone production (21). As the number of adrenal glands with a continuous zona glomerulosa declines with age, the number of these APMs and their total area increases in parallel (22). A theoretical, but plausible, interpretation of these findings is that, with a chronic high-salt diet and renin suppression, the normal zona glomerulosa atrophies. At the same time, adrenal precursor cells undergo selection for clones with somatic mutations in ion channel genes that allow survival and aldosterone production in the absence of angiotensin II stimulation (23). This process could give rise to the cells that proliferate into aldosterone-producing cell clusters (APCCs). The accumulation of APCCs translates to various degrees of autonomous aldosterone production, and if the burden becomes high enough, could result in unilateral or bilateral primary aldosteronism. Other subclones might undergo further genetic changes that drive formation of aldosterone-producing adenomas. This model could explain the development of various forms of primary aldosteronism and why the prevalence of this disease and of salt-sensitive hypertension increase with age.

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Like that of other axes, the dynamic behavior of the hypothalamic-pituitary-adrenal (HPA) axis undergoes changes with age, including a flattening of the diurnal rhythm and earlier morning peak (24,25). This results in higher 24-hour cortisol production rate and free cortisol levels, but no difference in cortisol binding globulin levels, with increasing age (26). In addition, the HPA axis appears to be more responsive to stress, with some differences between men and women (27), in part due to reduced negative feedback inhibition from cortisol (28). Similarly, the cortisol response to exogenous ACTH is prolonged at older ages (29). Given the potential contributions of cortisol to a multitude of age-dependent diseases and decline in physical function, these changes and individual variations in magnitude could have broad consequences (30).

Regulation of local glucocorticoid activity, independent of the HPA axis, may occur with cortisol regeneration from cortisone via the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1). The expression of 11βHSD1 in skin increases with age (31), which could potentiate the catabolic action of cortisol on skin without affecting adrenal cortisol production. 11βHSD1 expression in muscle is inversely correlated with strength in older individuals (32), suggesting that, in aging, enhanced catabolic action of cortisol could occur through this mechanism in several tissues.

The prevalence of overt Cushing syndrome does not rise with age, but the development of mild ACTH-independent hypercortisolemia due to adrenal adenomas and hyperplasia does rise over time (33). Several studies have provided evidence that even mild cortisol excess is not benign and is associated with hypertension, glucose intolerance, cardiovascular events, and vertebral fractures (34,35). Consequently, occult and smoldering hypercortisolemia could predispose to common disorders in older persons.

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Furthermore, although cortisol does not directly cause major age-related diseases, such as cancer and dementia, preclinical and human studies suggest that modulation of cortisol action could evolve into treatment strategies for these diseases. In castration-resistant prostate cancer, sustained treatment with the potent androgen-receptor antagonist enzalutamide results in up-regulation of glucocorticoid-receptor expression, which drives the expression of previously androgen-regulated oncogenes (36). In parallel, rapid degradation of 11β-hydroxysteroid dehydrogenase type 2, the enzyme that converts cortisol to inactive cortisone, potentiates cortisol action (37). Consequently, the glucocorticoid signaling pathway could be a target for the treatment of advanced prostate cancer (38). In patients with early Alzheimer's disease, higher morning plasma cortisol predicts more rapid progression of dementia symptoms and deterioration of temporal lobe function (39). In a rat model, glucocorticoid-receptor antagonists attenuated the augmented rise in morning corticosterone and hippocampal amyloid deposition, and some agents delayed the progression of cognitive dysfunction (40). These studies demonstrate that manipulation of cortisol bioactivity, particularly in a tissue-selective manner, could have benefits in certain maladies common in older individuals.

Circulating concentrations of DHEAS peak at about age 25 and then decline gradually with age, falling to childhood concentrations by age 80 in most adults (41), reflecting a gradual reduction in the size of the zona reticularis (42). The reason for this change is not known, and rodents secrete small amounts of DHEA and therefore cannot serve as a research model for this hormone. The peak concentrations and trajectory of decline, however, vary significantly amongst individuals, and in population studies, DHEAS concentrations are higher in men than women. The developmental changes and age-related decline in DHEAS have attracted considerable

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attention as a potential mediator of the aging process (43), reflecting the anabolic actions of androgens.

In women, half or more of circulating testosterone derives from 19-carbon androgen precursors from the adrenal cortex, including DHEA, DHEAS, and androstenedione (44). In contrast, the vast majority of testosterone in men derives from the testes throughout adult life. Consequently, an age-related decline in steroid production from the zona reticularis could have greater impact in women and in men with primary or secondary testicular dysfunction than in normal men. While the decline in DHEAS with age is well substantiated, many of the data about the consequences of this phenomenon derive from epidemiologic and cross-sectional studies (45,46), rather than large randomized-controlled trials of DHEA supplementation.

Another product of the adrenal cortex that has been understudied until recently is the robust synthesis of 11-oxygenated androgens, primarily 11β-hydroxyandrostenedione (11OHA4), which is converted through metabolism in other tissues from an inactive androgen to the androgen 11-ketotestosterone (11KT) (47). While the biosynthetic pathways of 11-oxygenated pro-androgen production via the human adrenal cortex have been described, the location(s) of their synthesis, the zona fasciculata and/or zona reticularis, is not known. In women, DHEA, DHEAS, androstenedione, and testosterone all decline from age 30 onward; however, 11OHA4 and 11KT increase slightly into the ninth decade and decline only slightly during this age window in men (48). For nearly all women (48) and prepubertal children (49), 11KT is the most abundant bioactive androgen in the circulation, and this adrenal androgen component is preserved throughout life. Because 11KT could theoretically provide negative feedback on the gonadal axes, this contribution could become important in older men, although direct evidence to this effect is lacking.

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Available therapies

Spironolactone and eplerenone, and more recently, firenonone, are available as aldosterone (mineralocorticoid) antagonists for the treatment of primary aldosteronism and hypertension. Although the FDA has approved several treatments for Cushing syndrome (mifepristone, pasireotide, osilodrostat, and levoketoconazole) in recent years, these drugs are not indicated for subtle ACTH-independent hypercortisolemia or the cortisol-mediated contributions to other diseases. DHEA (prasterone) administered as a 6.5 mg intravaginal insert improves symptoms of vulvovaginal atrophy in postmenopausal women and is FDA-approved for this purpose (50). DHEA is available over-the-counter as a dietary supplement and is not regulated by the US Food and Drug Administration.

Clinical trial data on efficacy and safety in older individuals

Small studies have found conflicting results from DHEA replacement in older women (51-53). A few moderately large studies of DHEA supplementation at 25-50 mg/d for 1 or 2 years in older men and women have consistently shown restoration of DHEAS concentrations to the young adult range, as well as increased circulating concentrations of testosterone in women and of estradiol in postmenopausal women (54,55). In these trials, postmenopausal women experienced small improvements in bone density at some sites, and these changes could be ascribed to the rise in estradiol. In one of these studies, no improvement of muscle cross-sectional area or strength was observed (56), and improvements in quality of life could not be demonstrated (55). These studies do not support the widespread use of DHEA supplementation as an anti-aging agent, despite claims otherwise to be found on the internet. Some studies of DHEA

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supplementation in women with adrenal insufficiency, in whom production of DHEA, DHEAS, testosterone, and all adrenal-derived androgens is low, have reported improvements in sexual satisfaction and interest (57), but similar results have not been obtained in trials with older women.

Key Points

- APCCs that autonomously produce aldosterone begin to develop in adulthood and accumulate with age.
- The HPA axis shows less sensitivity to negative feedback, blunted diurnal changes, and alterations in cortisol/cortisone interconversion with aging.
- Although circulating concentrations of DHEA and DHEAS decline with age, cortisol and 11-keto androgens do not decline or rise slightly.
- Modulation of cortisol signaling could be beneficial in a host of diseases that become more common in older men and women.
- Systemic DHEA supplementation has not shown major benefits in older individuals.

Gaps in the Research

Because rodent adrenals make neither cortisol nor androgens due to lack of the gene Cyp17, engineered or humanized strains that include Cyp17 and recapitulate the zonation and steroidogenic repertoire of the human adrenal would be valuable animal models to study human aging and targeted interventions.

Additional research is needed to chart the development of APMs in aging adrenals and to define the role of autonomous aldosterone production in the age-associated increase of salt-

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sensitive hypertension. Incorporation of cortisol modulation, including tissue-selective agonists and antagonists, into treatment regimens for diseases from cancer to Alzheimer's disease is only beginning to emerge. Previous conclusions regarding adrenal androgens during aging, including 11-oxygenated androgens, need to be reassessed using modern mass-spectrometry based steroid profiling. Studies designed to dissect the contributions of adrenal steroids to the aging process using longitudinal cohorts would add to the understanding of whether these changes are detrimental, compensatory, or clinically insignificant.

OVARIAN AXIS

Natural history/observational data in older individuals

Biology of Menopause/Ovarian Aging

In contrast to other endocrine axes, aging of the human ovary is programmed—before birth—for midlife senescence. A full complement of ovarian follicles develops *in utero*, peaking at approximately 7 months of gestation with 6 to 7 million follicles, then, via atresia, is gradually reduced to 1 to 2 million follicles by birth. The progressive decline in ovarian follicle number follows a curvilinear pattern, with accelerated loss with increasing age (58). Menopause, the final menstrual period, is diagnosed retrospectively after 12 months of amenorrhea, at an average age of 51 years, when total follicles number approximately 1000 (Figure 3)(59).

The average human reproductive life span, ranging from menarche to menopause, is currently estimated at 37 years in duration (60). Genetic, autoimmune, metabolic, environmental, and iatrogenic factors can accelerate follicular atresia resulting in early (40 to 45 years) or premature (<40 years) menopause (61). The progression of ovarian aging can be monitored by measurement of antimullerian hormone (AMH) and ultrasound determination of antral follicle

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count (AFC) (62,63). These parameters are useful for determining ovarian reserve and timing of menopause, but paradoxically, do not necessarily correlate with fertility, likely due to the multiple other factors influencing female fertility. By the time FSH increases during the late menopausal transition, AMH levels are low to undetectable.

Genetic Contributions to Age of Menopause

Population-based genome-wide association studies have identified 290 genomic loci associated with age of natural menopause (64). The loci identified harbor a broad range of DNA damage-response processes, highlighting the importance of these pathways in determining ovarian reserve (64). Additional factors include cohesion deterioration and chromosome mis-segregation, meiotic recombination errors, spindle assembly checkpoint, genetic mutations, telomere length and telomerase activity, reactive oxygen species, mitochondrial dysfunction, and ovarian fibrosis and inflammation (65,66). The inability to repair DNA damage in both somatic and germ cells could explain the link between reproductive and overall aging (67).

The "epigenetic clock," based on DNA methylation levels, provides more evidence that menopause accelerates at least some components of biological aging (68). Conversely, increased epigenetic age acceleration in blood is significantly associated with earlier menopause, bilateral oophorectomy, and a longer time since menopause (68). Furthermore, the age at menopause and epigenetic age acceleration share common genetic origins (68). The telomerase reverse transcriptase gene provides critical regulation of the epigenetic clock (69).

Hypothalamic-Pituitary Contributions to Ovarian Aging

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In spite of the primary focus on the ovary as the key determinant of reproductive senescence, the central nervous system has been explored as a critical pacemaker of reproductive aging with evidence that central changes (70-72), regulated by DNA methylation (73), contribute to the timing of menopause. Manifestations of aging on gonadotropin secretion include diminution of the preovulatory LH surge (74) and marked elevation of pituitary luteinizing hormone (LH) and follicle stimulating hormone (FSH) during the late reproductive phase and the menopause transition. Diminished pituitary responsiveness to GnRH after menopause (75) is accompanied by alterations in the forms of secreted LH and FSH, resulting in slower clearance and prolonged half-life (76). Pituitary-ovarian axis hormones—particularly FSH and estradiol--are also hypothesized to play a role in regulating ovarian mitochondrial activity (77,78). Elucidation of hypothalamic kisspeptin, neurokinin B, and dynorphin neuronal morphology and physiology in postmenopausal women provides insights regarding postmenopausal gonadotropin control and a new mechanism to reduce vasomotor symptoms (VMS) with NK3R antagonists (79-81).

Challenges to traditional thinking about the postmenopausal effects of elevated FSH have emerged. Mouse studies utilizing a blocking antibody to the FSH receptor revealed preservation of bone density (82), subsequent browning of white fat cells, decrease in subcutaneous and visceral fat accumulation, and improved muscle mass (83,84), though contrary evidence of bone anabolic effects of FSH, mediated through the ovary, has also been reported (85). Possible links of FSH with cardiovascular disease (CVD) risk have been proposed. However, in the Study of Women Across the Nation (SWAN), a multiethnic cohort of US women, higher FSH also predicted lower systolic blood pressure (86).

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Ovarian Steroid Hormone Status with Aging

Estradiol secretion is maintained in older, reproductive aged women by increased ovarian aromatase function (87,88). Granulosa cell production of estradiol, AMH, and inhibin eventually declines with age, possibly reflecting progressive mitochondrial aging (89). In the postmenopause, estrogen synthesis continues, but at much lower levels, via aromatase conversion of ovarian androstenedione to estrone, the predominant postmenopausal estrogen, and of testosterone to estradiol. Obesity, with an attendant increase in aromatase activity, is associated with higher serum concentrations of estrogens and testosterone (90,91).

Circulating testosterone concentration within the low female range declines with reproductive aging (92-94). Ovarian testosterone production falls in a linear pattern with age; in longitudinal studies, testosterone levels were not directly affected by menopause. The theca cells of the postmenopausal ovary continue to produce testosterone in response to elevated gonadotropins. With advancing age, to 70 (93,94) to 80 years (93-95), higher testosterone concentrations are associated with detrimental metabolic and cardiovascular effects (96) yet increased bone mineral density and lean body mass (91).

Clinical Aspects of Ovarian Aging

Regardless of the etiology of ovarian insufficiency, two key clinical sequelae arise: a progressive decline in fertility— reflecting the reduction in ovarian follicle number and quality, and the cessation of monthly menstrual cycles—reflecting the parallel decline of ovarian steroid hormones. Consequently, symptoms (VMS, genitourinary syndrome of menopause [GSM] (97),

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disordered mood, sleep disruption, sexual disorders) and systemic effects (amenorrhea, bone loss, metabolic syndrome, increased cardiovascular risk, cognitive decline) can result (98).

The Menopause Transition

The updated Stages of Reproductive Aging Workshop (STRAW+10) report provides standardized criteria for identifying the transition from the reproductive years to the postmenopausal, with the goal of enhancing the design and reporting of research studies of ovarian aging while establishing accepted nomenclature to be applied to patient care (59) (Figure 3). Prospective, longitudinal observational studies (99-104) (Table 1), such as SWAN (104), continue to clarify the timing of perimenopausal symptom onset, duration during and beyond the menopause transition, relationship with pituitary and ovarian hormone concentrations, clinical correlations with race and ethnicity, linkage of multiple perimenopausal symptoms, and association of symptoms with chronic diseases previously solely attributed to aging.

Clinical Sequelae of Ovarian Aging

Ovarian aging is associated with deteriorating lipid profiles, accelerated cardiovascular risk, adverse changes in body composition including distribution of adipose tissue, accelerated lumbar spine bone mineral density loss, and negative effects on sleep, cognition, and mood (105,106). Early (< age 45 years) and premature (< age 40 years) menopause (natural or surgical) appear to accelerate chronic diseases of aging, including type 2 diabetes, illustrated by studies of women experiencing bilateral oophorectomy before age 46 (107,108). A truncated 'reproductive life span' is associated with higher risk of CVD events and mortality (109). Alternatively,

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cardiovascular health has been hypothesized by some to contribute to the timing of menopause, so a bidirectional association could be considered (105,110).

Vasomotor symptoms and cardiovascular risk

Reports from longitudinal, prospective studies provide compelling evidence that for approximately a quarter of women, VMS start more than a decade prior to menopause and last more than a dozen years after (111-113). Long-term SWAN follow-up showed an association between frequency of VMS and increased CVD risk factors, subclinical CVD, and CVD events (113,114). Ongoing studies will examine whether this association reflects causation and if treating VMS modifies CVD risk.

Observations of VMS with Increasing Age

Observational studies and clinical trials with participants of advanced age suggest that approximately 7 % of older women continue to experience VMS (115). Whether VMS persist from the time of menopause, recur after a period of quiescence, or arise de novo decades later has not been ascertained. The complex interplay between VMS and a 5- to 9-fold increase of CVD events following menopausal hormone therapy (MHT) initiation in older women participating in the Heart and Estrogen/progestin Replacement Study (HERS) (116) and the Women's Health Initiative (WHI) (117) underscores the need for more research into the etiology, characteristics, and consequences of VMS with aging.

Available therapies

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The spectrum of evidence-based therapies for relief of VMS ranges from MHT to prescription nonhormonal drugs to mind-brain-behavioral approaches, including cognitive behavioral therapy and hypnosis (118,119). Decisions regarding the optimal choice for an individual woman incorporate her degree of symptom bother, personal preferences, CVD and breast cancer risk assessments, and uterine status (118,120,121). Treatment of GSM includes over the counter moisturizers and lubricants, vaginal estrogens, DHEA, and oral ospemifene (97,118). As no testosterone preparation is approved by the FDA for women, titration of approved therapies dosed for men has been recommended for treatment of hypoactive sexual desire disorders in women (122,123).

Clinical trial data on efficacy and safety in older individuals

For this discussion, 'older' encompasses women after menopause (usually > age 50), bearing in mind that hormone replacement therapy (HRT) is indicated for younger women who experience hypogonadism or primary ovarian insufficiency and is recommended until the anticipated age of natural menopause (61,118,120). Although preparations, routes of administration, and dosages of MHT have markedly expanded since the first use of conjugated equine estrogens (CEE) in the 1940's, the primary indication for MHT in women experiencing natural menopause remains treatment of symptoms (VMS and GSM) (118,120). Prevention of osteoporosis is another approved indication of MHT, for postmenopausal women at significant risk of osteoporosis for whom other approved therapies are neither tolerated nor appropriate. Additional preventive indications have been considered and are currently under review (124).

The results of secondary coronary heart disease (CHD) prevention trials have been disappointing (125). In contrast to anticipated CHD benefit based upon myriad observational

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studies, trials revealed an increase in myocardial infarction within the first year of therapy, and failure to reduce CHD events or coronary atherosclerosis progression (125).

The WHI clinical trials were initiated in 1992 to determine whether MHT (CEE +/- MPA, depending upon uterine status), when started in healthy women ages 50 to 79 at enrollment, reduced the incidence of chronic diseases of aging (myocardial infarction and CHD death, osteoporosis, colon cancer) while evaluating safety outcomes (stroke, venous thromboembolic disease, breast and endometrial cancer) (126). The combined therapy arm was halted after 5.6 years, and the estrogen only arm after 7.2 years, because overall risks (increased stroke in both trials and heart attack, pulmonary emboli, and breast cancer in the combined arm) exceeded preventive benefits (reduced fractures, colon cancer, diabetes) (117). Subsequent analyses showed a more favorable benefit/risk profile in younger women (ages 50 to 59) or those closer (< 10 years) to menopause, whereas stroke risk increased when MHT was initiated > age 60 (127), dementia risk increased > age 65 (126), and CHD events increased > age 70 (127). The 13-year cumulative follow-up provided additional supportive evidence (117). At 18 years, overall mortality was not increased for any group. Moreover, all-cause mortality decreased by 21% in those ages 50-59 at enrollment in the CEE alone arm (128), with maximal mortality benefit—a 40% decrease—for those with bilateral oophorectomy < age 45 (108).

Breast cancer outcomes at 13 years of cumulative follow-up showed persistence of the significant 28% increase in breast cancer risk with combined therapy initially reported at trial termination (117). In contrast, a 21% decrease with CEE-alone became statistically significant (117). At 20 years of cumulative follow-up, these findings persisted, with the added caveat that breast cancer mortality—without effect in the combined therapy arm—was significantly reduced in the CEE-alone arm (129). These findings reflect the complexities of these specific hormone

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preparations on breast cancer incidence and mortality and should not be extrapolated to other MHT preparations. Although adequately powered RCTs are lacking, observational studies do not suggest that estradiol administration inhibits breast cancer, whereas progesterone may have less breast cancer stimulating effects than MPA (118). The paucity of RCT safety evidence means that MHT is usually not prescribed for women with a history of breast cancer; symptom relief with nonhormonal options is recommended (118,130).

In summary, the WHI established the safety of MHT for younger postmenopausal women (< age 60 or < 10 years since menopause), highlighted the divergence of CVD and breast cancer outcomes for CEE alone versus combined therapy with MPA, and confirmed observational studies suggesting mortality benefit for women with early menopause who used CEE-alone following oophorectomy.

The Timing Hypothesis

The timing hypothesis suggests that MHT reduces atherosclerosis when initiated close to menopause, but not if started at a later point, possibly due to changes in estrogen receptor signaling with time since menopause and altered estrogen milieu (131,132). The timing hypothesis could also explain findings from a trial evaluating effects of transdermal estradiol on insulin sensitivity (133). Several RCTs designed specifically to examine the CHD effects of the timing hypothesis yielded inconsistent results (117,134-136) (Table 2). Current guidelines recommend against prescribing MHT solely for CHD prevention in naturally postmenopausal women (118,120,124,137).

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550 *Dose/Type of MHT and Duration of Therapy*

551 In the absence of adequately powered clinical trials, observational studies and meta-analyses
552 provide some evidence that safety outcomes—particularly for venous thromboembolic disease
553 (VTE) and possibly stroke risks—are improved with lower doses and transdermal estradiol
554 preparations (105,118,138).

555

556 Following the initial reports of the WHI, limiting MHT to 3 to 5 years was recommended to
557 minimize breast cancer risk. Both the North American Menopause Society (NAMS) and the
558 American College of Obstetricians and Gynecologists (ACOG) subsequently issued statements
559 allowing for longer duration of MHT in healthy women ≥ age 65 without contraindications,
560 following an annual discussion of anticipated risks and benefits, and reevaluation of individual
561 health status (120,139). The recommendation for shared decision-making reflects the absence of
562 long-term evidence to inform decisions regarding risks and benefits for women who initiate
563 MHT for symptom relief at menopause and continue for an extended time. Common sense
564 measures include progressively reducing the dose and switching to transdermal from oral
565 preparations (115,118,120).

566

567 **Key Points**

568 • Menopause and the postmenopausal state are natural, preprogrammed manifestations of
569 ovarian aging characterized by fertility loss and profound reduction in ovarian hormone
570 production.

571 • Menopausal symptoms are common, vary in degree of bother, and can be effectively

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treated with a variety of agents proven effective in RCTs.

- Initiation of MHT is safest when reserved for women in close proximity (< 10 years) to the menopause transition or less than age 60, without contraindications, and with acceptable CVD and breast cancer risks.
- Continuation of MHT can be considered individually depending on personal desires, health status, and documented shared decision making.
- Although oral MHT has been studied most extensively, depending upon health status and age, based upon prospective observational studies, lower doses and transdermal therapies may be safer with fewer VTE, fewer undesirable metabolic effects, and possibly fewer CVD events.
- Delineation of the physiological role of the kisspeptin, neurokinin Y, and dynorphin neurons in control of VMS and gonadotropin and sex steroid secretion allows for potential new treatment options as demonstrated in completed and ongoing RCTs of NK3R antagonists.

Gaps in the Research

Factors that affect the timing and consequences of menopause across diverse races, ethnicities, lifestyles, genetics, environmental influences, metabolic factors, and polycystic ovary syndrome (PCOS) require additional study. The SWAN study provides some insight into differences in reproductive aging and midlife health between black and white women, but additional work is needed (140).

The natural history and physiologic characteristics of VMS, including the prevalence of ongoing or recurrent VMS in older women, CVD impact of VMS, and safe and effective

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treatment options in this age group, require more study, optimally utilizing investigative techniques measuring both subjective and objective VMS.

Steroid hormone and gonadotropin concentrations with advanced age have not been well delineated. Additional follow-up of ongoing studies such as SWAN and new population studies is needed.

Adequately powered RCTs with clinical outcomes of MHT would ideally be completed in symptomatic, recently postmenopausal women. Head-to-head randomized trials in this population could confirm risks and benefits of transdermal estradiol and micronized progesterone versus oral estrogen therapies and synthetic progestins.

Further study of selective estrogen receptor modulator (SERM) therapies alone or in combination (eg. CEE with bazedoxifene) could expand therapeutic and preventive strategies for aging women for whom available estrogen and progestogen therapies may no longer be tolerated or appropriate.

Novel investigational techniques proposed to preserve or revitalize ovarian function--derivation of oocytes from stem cells (141); ovarian transplantation of mesenchymal stem cells from amniotic membrane, umbilical cord, placenta, human menstrual blood, adipose tissue, and bone marrow; intra-ovarian injection of autologous platelet-rich plasma; and in vitro activation of dormant primordial follicles (142)—merit additional study. Investigational approaches to maintain 'ovarian fitness' and promote reproductive longevity include dietary restriction, rapamycin, metformin, resveratrol, and melatonin administration (143,144).

TESTICULAR AXIS

Natural history/observational data in older individuals

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The three key dimensions of male reproductive health – fertility, sexuality, and androgenization – all interact with male general health, with the largest overlap with androgenization (Figure 4).

Biology of Testicular Aging

The twin functions of the testis – spermatogenesis to produce spermatozoa that can fertilize an oocyte and steroidogenesis to produce bioactive androgens, testosterone and dihydrotestosterone – are both impacted by aging with effects mediated mainly by accumulation of aging co-morbidities rather than aging itself. Hence, reproductive function of the healthiest of men remains largely undiminished throughout life, unless disrupted by intercurrent disease, a natural history differing starkly from female reproductive aging where an intrinsic, abrupt loss of ovarian function occurs at the midpoint of life for modern women.

Testosterone is necessary for reproduction (to make and deliver sperm) but not for life itself (as complete androgen insensitivity resulting from a genetic defect in XY individuals allows for a healthy but infertile life as a phenotypic woman). Uniquely among major human hormones, there is no naturally occurring excess testosterone syndrome in men, possibly reflecting the evolutionary role of the dramatic surge in androgens during male puberty required for species propagation. Testosterone is produced by all steroidogenic organs (testis, ovary, adrenal, placenta) and, while present in the circulation of all humans, blood testosterone displays a marked sexual dichotomy, with testicular secretion of 20 times more testosterone after puberty than is produced from non-testicular sources in children and women.

Male Fertility

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Paternity requires producing mature, fertile spermatozoa that are delivered by male sexual function to the female reproductive tract. After spermatogenesis is initiated at puberty, it is minimally affected by aging unless impacted by gonadotoxic chemicals or ionizing radiation (to which it is exquisitely sensitive) or severe withdrawal of gonadotropin drive essential to maintain the intratesticular androgen milieu required for completion of meiosis. Hence, on average the fertility of older men, either naturally or via in vitro fertilization, is only modestly diminished by reduced sperm output and motility (145,146) so that paternity at advanced age is well known (147). However, unexplained impairment of sperm production in otherwise healthy men, the most frequent cause of male infertility, remains an important research challenge for both younger and older men (148). Modern genetics has still more to reveal about the heritable origins of spermatogenic failure and sperm (dys)function through genetic (149) and epigenetic (150,151) mechanisms. Insight into acquired (non-genetic) causes of reproductive failure has, however, advanced only minimally. Data have been inconclusive about whether there is a secular trend for diminished human sperm production (152), due to potential bias from low participation of healthy, non-infertile men (153), whereas excellent animal studies are clearly negative (154). Many possibly damaging environmental impacts on spermatogenesis, from pre-natal to adult life, are proposed but remain speculative (155).

Genetic Risk of Old Fathers

Male aging has modest but significant effects of increasing the very low absolute risk of some rare autosomal dominant genetic disorders (e.g. achondroplasia, Apert syndrome, Noonan syndrome and Costello syndrome), genetic mutations, chromosomal defects and epigenetic changes (147) as well as neuropsychiatric disorders (156). These paternal age effects, arising

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from cumulative de novo DNA copying errors during hundreds of rounds of mitotic and meiotic replication during spermatogenesis over a man's lifetime, can become entrenched in the genome through selection of mutations that enhance proliferation of their own spermatagonial clone over others (157); however, their low prevalence makes them difficult to fully disentangle from more potent overlaid teratogenic effects of female aging and pregnancy. Further insight into the testicular origins of paternal age effects on reproductive outcomes (158) is highly desirable given the increasing rates of older men fathering children both naturally and via in vitro fertilization after remarriage to younger women.

Sexual Function in Male Aging

Male sexual function operates as a hydraulic neurovascular mechanism subserving erection and culminating in an autonomic neural reflex for ejaculation. Although initiation of adult male sexual function at puberty requires adult male blood testosterone exposure, maintenance of men's sexual function requires only a low blood testosterone threshold. Hence erectile dysfunction (ED), the most prevalent male sexual dysfunction, which is steeply age dependent, is both associated with age-related comorbidities and predicts future cardiovascular events (159). However, ED is rarely due to androgen deficiency when it is part of a pathologic form of hypogonadism. Furthermore, in a longitudinal cohort study, reduced sexual activity from any cause (drugs, depression, organic erectile dysfunction) was associated with decreases in blood testosterone concentrations (160), whereas concentrations increased with increased sexual activity (161). This overlooked observation often leads to confusing mildly reduced blood testosterone as the cause rather than the effect of reduced sexual activity, a major contributor to the excess of unjustified testosterone prescribing over recent decades (162). As a sound

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alternative, the safety and efficacy of phosphodiesterase type 5 inhibitors for ED in older men is now well established for many underlying medical causes of ED, subject to avoidance of adverse drug interactions such as with nitrates (163).

Testosterone Measurement

Analytical research into the impact of male aging on reproductive and general health depends crucially on accurate measurement of testosterone and its bioactive metabolites dihydrotestosterone and estradiol (as well as ideally precursors and other metabolites). For this purpose, steroid liquid chromatography-mass spectrometry (LC-MS) can provide accurate, multi-analyte profiles allowing for a dynamic picture of net androgen action. However, although steroid LC-MS is now dominant in clinical research as the steroid immunoassay era draws to a close, affordability and general availability of steroid LC-MS methods in clinical practice remains challenging. This is due to commercial lock-in of pathology labs to multiplex immunoassay platforms in which steroid analytes remain a minor component but provide quick, inexpensive, albeit often inaccurate results. Laboratory measurements of testosterone fractions ("free", "bioavailable") are technically demanding, laborious manual methods which remain unstandardized and lack reference standards, quality control or reference ranges (164). Consequently, lab measurements of derived fractions of blood testosterone are rarely available and are replaced by inaccurate calculational formulae. These formulae are inevitably a deterministic (inverse) function of age (165) but empirically add no significant prognostic information to accurate LC-MS testosterone measurements (166).

LC-MS measurement of testosterone and related steroids in population-based studies is supplanting immunoassay use in determining the natural history of blood testosterone levels in

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male aging (167-171). Whereas immunoassay studies reported a gradual, modest but inconsistent decline in testosterone levels with age among Western men (Figure 5), recent evidence shows no age-related changes in Japanese (172) or Chinese (173) men, nor in LC-MS data from pooled Western studies (174). These studies highlight lifestyle confounders of the age-related reduction in blood testosterone, notably overweight/obesity, insulin resistance or diabetes, smoking, cardiovascular disease and depression (175-177), which explain most or all apparent age-related reductions in serum testosterone. There is inadequate research on whether testosterone improves these co-morbidities of aging. In addition, there are interesting speculations based on limited interventional (178), observational (179), and mechanistic (180) studies suggesting androgen effects on telomerase, as a potential hormonal influence on an underlying mechanism of aging.

Although the sole unequivocal indication for testosterone treatment is for replacement therapy in men with pathological reproductive disorders, there is strong public interest in extending the use of testosterone outside endocrine disorders, notably for rejuvenation, an application with a deep aspirational history throughout human civilization long preceding modern endocrinology. The modern embodiment of this pre-scientific belief in testosterone as the pivot of male sexual, reproductive, and general rejuvenation was the re-emergence as "andropause" over the turn of the 21st century (181). That wishful thinking underlies the 100-fold increases in global pharmaceutical testosterone sales over 3 decades (182), including 10-fold increases in the US and 40-fold in Canada over the first decade of the 21st century (162), in the absence of any new approved indications for testosterone treatment. An important public health challenge is to evaluate the impact of this decades-long epidemic of testosterone prescribing, possibly abating recently (183,184), on underlying rates of cardiovascular and prostate diseases.

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Both of these diseases have displayed significant temporal changes over recent decades, which makes discerning an overlaid impact of changes in testosterone administration challenging.

Available therapies

While numerous testosterone products are approved for oral, transdermal, injectable, or implantable (and in some countries buccal and intranasal) administration to men with pathologic hypogonadism (185), none are approved for use in male aging. In men of any age without contraindications (nitrate vasodilators) or CYP3A drug interaction, PDE5 inhibitors (sildenafil, tadalafil and congeners) are highly effective and well tolerated for improving erectile function (186). Urinary hCG is approved for treatment of gonadotropin deficient male infertility but has little applicability to male aging where the predominant testicular defect is intrinsic Leydig cell failure, and hCG does not achieve sustained benefits. Likewise, clomiphene and aromatase inhibitors should not be used to increase endogenous testosterone due to their adverse effects on estrogen-dependent male sexual function and bone density.

Clinical trial data on efficacy and safety in older individuals

Based on testosterone's prominent effects on muscle structure and function, placebo-controlled interventional studies investigating potential effects of testosterone aiming to reverse age-related muscle loss (sarcopenia) or weakness (frailty) have been conducted. However, these studies have produced inconsistent and/or inconclusive findings, largely due to relatively small sample sizes (vs small magnitude of benefits) and heterogeneity of study cohorts and endpoints. Salutary findings were produced by the Testosterone in Older Men with Mobility Limitations (TOM) trial in which 209 men aged 65 years or over (average 74 years) with a high prevalence of obesity,

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hypertension, diabetes and hyperlipidemia were treated with daily transdermal testosterone or placebo gel for 6 months; however, the study was terminated prematurely for an excess of cardiovascular adverse effects (187). Analogous studies of testosterone treatment in frail and/or sarcopenic older men also had minor benefits but without these adverse cardiovascular effects (188-190).

The 1994 Institute of Medicine (IOM, now National Academy of Medicine) review of male aging concluded there was insufficient efficacy evidence to justify a large, placebo controlled RCT of testosterone for an age-related reduction in blood testosterone in men without reproductive pathology. They recommended short-term efficacy studies to justify a costly, large-scale trial. Subsequently, the NIH-funded Testosterone Trials, a series of seven well-integrated, overlapping RCTs involving daily transdermal testosterone or placebo gel for 12 months were conducted. These studies recruited 790 men aged 65 years and over who had consistently low serum testosterone (<9.5 nmol/L) and a high prevalence of obesity (63%), hypertension (72%), diabetes (37%) and current or former smoking (66%) (191). The key findings were a modest but transient benefit for sexual function, small and expected increases in hemoglobin and bone density, but no benefits for vitality, physical or cognitive function (192). Findings also included adverse effects of testosterone on erythyrocytosis and an increase of non-calcified coronary plaque size (192-194). Although the T Trials were not powered to detect cardiovascular endpoints, this latter safety signal needs evaluation given the widescale usage of off-label testosterone in older men.

An adequately powered long-term safety study is needed to determine whether testosterone treatment of older men without reproductive pathology causes adverse cardiovascular or prostate events. Although the Testosterone Trials failed to meet the IOM

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mandate for a public sector placebo-controlled efficacy study, a large-scale, long-term industry-funded FDA-mandated safety study (TRAVERSE) is underway aiming to define the cardiovascular safety of testosterone treatment of men with age-related low blood testosterone in the absence of reproductive pathology (195). In the interim, numerous meta-analyses aggregating smaller, shorter-term RCTs report inconsistent and inconclusive evidence for cardiovascular effects (196-198), largely due to underpowering (especially exposure duration), failure to recognize transient adverse effects (196,199), and industry source funding bias (200). In the T4DM study, 1007 men with impaired glucose tolerance were randomized to injectable testosterone undecanoate (1000 mg) or placebo every 3 months for 2 years, with a reduction in the incidence of diabetes along with an unacceptably high rate of erythrocytosis (22%) (201), together with a slow recovery of testicular endocrine function of at least 12 months (202).

Furthermore, the consequences of testosterone treatment on late-life prostate diseases including cancer and hyperplasia require elucidation. While strong evidence exists against any predictive relationship between endogenous testosterone and its metabolites with future diagnosis of prostate cancer over the following decade (203,204), and there is no evidence of increased prostate disease in meta-analysis of short-term trials of testosterone treatment (205), more powerful RCT evidence is required before the risk of exogenous testosterone administration accelerating late-life prostate diseases can be considered dispelled.

Key Points

- Spermatogenesis and steroidogenesis are both negatively impacted by co-morbidities associated with aging rather than aging itself.

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- ED is rarely due to androgen deficiency. Phosphodiesterase type 5 inhibitors are an effective treatment for older men with ED.
- Use of steroid immunoassays for measurement of testosterone rather than the preferred LC-MS assays may result in inappropriate diagnosis of low testosterone levels.
- The Testosterone Trials showed modest but transient benefits in testosterone treatment for sexual function, small and expected increases in hemoglobin and bone density, but no benefits for vitality, physical or cognitive function and an adverse effect of testosterone to increase non-calcified coronary plaque size. These data do not support the use of testosterone to treat these co-morbidities of older men.
- A large safety study (TRAVERSE) is underway to evaluate the cardiovascular events during 5 years of daily testosterone vs placebo gel treatment.

Gaps in the Research

Given the lack of convincing efficacy and uncertain safety of testosterone administration to aging men without reproductive pathology, future clinical research on testosterone treatment should focus primarily on whether testosterone administration improves the co-morbidities of aging and/or has direct effects on putative underlying mechanisms of aging. The potential adverse effects of long-term testosterone administration on cardiovascular and prostate diseases in such men also require additional research. Additionally, in the absence of any natural disorders of excessive testosterone secretion in men, possibly reflecting the evolutionary tolerance for sharp increases in testosterone secretion during male puberty, careful exploration of the efficacy and safety of short-term, higher doses of testosterone or other natural non-

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aromatizable androgens (e.g. DHT, non-steroidal androgens) for specific aging co-morbidities may be warranted.

While clinical therapeutics will always require adequately powered, placebo-controlled study of natural or synthetic androgens, analytical research into cellular and molecular mechanisms of androgen action in key target tissues (muscle, liver, erythroid cell lineages, bone, prostate, skin, brain) are needed to identify targeted paracrine or intermediary modulators of androgen action, which could point the way to gaining the benefits of target-specific androgen action while avoiding detrimental off-target effects. Further analytical research is also needed to understand the testicular origins of paternal age effects on reproductive outcomes and on the preservation of testicular function.

THYROID AXIS

Natural history/observational data in older individuals

Clearance of circulating T4 and T3 declines with age, resulting in an increase in half-life from 7 days in younger individuals to 9 days in those aged 80 years and older (206). There is a compensatory reduction in the production of T4 and T3. T4 production declines from 80 μg to 60 μg daily and T3 production declines from 30 μg to 20 μg daily (207). In euthyroid individuals with TSH and free T4 concentrations within the reference range, T3 concentrations are lower in community-dwelling older individuals without acute illness than in younger individuals, suggesting an age-related decline in 5′-deiodinase activity (208,209).

Both cross-sectional and longitudinal studies have shown an increase in TSH concentrations with age, even when limiting to a reference population of individuals without thyroid disease or anti-thyroid antibodies, without any changes in free T4 concentrations

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(208,210,211). The shape of the TSH distribution suggests a population shift to higher levels rather than increased incidence of hypothyroidism at older ages (Figure 6) (210). Accordingly, a TSH above the reference range is found in 14.5% of those aged 80 years and older, compared with 2.5% those aged 20-29 years (210). The prevalence of anti-thyroid antibodies also increases with age, particularly in women, consistent with an age-related increase in autoimmune thyroid disease (210). However, anti-thyroid antibody levels are lower in the oldest old (209).

The majority of older individuals with elevated TSH concentrations have normal free T4 concentrations, a combination of thyroid testing results known as subclinical hypothyroidism. It should be noted that subclinical hypothyroidism persists on repeat testing in only 38% of older individuals, with reversion to euthyroidism in the remaining 62% (212). Subclinical hypothyroidism is not associated with an increase in risk of coronary heart disease, stroke, heart failure, dementia, disability, or mortality, overall or in the subgroup of individuals with TSH concentrations of <7 mIU/L (213-217). Furthermore, older individuals with subclinical hypothyroidism may have better mobility and functional status than their euthyroid peers (218,219). Observational data have shown an increased risk of cardiovascular mortality and stroke in subgroups of patients with subclinical hypothyroidism with TSH 7-9.9 mIU/L and of coronary heart disease, cardiovascular mortality and heart failure for TSH ≥10 mIU/L (213,214,217). Clinical data do not suggest that levothyroxine treatment reduces the risk of cardiovascular events in older patients with subclinical hypothyroidism (220,221). Furthermore, overtreatment with levothyroxine to TSH concentrations below the reference range is common in older individuals (222).

Subclinical hyperthyroidism—low TSH concentrations with normal concentrations of free T4—is more common in older than in younger individuals due to an increase in autonomous

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thyroid hormone secretion from thyroid nodules. Subclinical hyperthyroidism is associated with an increased risk of atrial fibrillation, hip fracture, and dementia if left untreated (223-225). Even patients with low, but not suppressed TSH levels (TSH 0.1-0.44 mIU/L) are at increased risk of atrial fibrillation, coronary heart disease, and hip fracture (223,224). Because older patients have a high baseline risk of these outcomes, subclinical hyperthyroidism is more likely to have clinically meaningful effects in these patients. Furthermore, in euthyroid older patients, free T4 concentrations within the reference range are associated with increased risk of atrial fibrillation, coronary heart disease, heart failure, dementia, and mortality (226,227). These data support a potential role of free T4 concentrations in identifying increased risk of adverse events, independent of TSH concentrations.

Overt hypothyroidism and hyperthyroidism each are more common in older individuals, as are comorbid conditions or medications that affect thyroid function (228,229). Recognition of overt thyroid dysfunction can be challenging; the classic symptoms of hypothyroidism and hyperthyroidism are reported less frequently in older patients than in younger patients with a similar degree of thyroid dysfunction (230-232). Clinicians may fail to identify common age-related symptoms and syndromes, such as fatigue, depression, cognitive decline, constipation, and falls as related to thyroid dysfunction. In addition, older patients with hyperthyroidism are more likely to have atypical symptoms, such as apathy and anorexia, and less commonly have hyperadrenergic symptoms (231).

Available therapies

Treatment of both hyperthyroidism and hypothyroidism should take into account the underlying health status of the patient, particularly underlying cardiovascular comorbidities.

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Levothyroxine is the primary treatment for thyroid insufficiency. Levothyroxine doses in older individuals correlate with total lean body mass and renal function, leading to lower requirements at the time of diagnosis and increased risk of overtreatment (202). Patients with longstanding levothyroxine use may require a dose reduction over time (201). In addition, multiple over-the-counter and prescription medications affect absorption, protein binding, or metabolism of levothyroxine (233). Three options are available for management of an overactive thyroid: antithyroid medication, radioactive iodine, and thyroidectomy.

Clinical trial data on efficacy and safety in older individuals

There have been two randomized controlled trials (RCTs) of treatment of subclinical hypothyroidism in older individuals, one of 737 adults aged 65 years and older and the second of 105 adults aged 80 years and older (212,234). Data from individuals aged 80 years and older from the first trial (n=146) were merged with data from the second trial for analysis. Both RCTs were conducted in participants with persistent subclinical hypothyroidism who were randomized to levothyroxine or placebo and followed for 12 months. The primary outcome was improvement in hypothyroid symptoms or tiredness, with additional secondary outcomes of quality of life, hand-grip strength, cognitive function, blood pressure, weight, waist circumference, and activities of daily living. No benefit was found in either trial of a low dose of levothyroxine (mean dose 50 mcg daily) compared with placebo, as well as no increase in risk. These trials were not adequately powered to examine cardiovascular or other events, nor were they powered to examine subgroups of TSH 7-9.9 mIU/L or 10-19.9 mIU/L that observational data suggested were at higher risk of adverse events. Participants enrolled in both trials showed a low thyroid

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symptom burden, leaving residual questions about management of patients with symptoms of hypothyroidism.

There have been no trials of similar size in older patients with subclinical hyperthyroidism, and the management is based on thresholds established from observational data.

Key Points

- TSH concentrations above the reference range in conjunction with a normal free T4 concentration is common in older individuals. Isolated T3 concentrations below the reference range are also common in this age group.
- Older individuals with persistent subclinical hypothyroidism with TSH concentrations of <7 mIU/L should not be treated with levothyroxine. This recommendation is based on RCT data.
- Whether or not subgroups of older individuals with persistent subclinical hypothyroidism who have TSH concentration of ≥ 7 mIU/L or significant symptoms should be treated with levothyroxine is debated.
- TSH thresholds for treatment of subclinical hyperthyroidism have been established from observational data, but these treatment thresholds and optimal management have not been tested in RCTs.

Gaps in the research

The etiology of age-associated changes in thyroid function testing is not known. The Centers for Disease Control and Prevention Clinical Standardization program has created a standardization program for free T4 based on the International Federation of Clinical Chemistry

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and Laboratory Medicine reference system and is standardizing free T4 and harmonizing TSH testing globally. These efforts represent an important step toward establishing whether age-based reference ranges are needed for diagnosis and management of thyroid dysfunction. Potential causes of TSH elevation such as a decrease in the bioactivity of TSH or diminished response of the thyroid to TSH are untested. Whether the age-associated effect on T4 to T3 conversion is persistent and is due to declines in deiodinase activity in older individuals requires further study. In addition, methods to distinguish between age-associated adaptive changes in thyroid function and early hypothyroidism are needed.

RCT data are needed to assess the risks and benefits of treatment of older individuals with subclinical hypothyroidism with symptoms or higher TSH levels and with subclinical hyperthyroidism. RCT data are also needed in patients with subclinical thyroid dysfunction and pre-existing cardiovascular disease or cognitive impairment. Whether the target TSH range for treated thyroid dysfunction should be the same as the range used to define thyroid dysfunction in an older individual also requires evaluation. Additional study of the clinical importance of free T4 measurement in euthyroid older individuals is needed.

OSTEOPOROSIS

Natural history/observational data in older individuals

Osteoporosis is a chronic skeletal disorder resulting from progressive bone loss after menopause in women and with advancing age in both men and women (235). That bone loss gradually disrupts bone microarchitecture, impairing bone strength, predisposing to fracture. Patients at high risk of fracture can be readily identified, effective strategies for reducing fracture risk are

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available, and evidence-based guidelines for managing osteoporosis have been published (235-237).

The prevalence of osteoporosis, defined as bone mineral density (BMD) T-score of ≤ -2.5 at the lumbar spine or femoral neck, increases from 6.8% in women aged 50 to 59 years to 25.7% for those aged 70-79 years to 34.9% in women aged 80 years and older (238). Osteoporosis is present in 5% of men aged 70-79 years and 10.9% of men ≥80 years. In addition, about half of adults aged 70 years and older have low bone density which, in combination with other risk factors, conveys high fracture risk.

Rates and severity of fractures increase exponentially with age; vertebral (spine) and hip fractures account for 24% of all fractures in women aged 60-69 years, but account for 67% in the larger number of women aged 80 years and older with fractures (239) (Figure 7). About half of women and 20% of men will experience a fracture related to osteoporosis in their lifetime, two thirds of which occur after age 75 (240). More than 2 million osteoporotic fractures occur each year in the United States, including 700,000 vertebral (spine) fractures and 300,000 hip fractures, resulting in more than 500,000 hospital admissions (241).

Both hip and vertebral fractures are associated with substantial morbidity and mortality (242-245). Hip fractures, occurring on average at age 82, are associated with higher health care cost and disability than all other fracture types combined (246). Despite this knowledge and availability of effective treatments, most older patients with fractures do not receive osteoporosis therapy. Fewer than 15% of Medicare patients (average age 80.9 years) began osteoporosis therapy in the year following a fracture, >60% of which were hip or spine fractures (247). In the United States, age-adjusted rates of hip fracture began decreasing after 1997, but recent data suggests that those rates are increasing again due a widening of a treatment gap (248).

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Most fractures occur after a fall. Osteoporosis and sarcopenia, a risk factor for falls, frequently occur together in older adults (249). At least 1/3 of women aged 65 or older experience a fall each year, with the risk of falls increasing with advancing age (250).

Important interplays exist among the strongest risk factors for fracture: advanced age, low BMD and a history of prior fracture or fall. Older women are at higher risk than are younger women with the same T-score and can be at high fracture risk without low BMD (251) (Figure 8). A history of previous fracture results in a doubling of future fracture risk, and this risk is especially high in the first 2 years after an incident fracture (252). Additionally, the subsequent fracture in older adults is more likely to be a serious fracture (253).

Societal guidelines and the US Preventive Services Task Force (USPSTF) recommend BMD testing for all women age 65 and older (254-256). BMD testing in men has been suggested to begin at age 70 (257). Evaluation for secondary causes of osteoporosis is warranted, including endogenous and exogenous Cushing's syndrome, male hypogonadism, clinical hyperthyroidism, and severe vitamin D deficiency. The BMD result can be combined with other risk factors in FRAX™, a validated fracture risk algorithm, to estimate fracture probability in individual patients (258). FRAX™ underestimates fracture risk in patients with recent fractures or falls.

Available therapies

Therapy to reduce fracture risk begins by minimizing risk factors and with general measures including good nutrition, avoidance of smoking and regular physical activity. Multidisciplinary approaches to fall risk prevention including exercises to promote strength and balance, correcting visual deficits, avoiding or minimizing medications such as sedatives that are associated with fall risk, removing risks in the home, and appropriate use of assistive devices can reduce fall risk, but

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none of these studies have been large or long enough to demonstrate reduction in fracture risk. These general measures and fall prevention strategies are recommended for all older adults to promote bone health as well as general health, with pharmacological therapy reserved for patients at high risk of fracture (235).

Multiple drugs with varying mechanisms of action are government approved for treating osteoporosis (237) (Table 3). Each approved drug reduces vertebral fracture risk in postmenopausal women with osteoporosis, and all drugs except raloxifene and ibandronate reduce non-vertebral fracture risk. Hip fracture risk reduction has been demonstrated with alendronate, risedronate, zoledronate, denosumab, and romosozumab. Anti-remodeling agents reduce bone turnover and increase BMD and strength but do not repair the microarchitectural damage of osteoporosis. Osteoanabolic or bone-building agents increase bone formation and improve trabecular architecture. Osteoanabolic agents are more effective than oral bisphosphonates at improving BMD and reducing fracture risk in older adults (259). Bone-forming drugs are recommended for patients at very high fracture risk (T-score of ≤-3.0 in the absence of fragility fracture, T-score of ≤-2.5 plus a fragility fracture, severe or multiple vertebral fractures)(236,256,260). Details about the efficacy, safety and use of individual drugs are provided in an Endocrine Society Clinical Practice Guideline and its Guideline Update (235,236).

Recent data demonstrate a strong relationship between treatment-associated changes in BMD and fracture risk reduction (261). This has led to an emerging concept of goal-directed therapy using total hip BMD as a “target” informing the choice of initial therapy and decisions about subsequent therapies (262).

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Raloxifene, an estrogen agonist/antagonist, is a weak anti-remodeling agent that reduces the risk of vertebral but not other fractures.

Calcitonin-salmon is a weak inhibitor of bone resorption that may reduce vertebral fracture risk. Because of a possible cancer risk associated with calcitonin-salmon therapy, this drug is no longer approved in Europe. Short-term therapy may be considered for pain relief following an acute vertebral fracture (263).

Bisphosphonates are the most commonly used drugs for osteoporosis treatment. Except for ibandronate, the approved bisphosphonates reduce risks of vertebral, non-vertebral and hip fracture. While osteonecrosis of the jaw and femoral shaft fractures with atypical features have been described with long-term bisphosphonate therapy, the benefit:risk profile remains favorable for up to 10 years in patients at high fracture risk. However, bisphosphonate use beyond 5 years does not result in additional BMD increase or fracture risk reduction. Guidelines recommend re-evaluating fracture risk after 3-5 years of bisphosphonate therapy. For patients who are no longer at high risk of fracture and who no longer meet criteria for treatment, interruption of therapy can be considered until the patient again meets treatment criteria (235). For patients remaining at high risk of fracture after 5 years of bisphosphonate treatment, switching to denosumab or one of the bone-building agents could be considered.

Denosumab is a human monoclonal antibody administered subcutaneously every 6 months that reduces risks of vertebral, non-vertebral, and hip fracture. Progressive increases in BMD, maintenance or improved fracture risk reduction, and no major safety issues were seen over 10 years of therapy. While there is no limit on the duration of denosumab therapy, discontinuation of therapy results in a rebound in bone turnover markers, rapid loss of BMD and vertebral fracture protection, and increased risk of multiple fractures. While there is no limit on the

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duration of denosumab therapy, alendronate or zoledronate should be given whenever denosumab is discontinued to mitigate these effects (264).

Teriparatide and abaloparatide are parathyroid hormone receptor agonists that activate bone formation and, to a lesser extent, bone resorption. Both drugs have been demonstrated to reduce vertebral and non-vertebral fractures, but neither was shown to reduce hip fracture risk in the pivotal clinical trials that were not designed to evaluate that outcome. These drugs are administered by daily subcutaneous injection, usually for 18-24 months because their anabolic effects diminish with longer use. Potent anti-remodeling agents given after a course of these agents are recommended to maintain the skeletal benefits.

Romosozumab, an anti-sclerostin antibody that activates bone formation while inhibiting bone resorption, is administered by subcutaneous injection once monthly for 12 months, followed by either a bisphosphonate or denosumab. These regimens induce larger increases in BMD and greater reduction in fracture risk within 12 months when compared to placebo and to alendronate. Increased cardiovascular risk was observed compared to alendronate but not to placebo (265).

Clinical trial data on efficacy and safety in older individuals

The IOM, now the National Academy of Medicine, recommends a total daily intake of calcium of 1200 mg for older adults, based on inconsistent data (266). Higher daily calcium intakes are not beneficial and may be harmful. The role of vitamin D supplementation in older adults is even less certain and is discussed in detail in the following section. Based on available evidence, 1-1.2 g protein/kg body weight per day is recommended for older adults (267). High protein intake may slow muscle loss and reduce fall frequency (268).

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Weight-bearing exercises do not generally increase BMD in older adults whereas a regular walking program may attenuate bone loss in sedentary older adults (269). Multicomponent exercise programs targeting balance, gait and muscle strength reduce the frequency of falls and possibly fractures in older people (250). Correcting cataracts and limiting the use of neuroactive sedative drugs reduces fall risk. Hip protectors may be considered in patients at high risk for falling, especially for patients in supervised settings (270). The Centers for Disease Control and Prevention has provided useful tools for fall risk assessment and management, based on published guidelines (271). For older patients who have experienced fractures, individualized rehabilitation programs are helpful (272,273). Back strengthening exercises improve symptoms in patients with vertebral fractures and reduce subsequent fracture risk (274).

The average ages of participants in the pivotal fracture trials with drugs have been between 65 and 75 years; some have enrolled participants up to 100 years old. Subgroup analyses of responses to three bisphosphonates (alendronate, risedronate and zoledronate), denosumab, teriparatide and abaloparatide in subsets of older participants enrolled in the pivotal trials have been published (275-280). These analyses demonstrate that effectiveness, safety and tolerability of therapies in the oldest subgroups are generally similar to responses in the entire study cohorts. Importantly for older patients, fracture risk reduction is evident as early as 6 months after beginning therapy. Specific issues relevant to the use of these drugs in older patients with osteoporosis are presented here.

Because neither raloxifene nor calcitonin-salmon reduce the risk of non-vertebral or hip fracture, they are not recommended for treating older patients with osteoporosis. Bisphosphonates should be used with caution in patients with significantly impaired renal

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function. When oral bisphosphonate use is difficult because of dosing rules and/or too many other medications, annual or biannual zoledronate infusion is an alternative (281). In a randomized, controlled trial in patients treated within 3 months of a hip fracture, average age 74, zoledronate reduced both fracture risk (35%) and mortality (28%) compared to placebo (282). The twice-yearly parenteral dosing of denosumab is an appealing option for older patients taking many oral medications. Denosumab can be used in patients with impaired renal function, but the risk of hypocalcemia is higher in those patients. Compared to placebo, denosumab reduced hip fracture risk by 62% in patients aged 75 and older (277). Teriparatide and abaloparatide may be associated with palpitations and postural hypotension and are not recommended in patients at increased risk for osteosarcoma including those with a history of skeletal radiation. Patients at very high cardiovascular risk are not good candidates for romosozumab.

Key Points

- Fractures related to osteoporosis are common and often serious problems in older persons.
- Older patients at high risk of fracture can be readily identified, especially those with a recent fracture.
- Ensuring good nutrition and encouraging regular physical activity promote bone health.
- Drugs to reduce fracture risk are effective and well tolerated in older patients and should be considered in all older patients with osteoporosis, especially those with prior fracture.

Gaps in the Research

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Fractures are often not recognized as being related to osteoporosis. As a result, most older patients with fracture are not treated for osteoporosis. Studies evaluating strategies to educate patients and clinicians about the importance of osteoporosis and benefits of therapy would be helpful.

Studies are needed comparing the efficacy and safety of osteoporosis drugs, especially in older patients. None of the studies evaluating approaches to reducing the risk of falls have been designed to evaluate effects on fracture risk. The role of senolytic therapies to forestall effects of effects of aging through selective induction of death of senescent cells should include skeletal outcomes.

VITAMIN D

Natural history/observational data in older individuals

Vitamin D is a steroid hormone that controls several hundred genes (283,284). It modulates a wide range of molecular and cellular functions, including immune functions, inflammation, cellular senescence, and telomere biology (284,285). Vitamin D may play a dual role in aging, as a risk factor or marker of ill health, and as a possible therapeutic drug (286,287).

Vitamin D Physiology

Vitamin D is available in two major forms, ergocalciferol (vitamin D_2) originating from plant sources or supplements, and cholecalciferol (vitamin D_3), the animal form that represents its major (> 90%) source. Cholecalciferol is synthesized in the epidermis, from 7-hydrocholesterol after exposure to short UV-B sunlight radiation (290-315 nm, Figure 9). Both vitamin D_3 and vitamin D_2 are readily hydroxylated in the liver, in an unregulated, substrate dependent pathway,

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leading to the most abundant circulating, but biologically inactive form, 25-hydroxyvitamin D (25(OH)D, calcifediol). Serum 25(OH)D circulates in serum bound to a specific, high affinity, transport protein, vitamin D-binding protein (VDBP), with relatively low free levels. Biological activity is conferred by 1 α-hydroxylation by the renal CY27B1 enzyme into 1,25-dihydroxy vitamin D [1,25$(OH)_2D_3$]. This step is tightly regulated by parathyroid hormone (PTH), and under negative feedback by calcium, phosphate, fibroblast growth factor 23 (FGF23), 1,25$(OH)_2D_3$ itself, and to a lesser extent, calcitonin, GH/IGF1 and leptin. Calcitriol is the ligand for the nuclear vitamin D receptor (VDR), and its high affinity for its receptor and much lower affinity for VDBP favors its selective nuclear uptake, whereas its precursor (s) remain in the blood stream (288). 25(OH)D has the longest half-life, approximately 2-3 weeks, and is the best nutritional index of vitamin D. This prohormone can be inactivated (CYP24A1) or activated (CYP27B1) systemically or locally for autocrine/paracrine actions across organ systems (288).

The biological effects of 1,25$(OH)_2D$ are mediated through genomic effects via its nuclear receptor VDR, by forming a dimer with retinoid X receptor RXR, and activating vitamin D response elements VDRE; and non-genomic effects via intra-cellular signaling pathways through putative plasma membrane receptors (288,289). 1,25$(OH)_2D$ increases calcium absorption from the intestine through the genomic actions of 1,25$(OH)_2D_3$, an active, energy dependent, transcellular pathway, mostly in the duodenum and jejunum (290), and by a passive paracellular pathway. Other classical target organs for calcitriol are the skeleton and parathyroid glands. Calcitriol also modulates several other organ systems through autocrine and paracrine pathways.

Altered Vitamin D Metabolism with Aging

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Aging affects vitamin D metabolism at the level of several key organ systems (291-293). The large capacity of the skin to produce vitamin D_3 decreases with aging, by an estimated 13% each decade (294,295). Older individuals, are however still able to increase their serum vitamin D_3 in response to exposure to UVB (294). The age-related decrease in calcium absorption is multifactorial. It includes reductions in serum 25(OH)D levels, impaired 1α-hydroxylation to calcitriol from declining renal function, gut resistance to the effect of vitamin D, and post-menopausal reductions in estrogen levels (291,292). Renal resistance to the PTH stimulating effect on 1α-hydroxylase (CYP27B1), and FGF23 suppression of this hydroxylase, are other possible factors. Animal studies have also shown enhanced degradation and decreased production of calcitriol and age-related decrements in VDR and in the renal calcium transporter TRPV5 (292). The contribution of an age-related decrease in VDR to impaired organ function (muscle, intestine) is, however, debatable (292).

Because of these age-related alterations in vitamin D metabolism, and lifestyle changes, vitamin D deficiency is highly prevalent in high-risk populations, namely older individuals. A plethora of systematic reviews (SRs) and meta-analyses (MAs) have scrutinized the impact of vitamin D on health and disease over the last 5 decades (286,296). A few of the most recent and rigorous SRs and trials that enroll more than 2,000 participants are highlighted herein.

Associations of Vitamin D and Major Health Outcomes in Older Individuals

Significant and consistent inverse associations have been reported by many SR/MAs between vitamin D and many major health outcomes.

Musculoskeletal: Vitamin D deficiency results in calcium malabsorption, secondary hyperparathyroidism, increased bone resorption, bone loss, and fractures (297). The evidence

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regarding vitamin D levels and muscle performance in older individuals, based on large cohort studies from the US and Europe, is contradictory (298). A dose-response meta-analysis of individuals aged 62-79 years indicated that serum 25(OH)D levels are directly associated with the risk of frailty (299).

Cardiovascular and cerebrovascular: The Copenhagen City Heart Study revealed a stepwise increase in the risk of ischemic heart disease, myocardial infarction, and early death, with decreasing 25(OH)D levels, in individuals with mean age of 57 years, 56% women, after a 29-year follow-up (300). A similar increase in the risk of ischemic stroke in the same cohort after 21 years was reported (301). Both findings were substantiated in MAs inclusive of several major cohorts from Europe and the US (300,301).

Cancer: the most consistent relationship between serum 25(OH)D levels and cancers was for colorectal cancer, while no association could be detected for breast and prostate cancer (302,303). The mean age in individual studies ranged between 30 and 76 years (302,303).

Cognition: A meta-analysis of 26 observational studies of participants who were mostly older than 65 years revealed that low vitamin D was associated with worse cognitive performance and cognitive decline. Cross-sectional studies revealed a stronger effect compared to longitudinal studies (304).

Mortality: In an individual patient meta-analysis of 26,916 study participants from eight independent prospective European cohort studies, median age 61.6 years, 58% females, with a 25(OH)D concentration of 21 ng/ml, and follow-up time of 10.5 years, 6,802 of whom died, serum 25(OH)D was associated with overall mortality and cardiovascular mortality, but not cancer mortality (305).

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Available therapies

Treatment of vitamin D deficiency could be with cholecalciferol (Vitamin D_3), the most widely used form, ergocalciferol (Vitamin D_2), or calcifediol (25-hydroxycholecalciferol, that is 25(OH)D) (Figure 9). Calcifediol may be faster and more potent than cholecalciferol, and D_3 superior to D_2, in terms of increasing serum 25(OH)D levels (306-308). These findings may be explained by differences in absorption, as well as assay differences in detecting D_2, by many platform assays (309,310). Serum 25(OH)D levels reached with equivalent doses of vitamin D, given as daily, weekly, or monthly to patients post hip fractures, were comparable (311). High doses given periodically may increase the risk of falls or fractures (312,313). Therapy with an active oral vitamin D sterol such as calcitriol is required in patients with stage 3 or 4 chronic kidney disease (314).

Clinical trial data on efficacy and safety in older individuals

The negative associations between vitamin D and major disease outcomes from 290 prospective cohort studies contrast with null findings from 172 randomized trials, therefore suggesting that vitamin D may be a marker of ill-health (286). Interestingly, centenarians have a high frequency of severe vitamin D deficiency, and yet live beyond their expected country longevity (315). We summarize results of most recent and rigorous MAs and of large RCTs (Table 4).

Fractures: In a recent umbrella review of MAs of vitamin D RCTs, the only consistent significant findings were for Ca/D, not vitamin D alone, in reducing the risk of hip fractures, by 16-39%, in 8/13 MAs, and of any fracture, by 5-26%, in 8/14 MAs (316). Sub-group analyses by residential status suggested a reduction in hip fractures in 2 MAs, and any fractures in 4 MAs, but only with Ca/D, and in institutionalized but not community-dwelling adults. These findings

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were driven by two trials in older institutionalized vitamin D deficient individuals (297,317). These findings are also consistent with results of earlier SRs demonstrating that older age and 25(OH)D levels < 20 ng/ml may indeed be predictors of fracture reduction in response to vitamin D (318-320). Vitamin D, without calcium, did not have a beneficial effect on risk of fractures (296,316,317). Table 4 highlights four large vitamin D trials, including the WHI, that did not show any beneficial effect of vitamin D on fracture reduction (312,321-323). Only 2 trials were conducted exclusively in older subjects, and serum 25OHD levels were essentially not measured (3 trials) or had a mean above 20 ng/ml (1 trial) (Table 4). Recent analyses from the VITAL study did not show any beneficial effect of vitamin D_3 on fracture reduction compared to placebo, in generally healthy midlife and older adults, who were not selected for vitamin D deficiency (324).

Falls: The USPSTF SR assessed the impact of various interventions to prevent falls in 7500 older subjects recruited to 7 heterogeneous trials of vitamin D formulations (with or without calcium), with overall null findings (325). A Cochrane SR evaluated the effectiveness of various interventions in 159 RCTs inclusive of 79,193 predominantly older, community dwelling women, and concluded that vitamin D supplements did not reduce falls in this population (326).

Cardiovascular Diseases: Two MAs, one of 11 trials inclusive of 50,252 individuals, and another of 10 trials mostly inclusive of 79,111 older women, did not reveal any effect of calcium or vitamin D supplementation on major cardiovascular events, myocardial infarction or stroke when compared to placebo (327,328). These findings were corroborated by individual vitamin D trials, VITAL and VIDa, that were not included in these MAs (Table 4) (329-331).

Cognition: A Cochrane MA examined the effect of nutritional interventions on cognitive function, including vitamin D3 (400 IU/day) and calcium compared to placebo, and

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demonstrated no effect of vitamin D3 and calcium supplements, on overall cognitive function, at a follow-up of up to 10 years (332).

Cancer: A Cochrane SR/MA of 18 RCTs of over 50,000 community-dwelling women aged 47 to 97 years revealed that vitamin D, administered for a weighted mean of six years, did not have any significant effect on cancer incidence (333). This is consistent with results from the three larger RCTs with cancer as the primary outcome (Table 4) (330,331,334).

Mortality: A SR review inclusive of 172 randomized trials, consisting mostly of women living in institutions, concluded that supplementation in older people (mainly women) with 20 μg vitamin D per day seemed to slightly reduce all-cause mortality (286). A Cochrane MA of 56 randomized trials, with 95,286 participants, mostly women older than 70 years, revealed that vitamin D, administered over 4 years decreased mortality with RR 0.97 (95% CI 0.94 to 0.99) (335). This effect was seen in 38 trials of vitamin D_3, RR 0.94 (95% CI 0.91 to 0.98), but not with other forms of vitamin D (335). These findings were not validated in two trials of vitamin D3 supplements in adults older than 60 (Table 4) (312,336). However, neither of these trials reported serum 25(OH)D levels at study entry.

Desirable 25(OH)D level, recommended daily allowance (RDA), and safety

The IOM defined the sufficient 25(OH)D level based on observational BMD data, as ≥ 20 ng/ml (283,337). It defined the RDA, the dose covering the requirements of 97.5% of the population to the desirable level, at 600 IU/day in adults, and 800 IU/day if above 70 years, and for calcium to range between 1000 and 1200 mg/day (337). The Endocrine Society defined a sufficient 25(OH)D level as ≥ 30 ng/ml (338). These numbers were derived from and for White individuals. Noteworthy, all pivotal phase 3 osteoporosis trials that led to drug approval by the

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FDA co-administered Ca/D in their treatment arms. Age, BMI, ethnicity, season, baseline 25(OH)D level, type of vitamin D, treatment duration and dose, predict achieved level (339). In older individuals, the increment was 1.3 ng/ml per 100 IU/day with a weighted mean dose of 606 IU, whereas it was 0.68 ng/ml per 100 IU/day with higher doses of 3,900 IU/day (339). Obese, dark-skinned individuals have lower serum 25(OH)D levels and may need higher doses to reach desirable levels established for white individuals (340,341). However, the optimal concentration in these populations remains unknown. Most trials used vitamin D_3. Ca/D_3 increased the risk of nephrolithiasis in 4 trials with 42,876 participants, findings reported in individual trials (339). Another MA inclusive of three trials, 710 subjects, showed that alfacalcidol and calcitriol increased the risk of hypercalcemia (335).

Key Points

- There is consistent evidence for a beneficial effect of Ca/D (mostly as D_3), but not vitamin D alone, in reducing the risk of hip fractures and any fractures. This evidence may be driven by findings in older, institutionalized participants, mostly women. There is no benefit of such supplementation in vitamin D replete individuals.
- There are data to support the efficacy of vitamin D in reducing mortality.
- Data for falls, cardiovascular diseases, cognition, and cancer are mostly null, and consistent with individual results from the latest large RCTs.

Gaps in the Research

The RCTs and MAs published to date do not have adequate power to evaluate important subgroups, specifically those at high risk of adverse outcomes. This includes subjects with low

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25(OH)D levels, men, the oldest old, ethnic groups other than White individuals, and those from low-income countries. In addition, the mean 25(OH)D in these RCTs is ≥ 20 ng/ml, many lack measurement of vitamin D levels during treatment, used non-standardized assays, and used adverse events data to identify fractures.

Implementation of individual patient data (IPD) MAs and meta-regressions combining data from the latest mega-trials, to investigate the efficacy of vitamin D on pre-specified primary outcomes in these modern trials, with subgroup analyses by gender, ethnicity, baseline 25(OH)D level and dose are needed. Major organizations and scientific journals should require that vitamin D assays be standardized, with results traceable to universal standards, as a condition for publication. This is necessary to enable meaningful guidance on desirable 25(OH)D levels.

TYPE 2 DIABETES

Natural history/observational data in older individuals

Diabetes in older adults is a growing public health concern with one-quarter of U.S. adults aged 65 years or older having diabetes and an additional half of older adults having prediabetes (342). Of all age categories, the prevalence of diabetes is highest in the older U.S. adult population. More than 130 million people worldwide aged 65-79 years and older have diabetes; the global prevalence of diabetes increases with age with the highest (24.0%) observed in those 75–79 years of age (343).

Impaired glucose tolerance is associated with aging (344). Data from the Baltimore Longitudinal Study of Aging demonstrate an age-related increase in progression rate from normal glucose status to impaired glucose tolerance (IGT) that is markedly greater than the progression rate from normal to impaired fasting glucose (IFG) after 20 years of follow-up

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(Figure 10)(345). These findings suggest that oral glucose tolerance testing, in particular, is important to consider when characterizing abnormal glucose status in older individuals. Using the hyperinsulinemic-euglycemic clamp, whole body insulin sensitivity is demonstrably reduced in older versus younger adults (346). This is largely due to age-associated increases in insulin resistance and, to some extent, due to decreased beta cell function with aging. Body composition changes that occur during aging, including increased central adiposity and progressive declines in skeletal muscle mass, may increase insulin resistance (347). In addition, decreased physical activity, mitochondrial dysfunction, inflammatory pathways, and hormonal changes with aging (i.e. lower testosterone levels in men) contribute to insulin resistance (344). Insulin secretory defects have also been described, which may impair the compensatory beta-cell response to increases in insulin resistance with aging and further increase the risk for development of prediabetes and diabetes (348).

While rates of diabetes-related microvascular and macrovascular complications have declined over time in the U.S. population overall, the absolute rates of end-stage renal disease, acute myocardial infarction, stroke, and cardiovascular disease remain higher in older compared to younger adults (349). However, diabetes in the older adult population is heterogeneous and includes individuals with both middle-age and older-onset diabetes (350), with the latter group accounting for up to a third of older adults with newly diagnosed diabetes. Older adults with middle-age onset diabetes had a greater burden of retinopathy but similar burden of macrovascular complications compared to older-onset diabetes (350). Thus, the age of diabetes onset may impact the burden of disease and presence of diabetic complications in the older patient with diabetes.

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While the aging process can be associated with alterations in glucose metabolism, including both progressive insulin resistance and relative beta cell dysfunction, abnormal glucose metabolism is not present in all older adults. Descriptions of otherwise healthy Italian centenarians without impaired glucose uptake suggest that insulin resistance is not a necessary component of the aging process (351). Instead, insulin resistance may accelerate the aging process. Older adults with diabetes represent a vulnerable population at higher risk for geriatric syndromes such as depression, cognitive dysfunction, chronic pain, injurious falls, urinary incontinence, and polypharmacy (352). Other adverse geriatric conditions that have been described to occur more frequently in persons with diabetes include functional and mobility limitations, disability, and frailty (353,354)—all of which can significantly impact quality-of-life in the older patient. Importantly, frail older women have dysregulated glucose and insulin dynamics with higher postchallenge glucose and insulin levels during a 75-gram oral glucose tolerance test compared to non-frail women (355). Studies of older adults with diabetes have demonstrated decreased muscle strength and mass, especially in the lower extremities, compared to those without diabetes (356). Further, greater levels of hyperglycemia are related to steeper declines in muscle strength with aging (357). Even among persons without diabetes, the presence of greater degrees of insulin resistance and/or impaired glucose tolerance is associated with decreased muscle mass and strength in older adults (354,358).

Available therapies

As with younger persons, there are many treatment options available for the older person with prediabetes or diabetes, though with unique management considerations for the older population (359). Lifestyle recommendations for older adults may be more appropriate for obese older

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individuals than those who are underweight. Importantly, the oldest age (>60 years at of age at baseline) group in the Diabetes Prevention Program (DPP) had the largest reduction in the incidence of diabetes with the lifestyle intervention compared to placebo (71% reduction) and better adherence to lifestyle programs compared to younger age groups, whereas metformin was less effective in the older group (360). The Medicare Diabetes Prevention Program was officially launched in 2018 and is a structured behavior change intervention that aims to prevent development of type 2 diabetes among Medicare beneficiaries who have prediabetes. Such evidence-based, structured programs in the community can effectively facilitate lifestyle changes among older adults with prediabetes.

All antihyperglycemic therapies currently available can be prescribed in the older patient with diabetes, but the choice of pharmacologic therapy may be affected by changes in renal and hepatic functions with aging, susceptibility to hypoglycemia, and the physical and neurocognitive abilities of the individual, in addition to the presence of other comorbidities and potential side effects of medications. Further, newer classes of agents (i.e. DPP4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors) have generally demonstrated similar safety and cardiovascular outcomes in older versus younger individuals in their respective cardiovascular outcome trials, as mandated by the FDA since 2008 for all newly-approved antihyperglycemic therapies to date (361).

Optimal glycemic control is often the focus for health care providers when caring for patients with diabetes. However, data have emerged challenging the benefits of tight glycemic control in older adults due to concerns of potentially increased mortality with aggressive glucose lowering (362). Overtreatment is unfortunately common in older adults with diabetes and may be associated with significant hypoglycemia (363). On the other hand, observational studies have

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linked high blood glucose levels with an increased risk of cognitive impairment – an important comorbidity in older adults (364,365). Preferential utilization of medications with lower risk of hypoglycemia, as well as liberalization, deintensification, or simplification of diabetes regimens may also be considered where appropriate (366).

Other clinical considerations include evaluation of the older patient's living situation and presence of social support networks that may contribute to diabetes management. Self-monitoring of blood glucose may be implemented, depending on the patient's cognitive ability, functional status, and risk of hypoglycemia. Methods for monitoring of blood glucose in older persons with diabetes are similar to those for younger adults, though some glucose meters may have features that are preferred for older individuals with visual impairments (i.e. easy to read screens for low vision or "talking" glucose meters). Use of the continuous glucose monitor's vibratory function, instead of sound alerts for glucose levels that are too high or low may be beneficial for older adults with hearing impairments. Insulin pens may also provide advantages over use of syringes in older adults with vision and/or fine motor impairment. Regular exercise as tolerated, including a combination of both aerobic and muscle strengthening exercises, and weight loss can improve insulin sensitivity in older adults with diabetes. Cardiovascular risk factor control (i.e. lowering blood pressure, treating dyslipidemia, smoking cessation) is recommended for most older adults with diabetes based on health status. Of note, older adults living in long-term skilled nursing facilities or nursing homes or with substantial cognitive impairment may not be able to self-administer medications and often have additional considerations for goals of care.

Glycemic Targets in Older Adults with Diabetes

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The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that randomization of adults with newly diagnosed type 2 diabetes to the intensive versus standard glycemic control arms (mean attained A1C 7% versus 7.9%, respectively) reduced the risk of microvascular complications over 10 years of study follow-up (367). However, most participants were middle-aged; individuals aged over 65 years were excluded from trial enrollment. After study termination, a continued reduction in microvascular complications and emergent risk reductions for myocardial infarction and death from any cause in long-term observation were found; the average age of participants who had data available in the final year of post-trial monitoring was 62 years (368). Further, randomized trials that included older adults at study enrollment (average age 60 years or older) such as the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), Action to Control Cardiovascular Risk in Diabetes (ACCORD), and Veterans Affairs Diabetes Trial (VADT) did not demonstrate significant cardiovascular or mortality benefits with more versus less aggressive glucose targets in older adults (362,369,370). Older adults are also at a higher risk of hypoglycemia compared to younger adults; thus, glycemic targets in older adults need to be individualized based on cognitive and functional status, life expectancy, and the presence of comorbidities (371,372).

Key Points

- Diabetes and altered glucose metabolism commonly occur with aging but are not universal in aging.
- Oral glucose tolerance testing may reveal abnormal glucose status in the older population not detected through fasting glucose or A1C measurement.

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- Diabetes in this population is heterogeneous, with middle-age onset versus older-onset individuals possibly representing groups at different risk for the development of complications.
- Both hyperglycemia and hypoglycemia are related to an increased risk of geriatric syndromes such as cognitive impairment, depression, falls, fractures, and functional disability in most observational studies.
- Other geriatric conditions such as muscle loss, mobility disability, and frailty are more prevalent in older patients with diabetes.
- Treatment of diabetes in older individuals includes lifestyle recommendations when appropriate and the use of pharmacologic therapies which account for the presence of comorbidities, especially renal and hepatic impairment, as well as the physical and cognitive abilities of the patient, while seeking to minimize hypoglycemia.
- There have been few studies investigating glycemic targets in older adults; in general, more versus less aggressive targets have not been found to reduce cardiovascular events or mortality in this population
- Clinical care needs to be individualized for the older adult with diabetes with simultaneous goals of management of hyperglycemia, prevention, and treatment of both macrovascular and microvascular complications of diabetes, avoidance of hypoglycemia, and preservation of quality-of-life.

Gaps in the Research

Well-designed randomized controlled trials are needed to study the effects of more versus less aggressive glycemic goals in an older adult population with diabetes, beyond traditional microvascular and macrovascular complications, particularly for patient-reported outcomes such

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as quality-of-life and functional status. More studies are needed to better understand the bidirectional relationship between age-related insulin resistance and geriatric conditions such as skeletal muscle loss, mobility disability, and frailty in older persons with diabetes or at high risk for diabetes. Clinical research focused on management strategies that can slow or prevent functional decline in older persons with diabetes can advance our knowledge in this population. Potential ethical considerations for deintensification of therapy in older adults require continued investigation.

Effective strategies for the prevention of type 2 diabetes in older adults need to be better understood. Tools that may be embedded in electronic health records to help clinicians estimate life expectancy and inform glycemic targets will be helpful in the future for clinical care. Ongoing disparities in the treatment of cardiovascular risk factors by race or ethnicity need to be addressed and effective population-level approaches to reduce these disparities in older adults should be investigated. Optimal methods of delivering diabetes education to older adults with diabetes, and in particular the role of technology, need to be better understood. The ideal frequency and cost-effectiveness of self-monitored blood glucose testing in older adults with diabetes, many of whom have multimorbidity and may be limited in their functional status, requires further investigation.

Laboratory-based studies investigating the pathophysiology of insulin resistance and beta cell dysfunction with aging are needed. While mitochondrial dysfunction has been linked to both insulin resistance and aging, and studies have reported cellular senescence in persons with diabetes, the underlying mechanisms need to be better understood to facilitate the development of novel targeted therapies.

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THE HYPOTHALAMIC-NEUROHYPOPHYSEAL-RENAL AXIS

Natural history/observational data in older individuals

Aging causes distinct changes that impact normal water homeostasis at multiple locations responsible for maintaining normal water balance. The net result of these changes is that older individuals experience a loss of homeostatic reserve, with subsequent increased susceptibility to pathologic and iatrogenic causes of disturbed water homeostasis (373).

A clear age-related deficit in the thirst response appears to arise from decreased sensitivity to osmotic stimulation. The sensation of thirst and the appropriate drinking response to thirst in response to increases in plasma osmolality is compromised in older individuals (Figure 11) (374). It is likely that this defect occurs, at least in part, through decreased activity of neural pathways that convey osmotic sensory input to the higher cortical centers where thirst is perceived, and from which the thirst-activated drinking responses emanate (375). Studies have suggested that this defect may be due to a higher osmotic set point, leading to a blunted thirst response in older individuals (376). Other studies have demonstrated that there is also a change in baroreceptor-mediated control of thirst in older individuals; plasma volume expansion in older individuals does not generate the normal suppression of thirst found in the young (377). Importantly, the loss of appropriate thirst responses to both osmotic and volume stimuli compromises the critical compensatory mechanisms responsible for the drive to replace lost body fluid, the major physiologic means of correcting a hyperosmolar state.

Impaired glomerular filtration rate (GFR) and resultant loss of maximal urinary concentrating ability appear a common, if not certain, consequence of aging (378,379). The importance of such defects is clear: inability to maximally conserve free water favors development of body water deficits. This can contribute to the development of hyperosmolality

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and hypovolemia. In combination with decreased thirst, this represents a likely cause of the observed increase in the frequency of hypernatremia in older individuals.

Somewhat paradoxically, a decrement in maximal water excretion also occurs in older individuals (380,381). In addition, older individuals are at a higher risk of developing diseases such as heart failure and cirrhosis that are associated with volume overload. So too, they are at risk for inadvertent iatrogenic overhydration from intravenous and enteral hydration therapy. The inability to appropriately excrete fluid loads therefore predisposes to the development of hypo-osmolar hyponatremia in older individuals.

The secretion and end-organ effects of arginine vasopressin (AVP) account for two of the most interesting, and perhaps least well understood aspects of water homeostasis in older individuals. Although a few exceptions exist, most agree that basal AVP secretion is at least maintained, and more likely increased, with normal aging (382). Furthermore, the AVP secretory response, i.e., the osmoreceptor sensitivity to osmolar stimuli, is also increased in normal aging (383). Thus, AVP secretion represents one of the few endocrine stimulatory responses that appears to increase rather than diminish with age. It is likely that enhanced secretion of AVP in older individuals and inability to maximally suppress AVP secretion during fluid intake (375), combined with an intrinsic inability to maximally excrete free water (380,381), increase the likelihood that hypo-osmolar hyponatremia will occur with increased frequency in older individuals.

Hyperosmolality and hypernatremia with aging

Hypernatremia necessarily reflects an increase in plasma osmolality. Cross-sectional studies of both hospitalized older patients and older residents of long-term care facilities show incidences

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of hypernatremia that vary between 0.3 and 8.9% (384,385). While hypernatremia is a common presenting diagnosis in older individuals, 60-80% of hypernatremia in older populations occurs after hospital admission (384). Similarly, up to 30% of older nursing home patients experience hypernatremia following hospital admission (386).

As hypernatremia develops, normal physiologic responses preserve water homeostasis through osmotically-stimulated secretion of AVP to promote renal water conservation along with accompanying potent stimulation of thirst to restore body water deficits (382). Although renal water conservation can forestall the development of severe hyperosmolality, only appropriate stimulation of thirst with subsequent increase in water ingestion can replace body fluid deficits thereby reversing hyperosmolality (387). This entire physiologic response is impaired with aging: older patients have a decreased thirst perception (374), and blunted ability to maximally concentrate their urine in response to AVP (386). An additional factor that can cause and/or exacerbate hypernatremia in hospitalized older patients is osmotic diuresis from a variety of causes: mobilization of urea following hydration for pre-renal azotemia, increased protein load from parenteral or enteral nutrition, and increased tissue catabolism (388). Thus, older individuals have a greatly increased susceptibility to a variety of situations that can induce hypernatremia and hyperosmolality, with the attendant increases in morbidity and mortality that accompany this disorder (389-391).

The clinical implications of hypernatremia in hospitalized older individuals are significant. In a retrospective study, outcomes in 162 hypernatremic older patients, representing 1.1% of all older patients admitted for acute hospital care to a community teaching hospital, were reviewed (389). All patients were at least 60 years of age with a serum [Na^+] >148 mmol/L. All-cause mortality in the hypernatremic patients was 42%, which was 7 times greater than age-

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matched normonatremic patients. Furthermore, 38% of the hypernatremic patients who survived to discharge had a significantly decreased ability to provide self-care (389). More recent analyses of large registry databases have confirmed the relation between hypernatremia and increased all-cause mortality, as well as mortality from coronary events and infections (391).

Although hypernatremia is associated with worse outcomes in all patients, it is particularly associated with increased mortality in patients in intensive care units, with adjusted odd ratios for mortality ranging from 2.03 with serum [Na^+] 146-150 mmol/l to 2.67 with serum [Na^+] >150 mmol/L.

Hypo-osmolality and hyponatremia with aging

Hyponatremia is the most common electrolyte disorder encountered in clinical practice (392). Hyponatremia becomes clinically significant when accompanied by plasma hypoosmolality. When hyponatremia is defined as a serum [Na^+] of <135 mmol/L, the inpatient incidence is reported to be between 15 and 22%. Studies that define hyponatremia as a serum [Na^+] <130 mmol/L demonstrate a lower, but still significant, incidence of 1-4% (393). The incidence of hyponatremia in older populations has been reported to vary widely between 0.2 and 29.8%, depending on the criteria used (385). While the true incidence of hyponatremia in older individuals is difficult to define given differing diagnostic criteria across studies, it is clear that the problem is common.

The most common causes of hyponatremia in older individuals are the syndrome of inappropriate antidiuresis (SIAD), drug therapy, and low solute intake. SIAD is the most common cause of hyponatremia in older populations. SIAD can be caused by many types of diseases and injuries common in older individuals, including central nervous system injury and

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degeneration, pulmonary diseases, paraneoplastic malignancy, nausea, and pain. An idiopathic form of SIAD associated with aging is also quite common. Several studies have demonstrated that SIAD accounts for approximately half (50-59%) of the hyponatremia observed in some older populations (394-396), and 26 to 60% of older patients with SIAD appear to have the idiopathic form of this disorder (394-396).

Many drugs can cause or exacerbate hyponatremia in older individuals. Some have been associated with SIAD, including many antipsychotic, antidepressant, and antiepileptic drugs (397). Risk factors for the development of hyponatremia with selective serotonin reuptake inhibitor (SSRI) antidepressants include older age, female gender, concomitant use of diuretics, low body weight, and lower baseline serum sodium concentration (398). However, the drug class most commonly implicated with causing hyponatremia in older patients is thiazide diuretics, which does not cause SIAD but rather secondary AVP secretion due to solute depletion and baroreceptor stimulation (399). The incidence of hyponatremia in patients treated with a thiazide diuretic in a primary care database was 13.7%, even higher than hypokalemia (8.5%), and the odds ratio for hyponatremia in patients >70 years was 3.87 compared to those under 70 (400). Although thiazide diuretics cause hyponatremia in part by solute depletion, this can also occur in the absence of diuretic therapy in individuals eating a low sodium and low protein diet, called the "tea and toast" syndrome (401).

Hyponatremia in older individuals is associated with multiple clinically significant outcomes including neurocognitive effects and falls (402,403), hospital readmission and need for long-term care (404), incidence of bone fractures (405), and osteoporosis (406). Hyponatremia is a strong independent predictor of mortality, reported to be as high as 60% in some series (384,407), in outpatient as well as inpatient studies (408). In a study of the association between

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asymptomatic hyponatremia and gait instability and attention deficits, a subset of 12 patients with hyponatremia secondary to SIAD with [Na+] in the range of 124-130 mmol/L demonstrated significant gait instability that normalized with correction of hyponatremia (409). The patients were asked to walk a tandem gait on a computerized platform that measured the center of gravity on the ball of their foot. Deviation from the straight line was measured as "Total Traveled Way". The hyponatremic patients wandered markedly off the tandem gait line in terms of their center of balance, but corrected significantly once their hyponatremia was corrected (Figure 12). When performing a series of attention tests, patients in the hyponatremic subset (mean [Na^+] = 128 mmol/L) had prolonged response latencies compared with a group of patients after acute alcohol intake (blood alcohol concentration 0.6 g/L). These impairments suggested a global decrease of attentional capabilities that is more pronounced in hyponatremic patients (409), which may contribute to gait instability and falls in older individuals.

Verbalis et al. explored the effect of hyponatremia and bone quality and demonstrated a link between chronic hyponatremia and metabolic bone loss (406). This study demonstrated that chronic hyponatremia causes a significant reduction of bone mass at the cellular level. Subsequent epidemiological analysis of 2.9 million patient records showed that chronic hyponatremia was associated with odds ratios of 3.99 for osteoporosis and 3.05 for fractures, thus confirming the translational significance of the animal studies (410). Hyponatremia-induced bone resorption and osteoporosis are unique in that they represent attempts of the body to preserve sodium homeostasis at the expense of bone structural integrity (411).

Available therapies

Hyperosmolality and hypernatremia

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Adequate hydration is the cornerstone of preventing hyperosmolality and hypernatremia in older patients. Aggressive hydration with hypotonic fluids (D5W or D5/0.5 NSS) is indicated to lower the serum [Na^+] to normal levels in the first 48 hours of hospital admission. A recent retrospective study of 449 patients hospitalized with a serum [Na^+] >155 mmol/L showed that there was no evidence that rapid correction of hypernatremia (>0.5 mmol/L/h) was associated with a higher risk for mortality, seizure, alteration of consciousness, and/or cerebral edema in critically ill adult patients with either admission or hospital-acquired hypernatremia (412).

Older patients with an established diagnosis of AVP-deficiency (cranial diabetes insipidus) should be treated with desmopressin as other adult patients (413). However, because desmopressin is largely metabolized through renal excretion, older individuals are more prone to hyponatremia with desmopressin therapy because of age-associated decreases in GFR.

Hypo-osmolality and hyponatremia

Treatment of hypoosmolality and hyponatremia in older individuals should follow the same guidelines as in younger individuals, particularly with regard to limits of daily correction of serum [Na^+] to avoid the osmotic demyelination syndrome. Fluid restriction is usually the first therapy employed, but has limited efficacy with mean increases in serum [Na+] in the range of 3-5 mmol/L in RCTs (414). If pharmacologic treatment is necessary, the choices include urea, furosemide in combination with NaCl tablets, demeclocycline, and the vasopressin receptor antagonists (393,415). Although each of these treatments can be effective in individual circumstances, the only therapies currently approved by regulatory agencies for treatment of hyponatremia are vasopressin receptor antagonists.

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Clinical trial data on efficacy and safety in older individuals

Hyperosmolality and hypernatremia

No recent clinical trials on the efficacy and safety of acute and chronic treatments for hypernatremia in older individuals have been published. However, several trials have been published on the use of desmopressin for treatment of nocturia (416). These have uniformly found that older individuals are at higher risk for the development of hyponatremia even with a single night-time low dose of desmopressin (417), which was particularly true of older females because of an enhanced response to desmopressin likely due to a sex difference in vasopressin V2 receptor expression in the kidneys (418,419).

Hypoosmolality and hyponatremia

Several randomized controlled clinical trials have been published on the efficacy and safety of vasopressin antagonist treatments for hyponatremia (420,421). However, none of these have focused specifically on older individuals even though many older individuals were included in the clinical trials.

Key Points

- Deficits in renal function, thirst, and AVP responses to osmotic and volume stimulation have been repeatedly demonstrated in the older population, increasing risk for disturbances of water homeostasis due to both intrinsic disease and iatrogenic causes.
- These disturbances have clinical implications in terms of neurocognitive effects, falls, hospital readmission and need for long-term care, incidence of osteoporosis and bone fractures, and both inpatient and outpatient mortality.

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- Effective treatments for hyponatremia are available, but recommended indications for treatment of chronic hyponatremia based on demonstrated improvements in clinical outcomes are lacking.

Gaps in the Research

Clinical trials evaluating the efficacy and safety of treatments of hypernatremia and hyponatremia in older individuals are required. Studies are needed to determine the etiology of "idiopathic" hyponatremia, particularly in older individuals. Additional studies of the effects of chronic hyponatremia on the brain, bone, and other organs, and evaluation of the reversibility of these effects with correction of hyponatremia, should be performed (422). Of special interest will be studies to assess whether more effective treatment of hyponatremia can reduce the incidence of falls and fractures in older patients, the use of health care resources for both inpatients and outpatients with hyponatremia, and the increased morbidity and mortality of patients with hyponatremia associated with multiple disease states. Consequently, the indications for treatment of water-retaining disorders in patients without symptomatic hyponatremia must await further studies specifically designed to assess the effects of treatment of hyponatremic patients on clinically relevant outcomes, as well as clinical experience that better delineates efficacies and potential toxicities of all treatments for hyponatremia.

Conclusions

This Scientific Statement provides a broad overview of the research conducted to date on the hormonal changes that occur in nine separate areas in endocrinology. It also describes specific unanswered questions where more research is needed. The potential for improved health through

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enhanced identification and prevention and/or treatment of the factors that impact hormonal changes with age is both exciting and substantial.

Existing knowledge of hormones and aging is largely based on results of observational and uncontrolled studies. Limitations of findings from these study designs include residual confounding, inability to make causal inferences, and the potential for reverse causality. Randomized, appropriately controlled clinical trials that are adequately powered to examine efficacy specifically in older individuals are required. Both the assessment of clinically meaningful outcomes and the risk of the older study population for these outcomes should be carefully considered in the study design. Possible outcomes include frailty, cognitive impairment, fractures, mood, patient-reported outcomes, cancer, and cardiovascular events, which should be measured using validated measures with adequate sensitivity to change.

Additional research is needed to improve understanding of the underlying mechanisms, methods of detection, and management of age-associated endocrine changes. Correlations between altered hormonal output and age-associated phenotypes have been identified in multiple hormonal axes, with decreased physical activity and increases in comorbid diseases contributing to the lower hormonal output in the growth hormone and testicular axes, for example. A thorough investigation of causal factors for age-related change is needed across all hormonal axes and endocrine diseases. In addition to these causal factors, the confounding effects of acute and chronic illness, multimorbidity, and polypharmacy on clinical manifestations, laboratory evaluation, diagnosis, monitoring, and prognosis need to be determined. Additional direct effects of aging on mitochondrial function, telomeres, and epigenetic effects, possibly mediated through inflammation and stress, require further examination across endocrine axes and organ-specific endocrine diseases. Use of humanized models in areas where animal models do not sufficiently

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replicate human physiology, such as for the adrenal gland, could improve understanding about human aging. Animal models should also replicate the time sequence of age-associated changes. Modern mass-spectrometry assays should be used in all research studies of steroid hormones in older individuals. The use of accurate and standardized hormone assays and harmonized reference ranges are needed in research and clinical practice in all endocrine axes.

Research is needed to provide the evidence base to support when hormonal therapeutics are appropriate and, equally importantly, when they are not. Hormones have been a frequent target for the anti-aging industry, despite evidence that supports harms of GH and sex steroids outweighing benefits in unselected populations of older individuals. RCTs in model organisms and humans should consider the timing, dose, duration, and target population for hormonal therapeutics, in populations with and without age-associated cognitive and functional decline. Hormone therapeutics should also consider the safety of treatments. Pharmacokinetics may be altered in older individuals, affecting the dosage. Whether these therapeutics should be delivered in combinations with each other, and with interventions such as exercise or senolytics that broadly target fundamental aging processes, should also be evaluated (423,424). Hormonal modulation may also benefit non-endocrine diseases, such as cancer, especially through therapeutics with target-specific actions. Approaches to preserve or revitalize gland function should also be developed and tested. Permeating this research should be inclusion of representative populations by gender (including transgender persons), race, ethnicity, and environmental exposures.

Additional Information

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Disclosures: RA has performed contracted research for Corcept Therapeutics and Sparrow Pharmaceuticals and has served as a consultant for Quest Diagnostics, Corcept Therapeutics, PhaseBio Pharmaceuticals, and Recordati Rare Diseases. GEHF is a member of the panel of experts convening at the International Conference on Controversies in Vitamin D in September 2023. Travel and housing to the meeting are covered by Abiogen for all participants, no honorarium received. MM has received honorarium and consulting fees from Amgen, honorarium from Alexion, and consulting fees from Myovant. CAS serves as a member of the Data and Safety Monitoring Board for Mithra Pharmaceuticals. MOT is a consultant for and has an equity position in Lumos Pharma Inc.

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ABBREVIATIONS

11βHSD1: 11β-hydroxysteroid dehydrogenase type 1

11OHA4: 11β-hydroxyandrostenedione

11KT: 11-ketotestosterone

1,25(OH)2D3: 1,25-dihydroxy vitamin D

25(OH)D: 25-hydroxyvitamin D

A1C: hemoglobin A1c

ACCORD: Action to Control Cardiovascular Risk in Diabetes

ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation

AFC: antral follicle count

AMH: antimullerian hormone

APCC: aldosterone-producing cell cluster

APM: adrenal-producing micronodules

AVP: arginine vasopressin

BMD: bone mineral density

Ca/D: calcium and vitamin D (Ca/D)

CEE: conjugated equine estrogens

CHD: coronary heart disease

CVD: cardiovascular disease

CYP11B2: aldosterone synthase

DHEA: dehydroepiandrosterone

DHEAS: dehydroepiandrosterone sulfate

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DPP: Diabetes Prevention Program

DPP4: dipeptidyl peptidase 4

ED: erectile dysfunction

FGF23: fibroblast growth factor 23

GFR: glomerular filtration rate

GHRH: growth hormone-releasing hormone

GLP-1: glucagon-like peptide 1

GnRH: gonadotrophin-releasing hormone

GSM: genitourinary syndrome of menopause

HHNS: hyperosmolar hyperglycemic nonketotic syndrome

HPA: hypothalamic-pituitary-adrenal

HRT: hormone replacement therapy

IFG: impaired fasting glucose

IGHD: isolated GH deficiency

IGT: impaired glucose tolerance

IOM: Institute of Medicine

IU: international units

LC-MS: liquid chromatography-mass spectrometry

MA: meta-analysis

MHT: menopausal hormone therapy

MPA: medroxyprogesterone acetate

NK3R: neurokinin3 receptor

OGTT: oral glucose tolerance test

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RCT: randomized controlled trial

RDA: recommended dietary allowance

rhGH: recombinant human GH

SERM: selective estrogen receptor modulator

SGLT2: sodium-glucose cotransporter-2

SIAD: syndrome of inappropriate antidiuresis

SR: systematic review

SSRI: selective serotonin reuptake inhibitor

SWAN: Study of Women's Health Across the Nation

UKPDS: United Kingdom Prospective Diabetes Study

USPSTF: United States Preventative Services Task Force

VADT: Veterans Affairs Diabetes Trial

Vitamin D_2: ergocalciferol

Vitamin D_3: cholecalciferol

VDBP: vitamin D binding protein

VDR: vitamin D receptor

VDRE: vitamin D response elements

ViDA: Vitamin D Assessment Study

VITAL: Vitamin D and Omega-3 Trial

VMS: vasomotor symptoms

VTE: venous thromboembolic disease

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3141 **Table 1.** Prospective longitudinal studies of the menopausal transition

Study Name	**N**	**Age at Baseline (y)**	**Dates**	**Duration (y)**
The Massachusetts Women's Health Study (99)	2570	45-55	1981-1986	5
The Melbourne Women's Midlife Health Project (100)	438	45-55	1996-2005	9
Penn Ovarian Aging Study (101)	436	35-47	1996-2014	18
The Seattle Midlife Women's Health Study (102)	508	35-55	1990-2013	23
University of Pittsburgh Healthy Women Study (103)	532	42-50	1983-2008	25
Study of Women's Health Across the Nation (104)	3302	40-55	1994-ongoing	28

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Table 2. Randomized primary prevention trials evaluating effects of menopausal hormone therapy on clinical and surrogate cardiovascular outcomes in healthy, recently postmenopausal women

Trial	MHT preparation and dose	N	Age (y)	Duration (y)	Outcomes
Clinical Outcomes					
WHI E-alone (117)	CEE 0.625 mg/d po	3313	50-59	7.2	Reduced MI, CAC, and revascularization
WHI E+P (117)	CEE 0.625 mg/d and MPA 2.5 mg/d po	5520	50-59	5.6	No benefit
DOPS (134)	17-B E2 2 mg/day and norethisterone acetate 1 mg 10 d/mo po	1006	45-58	10	Reduced composite serious adverse events: death, hospitalized MI, or CHF
Surrogate Outcomes					
KEEPS (135)	CEE 0.45 mg/d po or TD E2 50 mcg and progesterone 200 mg 12 d/mo po	727	42-58	4	No benefit cIMT or CAC
ELITE (136)	17-B E2 1 mg/d po and progesterone 45 mg vaginal gel 10 d/mo	596	55-64	5	Reduced cIMT early group No benefit CAC

MHT, menopausal hormone therapy; y, years; WHI, Women's Health Initiative; E-alone, estrogen alone trial; CEE, conjugated equine estrogens; po, oral; MI, myocardial infarction; CAC, coronary artery calcium; E+P, estrogen plus progestogen; MPA, medroxyprogesterone acetate; DOPS, Danish Osteoporosis Prevention Study (randomized, not blinded); E2, estradiol; CHF, congestive heart failure; KEEPS, Kronos Early Estrogen Prevention Study; TD, transdermal; cIMT, carotid intima-medial thickness; ELITE, Early versus Late Postmenopausal Treatment with Estradiol; Early < 6 years since menopause versus late $\geq$ 10 years since menopause

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Table 3. Drugs approved in United States for treating osteoporosis

Drug	Drug class	Dose, route of administration and dosing interval	Approved for treating men with osteoporosis	Fracture risk reduction (in primary analyses of registration trials)			Subgroup analysis of older study participants
				Vertebral fracture	Nonvertebral fracture	Hip fracture	
Raloxifene	EAA	60 mg po daily		✓			
Alendronate	bisphosphonate	70 mg po once weekly	✓	✓		✓	✓
Risedronate	bisphosphonate	35 mg po once weekly or 150 mg po once monthly	✓	✓	✓	✓	✓
Ibandronate	bisphosphonate	150 mg po once monthly or 3 mg IV every 3 months		✓			
Zoledronate	bisphosphonate	5 mg IV every year	✓	✓	✓	✓	✓
Denosumab	RANK ligand inhibitor	60 mg SQ once every 6 months	✓	✓	✓	✓	✓
Teriparatide	PTH receptor agonist	20 ugm SQ daily	✓	✓	✓		✓
Abaloparatide	PTH receptor agonist	80 ugm SQ daily		✓	✓		✓
Romosozumab	sclerostin inhibitor	210 mg SQ once monthly		✓	✓	✓	
Calcitonin-salmon	calcitonin	200 USP units by nasal spray daily		✓			

EAA, estrogen agonist/antagonist; IV, intravenous; PTH, parathyroid hormone; SQ, subcutaneous

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Table 4. Major placebo-controlled megatrials* of Vitamin D therapy and impact on major outcomes.

Trial	N	Baseline 25OHD ng/ml	Age years /Gender	Doses & Frequency	Median Duration	Primary outcomes
Trivedi, 2003 (312)	2,686	NA**	65-85; both	Monthly 100 000 IU oral vitamin D3	5 years	Vitamin D reduced any first fracture (RR=0.78 [0.61-0.99]) and first hip, wrist or forearm, or vertebral fracture (RR =0.67 [0.48 - 0.93]) and did not significantly reduce mortality (RR=0.88 [0.74-1.06]).
RECORD Grant, 2005 (321)	5,292	15.2±6.5 [n=60]	>70; both	Daily 800 IU oral vitamin D3	45 months	Vitamin D did not significantly reduce the incidence of new, low-trauma fractures (HR = 1.02 [0.88-1.19]).
WHI Jackson, 2006 (322)	36,282	NA**[1]	50-79; women	Daily 400 IU oral vitamin D3	7 years	Vitamin D with calcium did not significantly reduce hip fracture (HR=0.88 [0.72-1.08]), clinical spine fracture (HR=0.90 [0.74-1.10]), and total fractures (HR=0.96 [0.91-1.02]).
CAPS Lappe, 2017 (334)	2,303	32.8±10.5	≥ 55 women	Daily 2,000 IU oral vitamin D3	4 years	Vitamin D did not reduce cancer incidence (difference of 1.69% [-0.06-3.46%]).
ViDa Study Scragg, 2017 (329)	5,110	26.5±9	50-84; both	Monthly 100,000 IU oral vitamin D3	3.3 years	Vitamin D did not significantly reduce the primary endpoint of incident cardiovascular disease (HR = 1.02 [0.87-1.20]).
D2d Pittas, 2019 (425)	2,423	28.0±10.2	>30; both	Daily 4,000 IU oral vitamin D_3	2.5 years	Vitamin D did not significantly reduce the risk of diabetes among persons at high risk for type 2 diabetes (HR = 0.88 [0.75-1.04]).
VITAL Manson, 2019 (330)	25,871	30.8±10.0 [n=15,787]	Men ≥ 50 Women ≥ 55	Daily 2,000 IU oral vitamin D3	5.3 years	Vitamin D did not significantly reduce the co-primary endpoints of any invasive cancer incidence (HR = 0.96 [0.88-1.06]) or major cardiovascular events (HR = 0.97 [0.85-1.12]).
DO-HEALTH Bischoff-Ferrari, 2020 (323)	2,157	22.4±8.4	≥70; both	Daily 2,000 IU oral vitamin D3	3 years	Vitamin D did not significantly reduce incident non-vertebral fractures, cognitive decline or rate of infections, or improve physical performance or systolic and diastolic blood pressure.
D-Health Trial Neale, 2022 (336)	21,315	NA**[2]	≥ 60; both	Monthly 60,000 IU oral vitamin D3	5.7 years	Vitamin D did not significantly reduce mortality (HR = 1.04 [0.93-1.18]).
FIND Virtanen, 2022 (331)	2,495	29.9 ± 7.3 [n=551]	Men ≥ 60 Women ≥ 65	Daily 1,600 IU or 3,200 IU oral vitamin D3	5 years	Vitamin D did not significantly reduce the incidence of major cardiovascular events (HR = 0.90 [0.62-1.32]) or invasive cancer (HR = 1.04 [0.72-1.51]).

*Megatrials are trials that included ≥ 2,000 study subjects

** not available

**[1] Mean 25(OH)D in a nested case–control assessment was 18.42±9.1 ng/ml for participants who had hip fracture and 19.39±9.41 ng/ml among their controls (P = 0.17).

**[2] Predicted de-seasonalized serum 25(OH)D concentration [N (%)]: < 50 [2562 (24.0)] Vitamin D group; [2638 (24.8)] placebo group ≥50 [8099 (76.0)] Vitamin D group; [8011 (75.2)] placebo group

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FIGURES

Figure 1. Twenty-four-hour mean (±SEM) profiles of acyl-ghrelin (left axis) and GH (right axis, note log scale) in six healthy older adults (A) and eight healthy young men (B); young adults are included for comparison. Note different scales for old (upper panel) and young (lower panel) between groups. Arrows indicate standardized meals at 8:00 am, 1:00 pm, and 6:00 pm. Subjects were allowed to sleep after 9:00 pm. Also, note that in the older adults, GH was assayed in singlicates, which may contribute to some additional measurement variability in this group. Reproduced from Nass 2014.

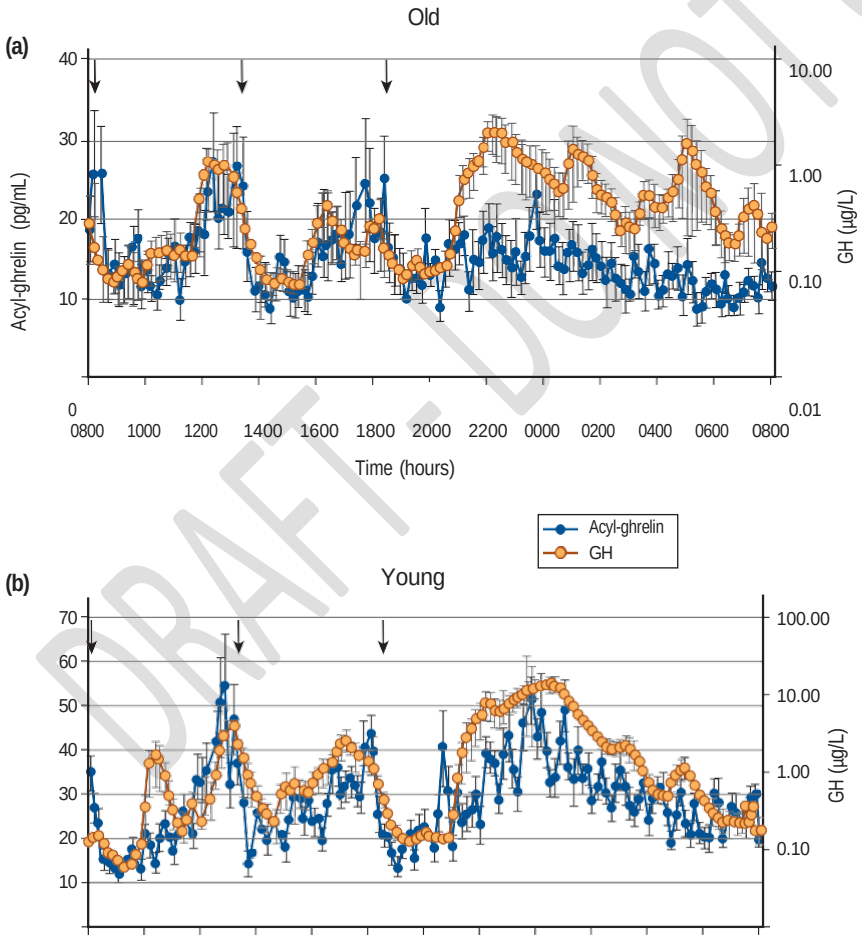

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Figure 2. The hypothalamus integrates signals from the environment and higher brain centers to release corticotropin-releasing hormone (CRH), which stimulates pituitary production of adrenocorticotropin (ACTH). ACTH drives production of cortisol, as well as neurosteroids and their precursors, 11β-hydroxyandrostenedione (11OHA4), and dehydroepiandrosterone and its sulfate (DHEA[S]). Cortisol provides negative feedback (red lines) to the hypothalamus and pituitary, not just to cortisol but also to all other ACTH-stimulated steroids. DHEA and DHEAS can be metabolized to the androgens testosterone and dihydrotestosterone (T, DHT), whereas 11OHA4 is metabolized to the androgens 11-ketotestosterone (11KT) and 11-ketodihydrotestosterone (11KDHT). Cortisol and neurosteroids exert important actions on the brain that control mood, memory, and cognition. Independently, aldosterone is produced under the renin-angiotensin 2 (AT2) system, or autonomously such as from aldosterone-producing micronodules (APMs). Aldosterone regulates sodium balance, and aldosterone excess causes hypertension and cardiovascular (CV) disease. In aging, cortisol negative feedback is attenuated, and while DHEAS production falls, Cortisol and 11OHA4 synthesis is preserved. APMs increase with age, and the potential deleterious effects of cortisol and aldosterone excess are magnified with aging.

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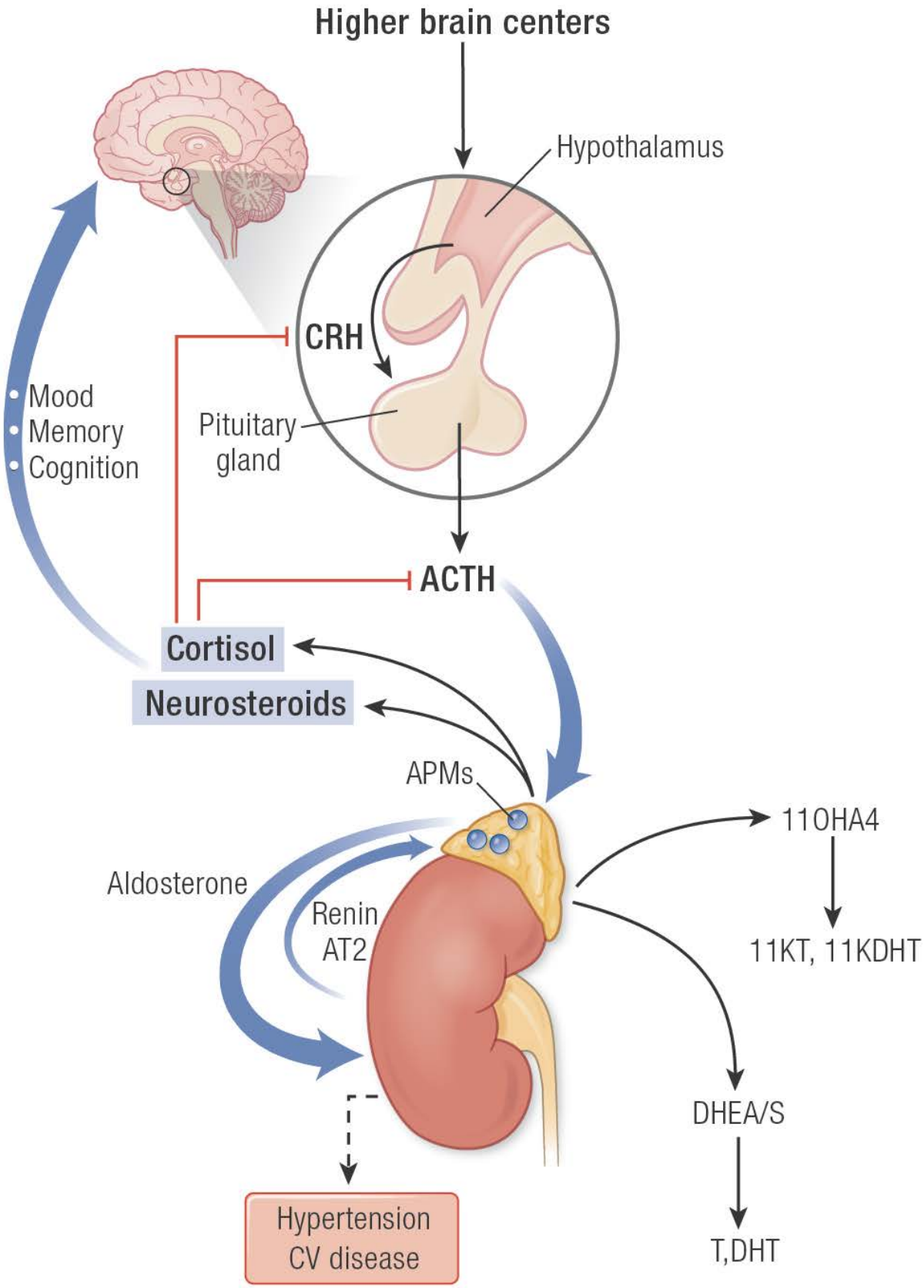
Higher brain centers
Hypothalamus
CRH
Pituitary gland
Mood
Memory
Cognition
ACTH
Cortisol
Neurosteroids
APMs
Aldosterone
Renin
AT2
11OHA4
11KT, 11KDHT
DHEA/S
T,DHT
Hypertension
CV disease

Figure 3. The Stages of Reproductive Aging Workshop + 10 staging system for reproductive aging in women. FMP, final menstrual period; FSH, follicle stimulating hormone; AMH, antimullerian hormone. Reproduced from Harlow, 2012.

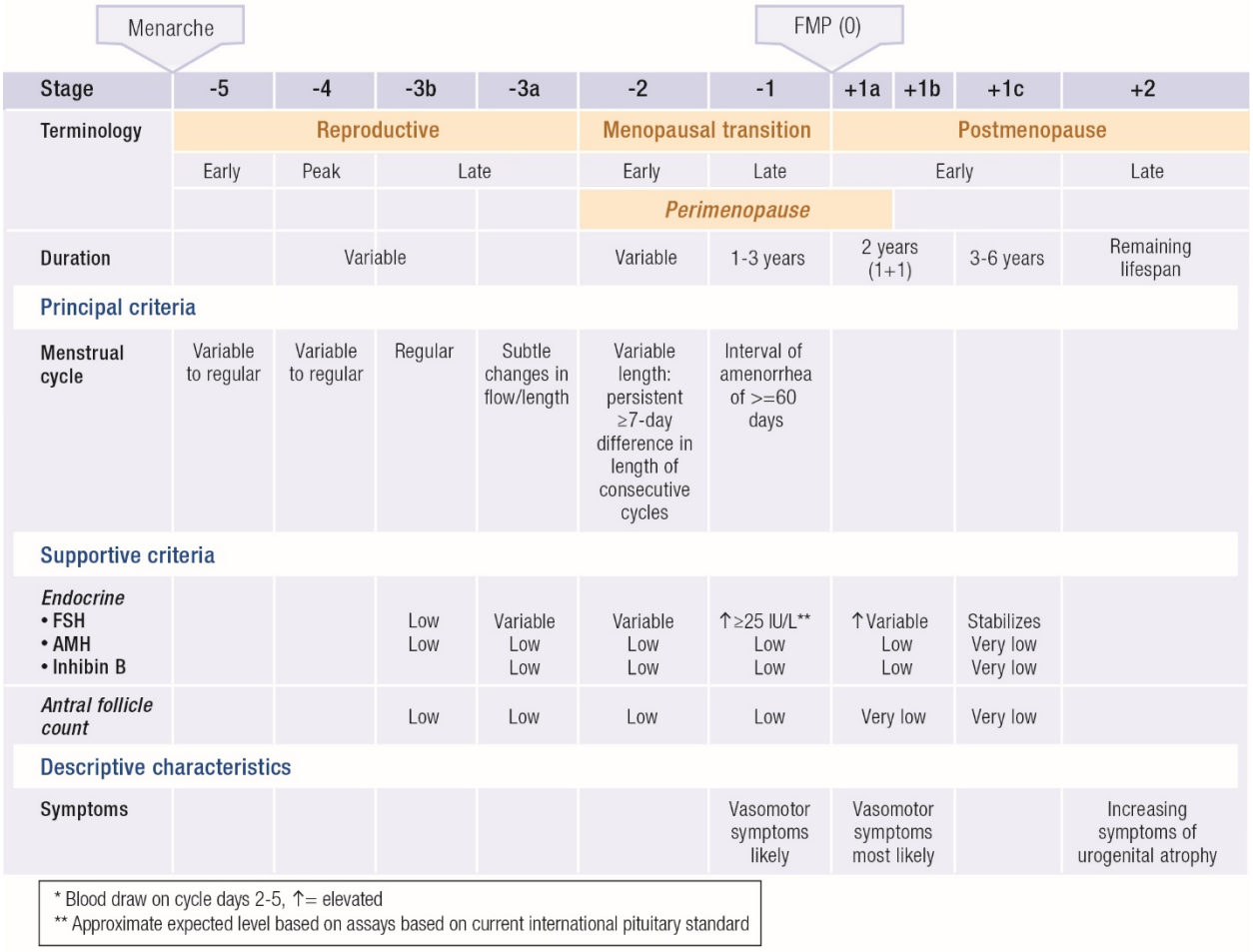

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Figure 4. Overlap of the 3 dimensions of men's reproductive health – fertility, sexuality and androgenization – with general health. There is overlap of all dimensions but greatest for androgenization.

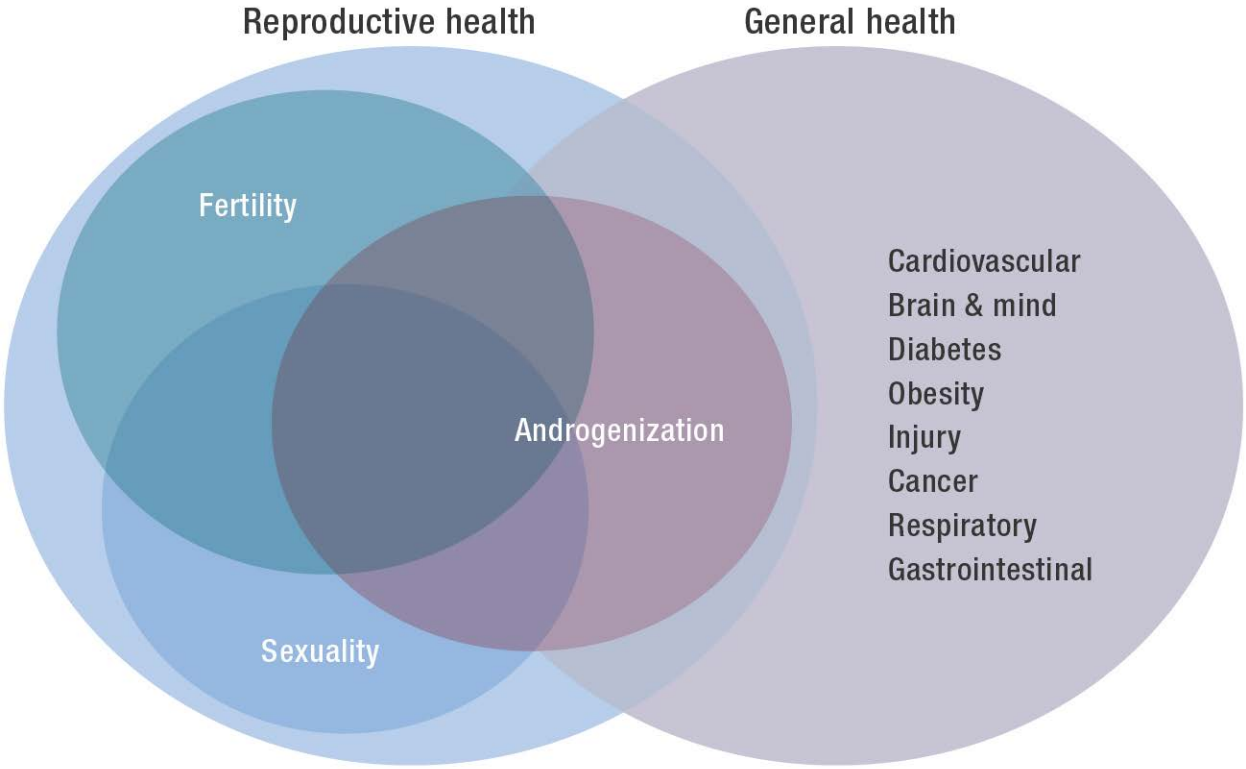

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Figure 5. Age-specific profile of serum testosterone of serum testosterone in men. Left panel comprises 58,374 consecutive serum samples over 7 years measured in a single immunoassay and pathology laboratory with population centiles deduced by smoothed GAMLSS methodology. Right panel comprises 10,900 serum samples pooled from three population-based Australian studies showing the raw scatter (black dots), height and weight-adjusted scatter (red dots) and the smoothed median (green solid line) deduced by GAMLSS methodology. Reproduced from Handelsman, Ann Clin Biochem, 2015 and Handelsman, Eur J Endo, 2015.

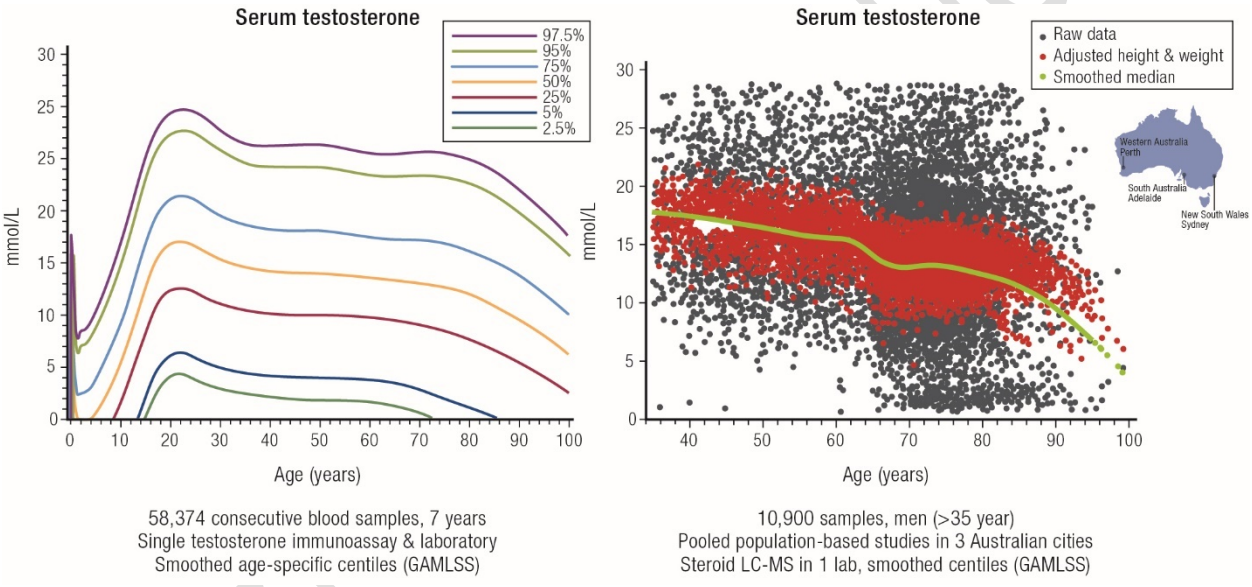

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Figure 6. Distribution of TSH concentrations in a reference population from the National Health and Nutrition Examination Survey. Reproduced from Surks, 2007.

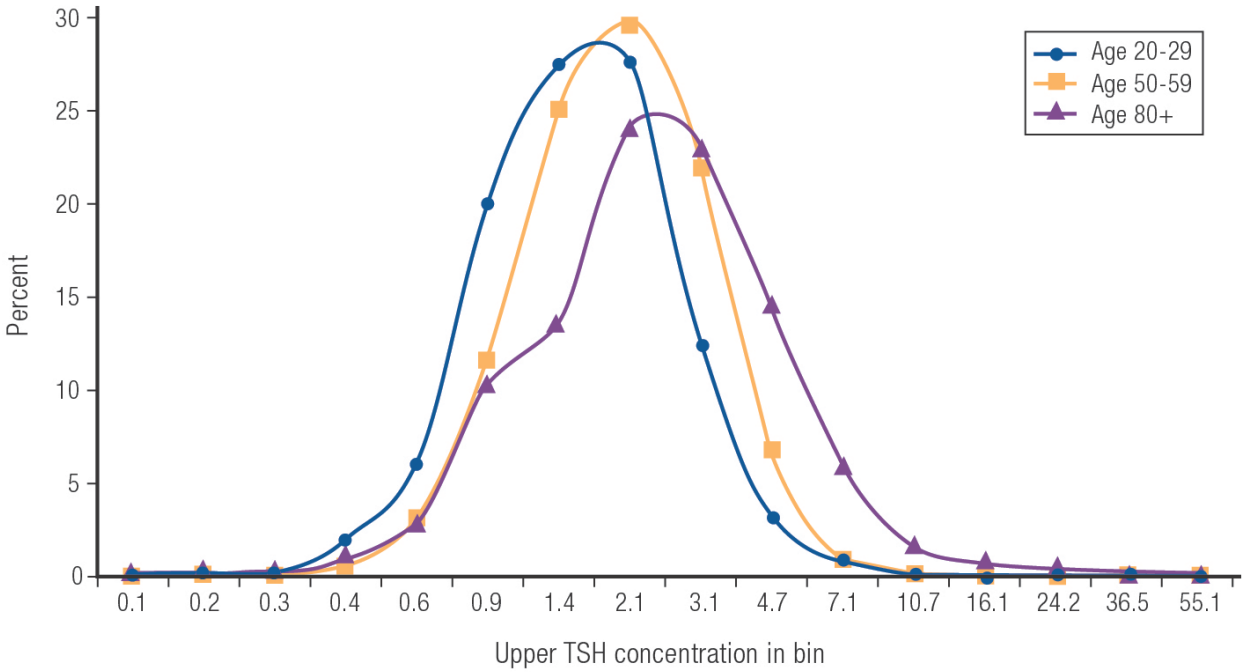

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Figure 7. Prevalence of hip, spine and all fractures in women by decade of age in the DUBBO Study. The combinaton of hip and spine fractures comprised 24% of all fractures between ages 60-69, 44% between ages 70-79 years and 67% in those 80 years and older. Adapted from Center, 1999.

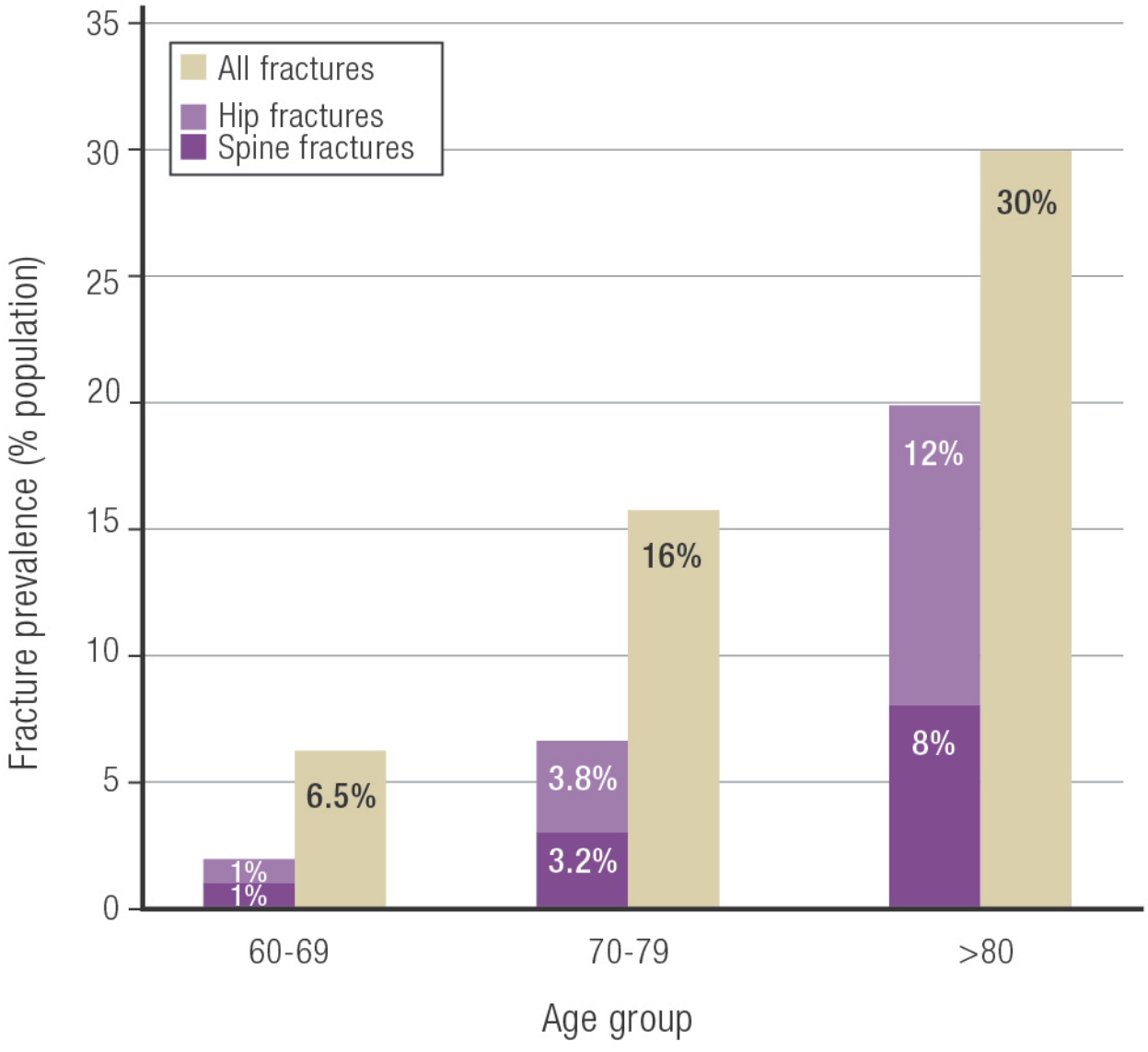

Figure 8. Relationship between age and hip fracture risk in women with femoral neck T-score values of < -1 and < -2.5. Adapted from Kanis, 2001.

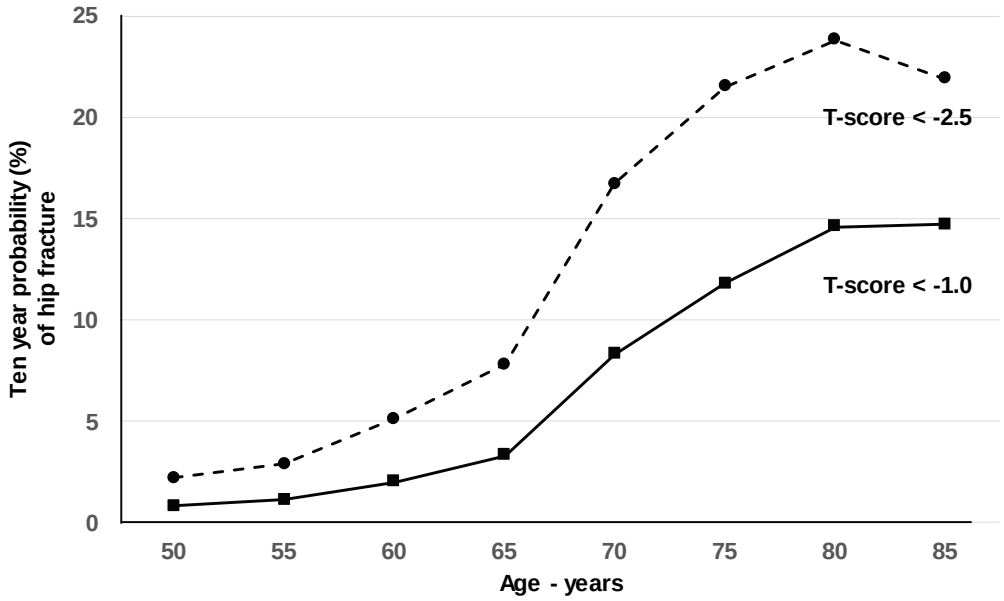

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Figure 9. Vitamin D metabolism.

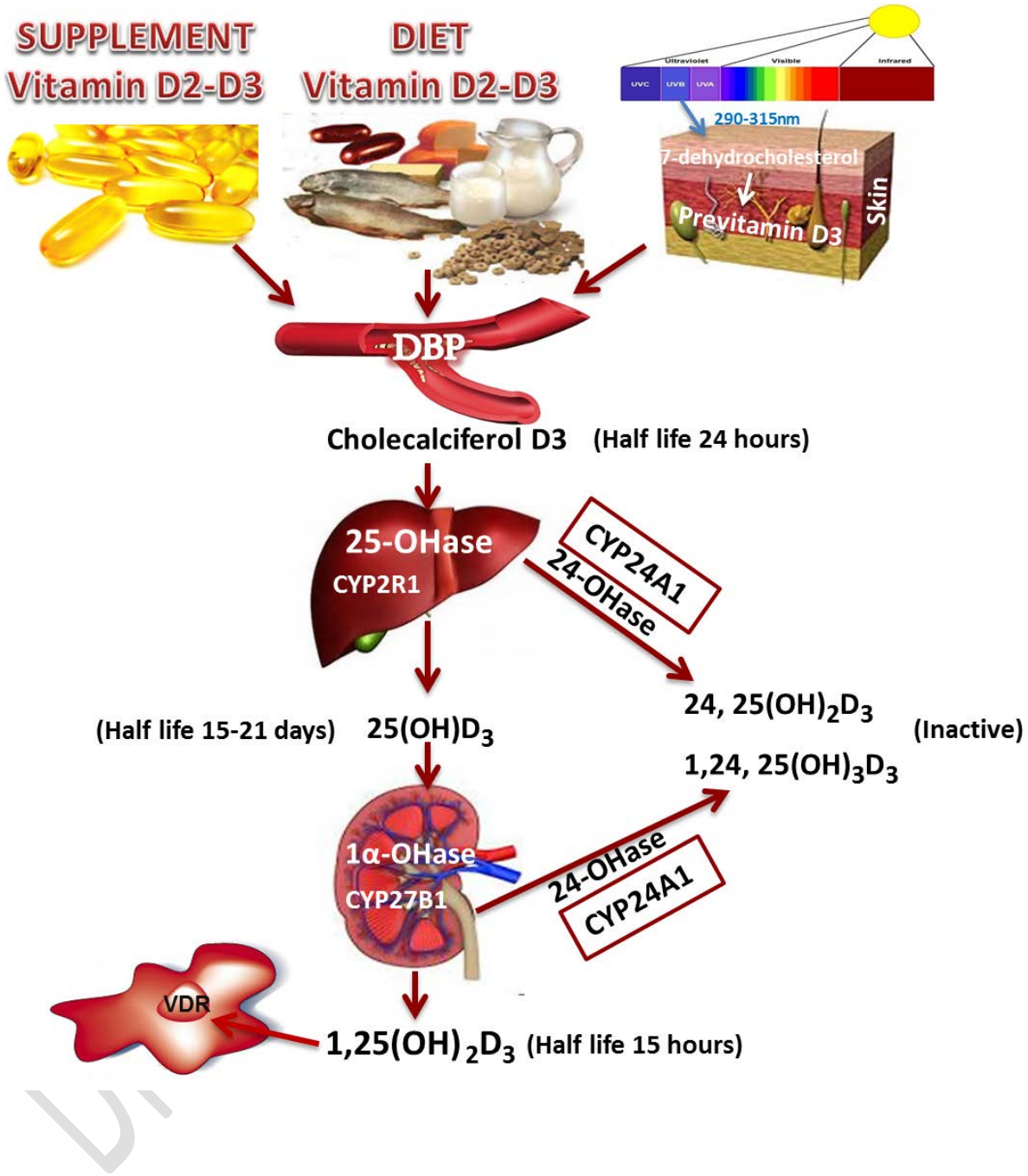

Figure 10. Natural history of progression from normal glucose tolerance to type 2 diabetes with aging, Baltimore Longitudinal Study of Aging. Reproduced from Meigs, 2003.

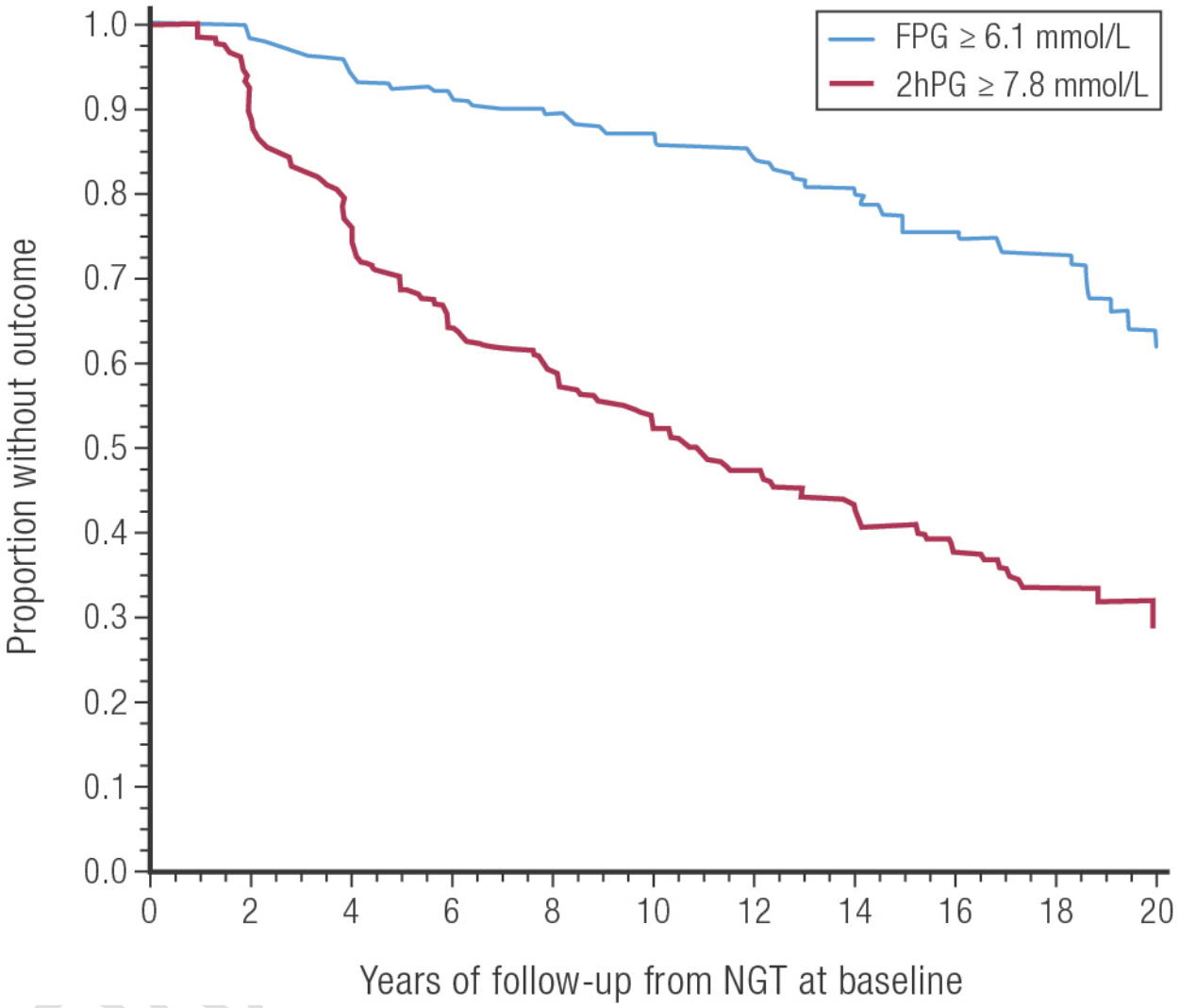

Figure 11. Plasma sodium concentration (Na^+]) and total water intake in healthy older and younger subjects following 24 hours of dehydration. Baseline sodium concentrations before dehydration (Pre) and after dehydration (Post) are shown. Free access to water was allowed for 60 minutes following dehydration starting at time = 0 minutes. Cumulative water intake during the free drinking period by young and old subjects is depicted in the bar graph. Despite a greater initial increase in serum [Na^+], older participants drank significantly less water, resulting in lesser correction of the elevated serum [Na^+]. Reproduced from Phillips, 1993 with permission.

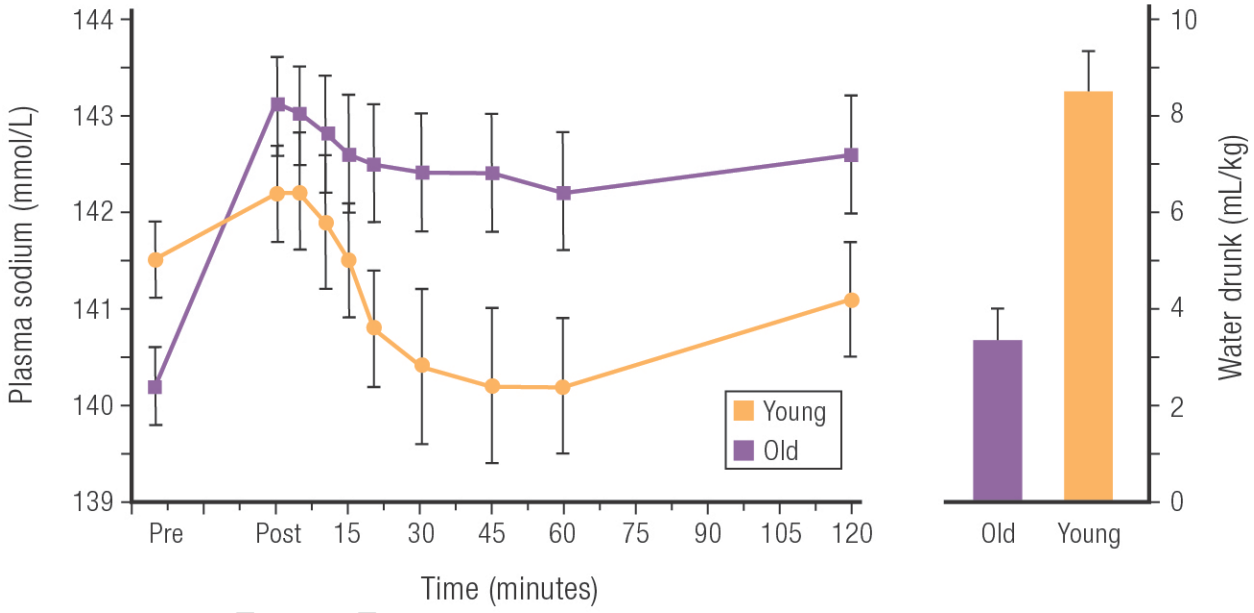

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Figure 12. Total traveled way measured by the center of pressure during a dynamic walking test consisting of 3 stereotyped steps “in tandem,” eyes open, in 3 patients (A–C) with mild asymptomatic hyponatremia before (left) and after (right) correction. Patients are walking from right to left. Markedly irregular paths of the center of pressure were observed in the hyponatremia condition (arrows). Reproduced from Renneboog, 2006 with permission.