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PHYSIOLOGY AND DISEASES OF THE HYPOTHALAMIC-PITUITARY AXIS IN THE ELDERLY

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ABSTRACT

Aging is characterized by changes in virtually all biological systems, and the hypothalamic-pituitary axis is no exception. With aging, the secretory patterns of the hormones produced by the hypothalamic–pituitary axis gradually shift with the axis becoming less responsive to feedback from end hormones. This is accompanied by physical and cognitive changes that coincide with decreases of main anabolic hormones, such as growth hormone and sex steroids. In addition, aging-induced effects are difficult to disentangle from the influence of other factors that are more prevalent in the elderly, such as chronic diseases, inflammation, and poor nutrition; all of which can affect the integrity of the hypothalamic-pituitary axis. Aging is also associated with an increased detection of pituitary tumors found incidentally in magnetic resonance imaging studies performed in older individuals, most of which are slow growing, non-functioning micro-incidentalomas. Clinical manifestations are generally observed with macroadenoma mass effects, symptoms of hormonal deficiency, and rarely hormonal excess. Transsphenoidal surgery, especially when performed in the hands of an experienced neurosurgeon, is generally safe and effective in elderly patients with pituitary tumors, although there are some increased comorbidity and anesthetic risk. Hormone replacement therapies to treat hypopituitarism should be individualized to account for physiological changes of aging and associated pathologies, and hormonal intervention to reverse aging is not recommended due to lack of clinical benefits and potential adverse effects. Managing functional pituitary tumors, especially Cushing disease and acromegaly, in the elderly are often more challenging than in younger patients due to many potential pitfalls in terms of symptom recognition, diagnostic workup and reliability of hormone testing, greater burden of concomitant comorbidities, and limited data on treatment outcomes in this population.

INTRODUCTION

Healthy aging of the hypothalamic-pituitary axis is a multifactorial process with considerable inter-

individual variability. As individuals age, it is inevitable that physical and cognitive functions decline (1). However, the extent to which age-related changes in hormonal regulation and the rising prevalence of hypothalamic-pituitary hormone disorders that contribute to the decline in physical and cognitive function remains incompletely understood. This aspect of geriatric medicine will inevitably expand in importance in the coming years as the number of older individuals increases due to increased general lifespan. Aging of the adenohypophysis is associated with a reduction in size, increased fibrosis, altered vascularization, and a higher incidence of microadenomas; all of which can affect its hormonal secretory patterns (2). These alterations are further compounded by reduced tissue sensitivity to hormonal action and changes to the circadian rhythm associated with aging (3). Collectively, these age-related endocrine changes are characterized by progressive reductions in the synthesis and/or peripheral action of anabolic hormones, such as growth hormone (GH) and gonadal hormones, and the increase in the synthesis of hormones with catabolic properties, such as cortisol (Figure 1) (4). Notably, these hormonal shifts are part of the normal aging process and may not necessarily indicate pathological conditions (Table 1). Compared to younger individuals, healthy older adults typically exhibit altered body composition, marked by decreased skeletal muscle mass and increased adipose tissue, as well as reduced bone mineral density and muscle strength (1). Despite these findings, multiple studies have shown that hormonal supplementation aimed at restoring "youthful" hormone levels in the elderly does not offer proven clinical benefits and may, in fact, pose inherent risks and cause unwanted side-effects (5). Therefore, supplemental hormonal therapy in the elderly should only be reserved for treating specific diseases rather than attempting to counteract the natural aging process.

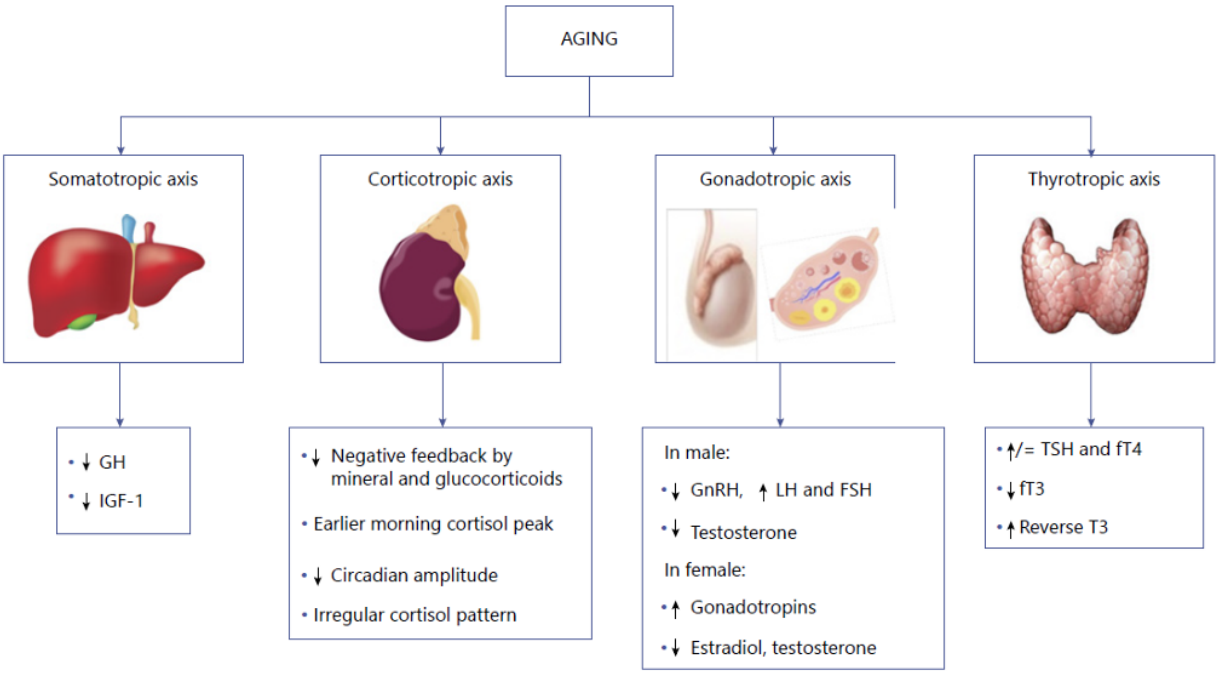

Figure 1. Summary of changes of hormones of the hypothalamic-pituitary axis associated with aging. Reproduced with permission from Caputo *et al.* 2022 (4).

Table 1. Aging and Age-Related Changes in Hypothalamic-Pituitary Axis Function: Similarities and Differences					
Signs/symptoms	**Advancing age**	**GH levels**	**Cortisol levels**	**Thyroid hormone levels**	**Sex hormone levels**
Fatigue	↑	↓	↑↓	↓	↓
Sleep disturbances	↑	↓	↑↓	↓	↓*
Muscle loss and sarcopenia	↑	↓	↑↓	↓	↓
Bone loss	↑	↓	↑	↔	↓*
Body fat increase	↑	↓	↑	↓	↓
Glucose intolerance	↑	↓	↑	↓	↓
Dry skin and hair loss	↑	↓	↑	↓	↓
Hypertension	↑	↓	↑	↓	↓
Dyslipidemia	↑	↓	↑	↓	↓

*Especially in women during peri- and post-menopause.

PHYSIOLOGICAL EFFECTS OF AGING ON THE HYPOTHALAMIC-PITUITARY AXIS

Growth Hormone and Insulin-Like Growth Factor-I Axis

Growth hormone secretion occurs physiologically in a pulsatile fashion and in a circadian rhythm with maximal releases in the latter half of the night (6). Peak GH secretion occurs around mid-puberty (7), and declines after the age of 30 by approximately 14% per decade (8). The reduction in GH secretion mainly results from marked reductions in GH pulse amplitude, with only very little change in pulse frequency (9). By the eighth decade, GH levels are so low that they are comparable to those of GH-deficient young adults (10). Pulse frequency is similar across age, with approximately 18 secretory episodes of GH per 24 hours in children, younger adults, and older individuals (11). The decline in GH with aging is primarily seen in the amplitude of the secretory episodes, although interpulse levels also decline (Figure 2) (12). The mechanism that underpins the decline in GH secretion is incompletely understood but has been postulated to be based in the hypothalamus, as somatotroph cells tend to maintain normal secretory responses to GH-releasing stimuli (13). Circulating IGF-I levels, the main mediator for the trophic effects of GH primarily generated from the liver, also decline with age by > 50% from the 3rd to the 9th decade (14) as a consequence of decreased GH secretion (Figure 3). Notably, the action of GH on the liver to generate IGF-I is preserved in aging (15). The decline in GH and IGF-I is further accentuated by metabolic changes and common comorbidities in the elderly, such as diabetes mellitus (DM), chronic kidney disease, chronic liver disease, malnutrition, and sarcopenia (16-20), which independently also contribute to reduce IGF-I levels. Furthermore, obesity is more prevalent in individuals over 60 years, which is associated with lower IGF-I levels (21, 22). Tausendfreund *et al.* (23) recently provided valuable insights into the significant variability of IGF-I levels in the elderly. Retrospectively reviewing 246 blood tests from 89 multimorbid elderly outpatients with a mean age of 83 not on GH treatment, these investigators found a mean intra-individual coefficient of variation for IGF-I of 14.7% and high reference change values (increase 44.3% and decrease 30.7%) indicating that IGF-I levels in the elderly can change substantially within an individual over time. Thus, these factors contribute to a high degree of variability in IGF-I levels in the elderly that

does not always reflect GH activity, making the evaluation of disorders of GH/IGF-I axis particularly challenging.

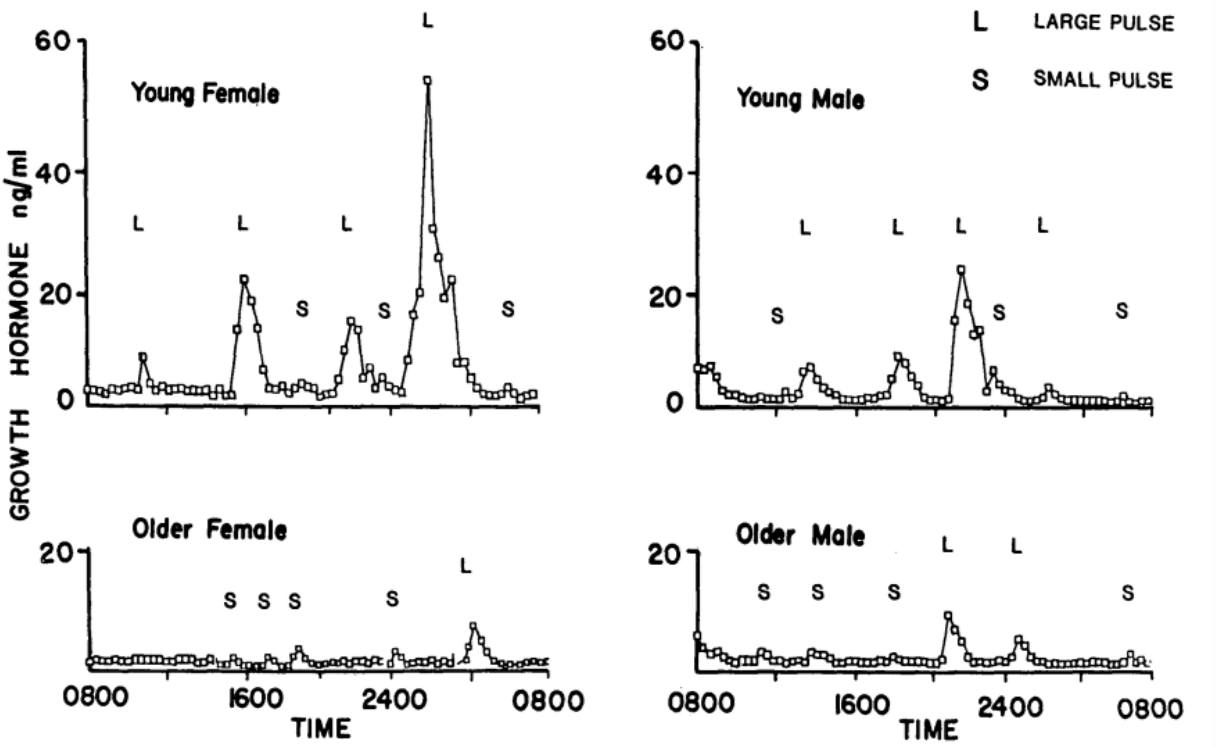

Figure 2. Differences in patterns of GH secretion in younger and older women and men. There is a marked age-related decline in GH secretion in both sexes and a loss of the night-time enhancement of GH secretion seen during deep (slow wave) sleep. This decrease is primarily due to a reduction in GH pulse amplitude, with little change in pulse frequency. L = large GH pulses, S = small GH pulses. Reproduced with permission from Ho *et al.* 1987 (9).

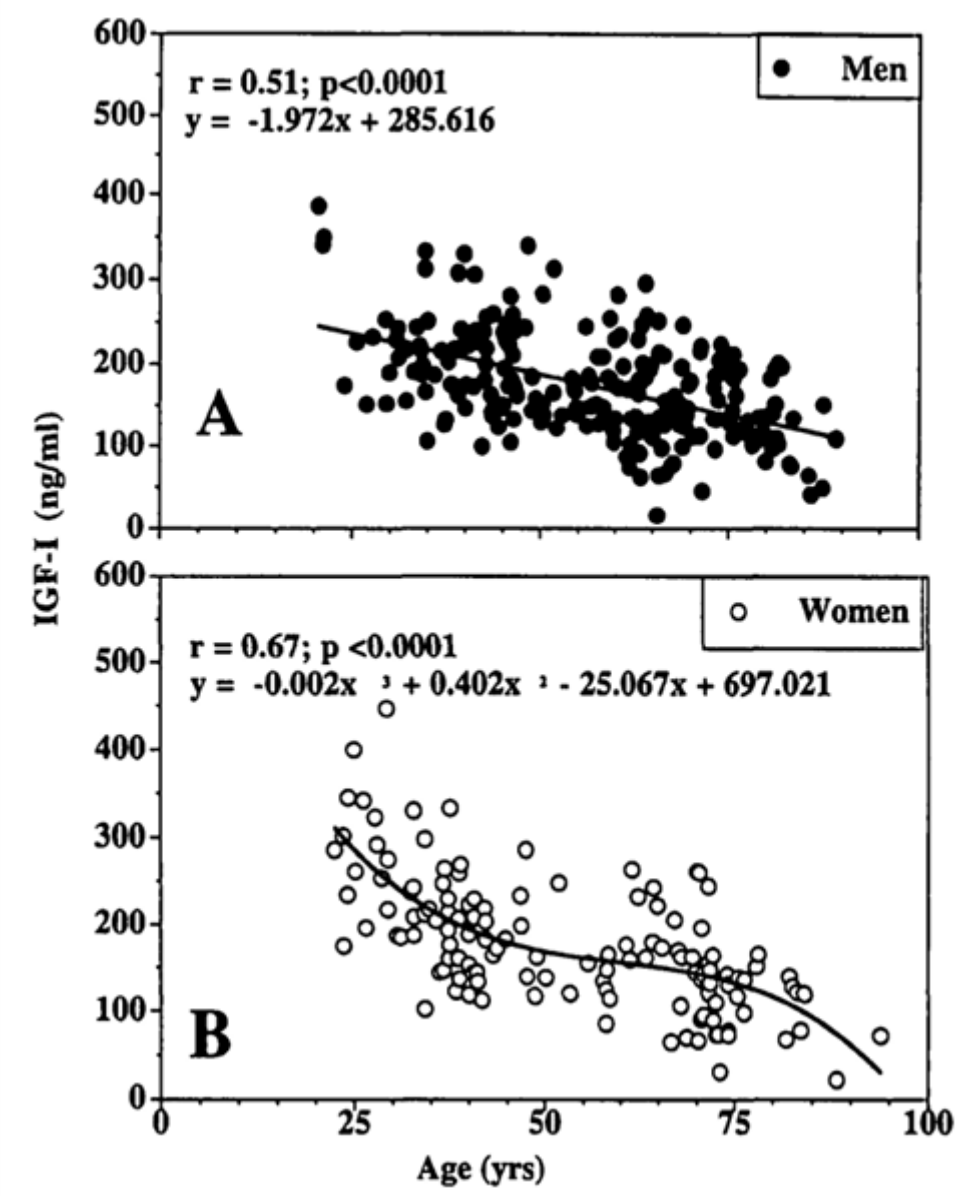

Figure 3. Serum IGF-I changes with age in the Baltimore Longitudinal Study of Aging. Lines represent best fit equations, for men a first order function and for women a curvilinear third order expression. IGF-I decreases significantly with age in both sexes Reproduced with permission from O'Connor *et al*. (14).

Between genders, peak GH levels are higher in premenopausal women than in men due to reduced hepatic GH receptor sensitivity (9, 24); therefore higher GH secretion is required to maintain normal circulating IGF-I levels. In women, if oral estrogen is ingested, hepatic IGF-I synthesis is blunted resulting in increases in GH secretion through reduced feedback inhibition (25). When oral estrogen is discontinued or switched to the transdermal route, IGF-I levels increase and GH secretion is unchanged, indicating that the route of administration is the major determinant of the effects of exogenous estrogens on hepatic GH receptor sensitivity (26). After menopause, GH levels decline and become comparable with men of similar age due to further estrogen reductions in this phase of life (9).

In healthy older men, previous studies have reported that co-administration of GH and testosterone increased muscle IGF-I gene expression without altering body composition or muscle strength (27) but did result in significant changes in lean body mass and fat mass (Figure 4) (28, 33), suggesting that testosterone acts additively with GH in reversing this GH secretion decline. By contrast, in healthy older women, lean body mass increased and fat mass decreased after administration of GH, similarly in the absence and presence of estrogen plus progestin (33). Other mechanisms that could explain the age-related decrease in GH secretion include decreased GHRH or ghrelin secretion, increased somatostatin inhibition, increased sensitivity of somatotrophs to negative feedback inhibition by IGF-I, and decreased pituitary responsiveness to GHRH and hypothalamic-pituitary responsiveness to ghrelin (29). The aging pituitary is also less responsive to exercise, sleep, and fasting (30). Furthermore, decreased GH secretion in the elderly could be related to changes in lifestyle, including decreased physical fitness and energy intake, and decline in sleep quality (30). Therefore, it can be surmised that the age-related decline in GH secretion is multifactorial in etiology and is caused by changes at and above the level of the pituitary.

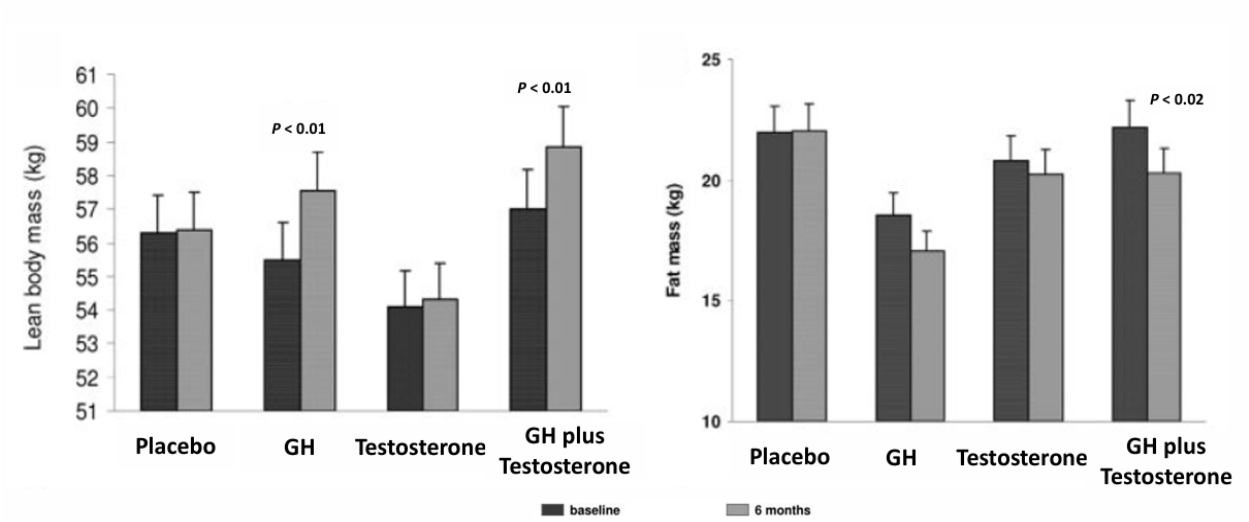

Figure 4. Co-administration of GH with testosterone is more effective in improving body composition than with either GH or testosterone alone. Reproduced with permission from Giannoulis *et al.* (28).

Alterations in body composition associated with normal aging include reductions in bone mineral density and in muscle mass and strength, increased body fat and adverse changes in lipid profiles (31, 32). This decline in GH secretion is initially clinically silent, but over time may contribute to the development of sarcopenic obesity and frailty (Figure 5). Studies investigating short-term GH supplementation in healthy elderly individuals have shown modest improvements in body composition, including reduced visceral fat, increased lean body mass, and lower LDL-cholesterol levels. However, these benefits did not extend to other clinical outcomes such as bone mineral density, balance, strength, coordination, or endurance. Conversely, GH-treated individuals experienced a higher incidence of adverse effects, including soft tissue edema, arthralgias, carpal tunnel syndrome, and glucose intolerance (27, 33, 34). Thus, the long-term safety of GH supplementation remains uncertain, particularly regarding the risk of cancer development in individuals > 80 years of age. Given these limitations and potential risks, GH supplementation should not be considered for healthy elderly adults without confirmation and documentation of *pathological* GH deficiency (GHD).

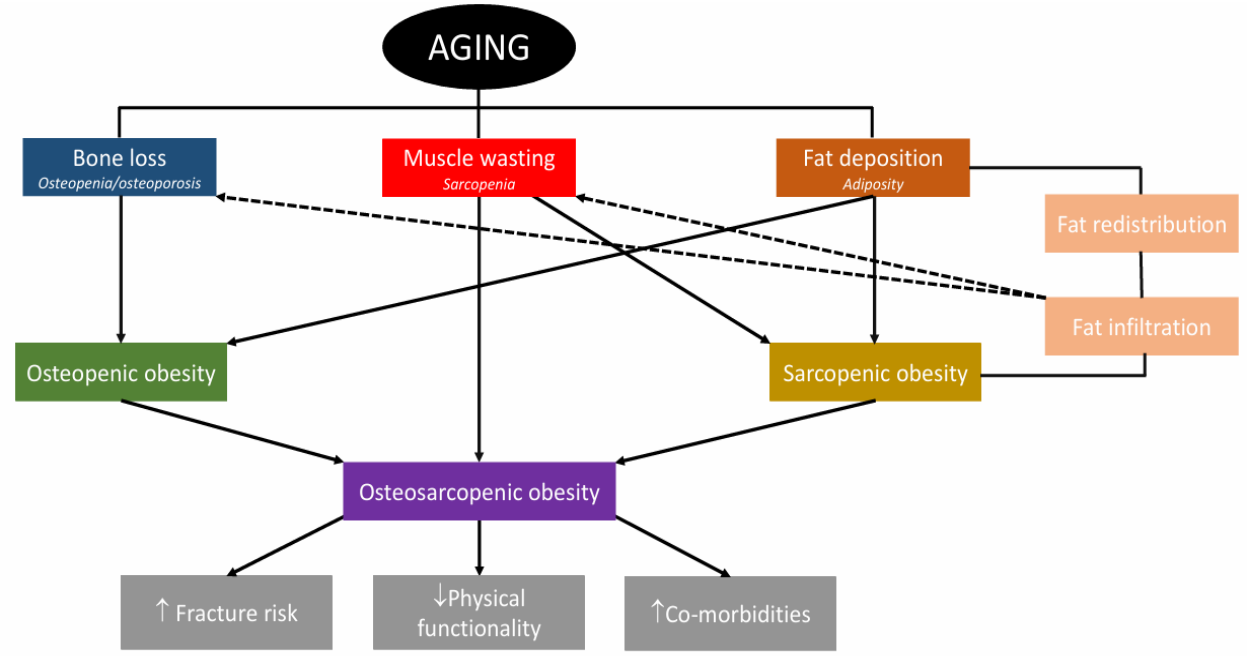

Figure 5. Aging is associated with bone, muscle and fat tissue deterioration leading to osteosarcopenic obesity and its consequences.

Hypothalamic-Pituitary-Gonadal (HPG) Axis

In men, aging leads to a progressive decline in function of the HPG axis and subsequently, gonadal function. Testosterone levels peak at ~age 30 years, followed by a gradual decline thereafter at a rate of 1-2% annually (12, 35) and this is a net effect of a decreased testosterone production that is not fully compensated by reduced metabolic clearance. While women become infertile after menopause, fertility decline in aging men does not necessarily involve complete cessation of spermatogenesis (36). Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) rise gradually in aging men, while gonadotropin pulsatility and total testosterone secretion decline due to impairment of hypothalamic gonadotropin-releasing hormone (GnRH) secretion and reduced pulse size (Figure 6) (37). Additionally, the pulse amplitude of LH is reduced and its efficacy in driving testicular steroidogenesis is impaired. Testicular volume in men > 75 years is decreased by 30%, and the number of Sertoli cells is also reduced (38). Because testicular response to LH stimulation is attenuated, administration of pharmacological hCG doses is ineffective in stimulating testosterone production in many older men (39). Age also impairs testosterone-mediated negative feedback on GnRH and pituitary LH secretion, Furthermore, at the beginning of the sixth decade of life, there is a decrease in 5α-reductase activity despite normal testosterone levels. However, the mechanism of how age affects local conversion of testosterone to dihydrotestosterone in the hypothalamus and pituitary gland remains unclear. Conversely, sex hormone binding globulin (SHBG) levels increase as men age (37, 40) contributing to a disproportionate reduction in free testosterone levels (Figure 6).

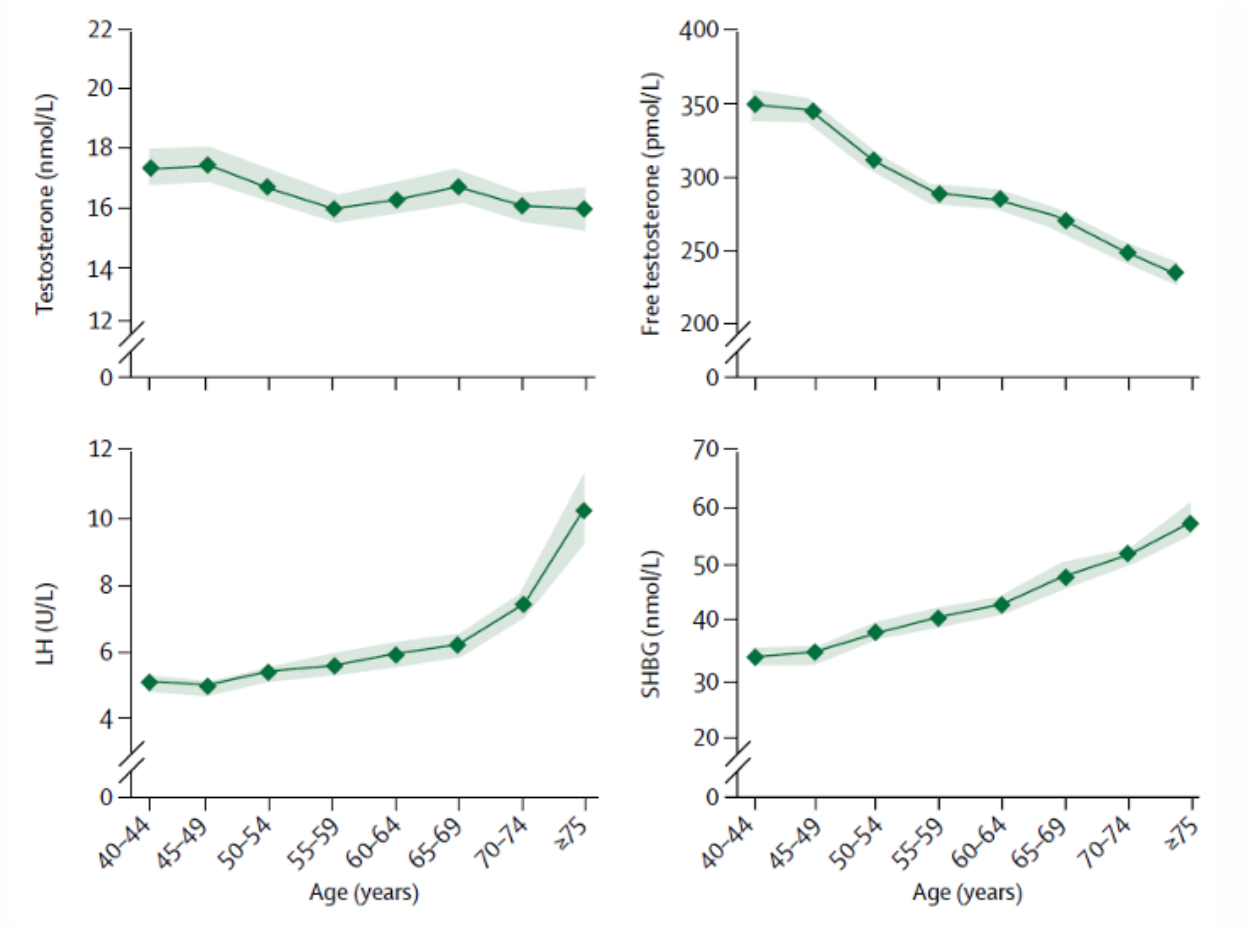

Figure 6. Mean hormone concentrations with 95% confidence intervals (shaded area) presented in 5-year age ranges for a cohort of 3220 men. Mean hormone concentrations with increasing age were interpolated to approximate the age trend. Total testosterone and, disproportionately free testosterone, were lower, and the concentrations of LH and SHBG were higher in the older age groups. Reproduced with permission from Wu *et al*. (37).

Testosterone decline in aging is associated with several consequences, such as muscle mass loss, increased fat mass, decreased bone mineral density, fatigue, depression, insulin resistance, decreased libido, erectile dysfunction, diminished working memory, decreased executive-cognitive function, and increased cardiovascular risk (41, 42). The terms "andropause" or "late-onset hypogonadism" are coined to define a clinical and biochemical state occurring in men with advancing age, characterized by symptoms and low morning serum testosterone levels (43). Although it is difficult to establish the correct criteria for identifying testosterone deficiency in older men who do not have pathological hypogonadism, late-onset hypogonadism has been previously defined by the presence of at least three sexual symptoms associated and a total testosterone level < 320 ng/dL (44). In the absence of other pituitary hormone deficiencies, it is difficult to differentiate mild central hypogonadism from andropause. While age-appropriate testosterone replacement in older men with evidence of hypopituitarism or primary hypogonadism is recommended, the question of whether treating normal aging males to replete testosterone levels to “youthful” levels remains controversial.

On the other hand, menopause in women is the only well-defined universal change which is a function of aging that significantly impacts clinical changes on bone and lipid metabolism, and neurocognitive, cardiovascular and genitourinary systems. Menopause begins with the depletion of the ovarian pool of primordial follicles, with lower oocyte quality in the remaining follicles contributing to decreased fertility starting from the fourth decade of life onwards (45). Conversely, FSH elevations may precede clinical menopause by 5-10 years (46) caused by increased secretion of GnRH, which in turn, is regulated by several other factors, including ovarian hormones and kisspeptin (47). After the marked rise in FSH and LH levels in response to the decline in ovarian feedback, there is a concurrent steady decline in LH and FSH levels with age. Additionally, decreased pituitary responsiveness to GnRH occurs with aging that likely contributes to the overall decline in gonadotropin secretion. With advancing age, when follicle availability declines, cycle irregularity (> 7 days longer than previous cycles) occurs that signals the onset of menopause transition, generally at a mean age of 46 years. This is followed by increased intervals of the menstrual cycle, including delayed dominant follicle growth, anovulatory bleeding and missed periods that culminates in the depletion of ovarian follicles and the final menstrual period which retrospectively marks the onset of menopause after 12 months of amenorrhea, generally around the age of 51 years (45). Therefore, although it is clear that the ovary plays a primary role in the loss of reproductive function in women, the potential contributions of the neuroendocrine components of the reproductive axis to the changing reproductive phenotype with aging have to be considered (48). The resultant estrogen deficiency subsequently contributes to the development of dyslipidemia (elevations in serum total cholesterol, LDL-cholesterol, apolipoproteins, and triglycerides, and decreases in HDL cholesterol), increased cardiovascular risk and events, vasomotor instability, and cognitive disturbances in menopause (49).

Hypothalamic-Pituitary-Adrenal (HPA) Axis

The HPA axis is involved in life-sustaining homeostatic and allostatic adjustments to internal and external stressors. This stress-adaptive axis is a dynamic feedback network with circadian rhythmicity and pulsatile neurohormone secretion (50). Older individuals exhibit HPA axis hyperactivity to stress, partly due to reduced negative feedback from cortisol acting at the hippocampal level (51) and prolonged cortisol response to exogenous adrenocorticotropin (ACTH) administration (52). Sleep disruption is common in the elderly and is associated with elevated daytime cortisol levels (53). Beyond systemic regulation, aging can increase local cortisol activity in several tissues through the enhanced conversion of cortisone to cortisol by the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). In skin, 11β-HSD1 expression is increased with aging which can enhance local catabolic actions without affecting adrenal cortisol secretion (54), whereas in muscle, 11β-HSD1 expression is increased with decreasing strength in older individuals (55). By contrast, although overt Cushing syndrome is rare in the elderly, mild ACTH-independent hypercortisolemia, often caused by adrenal adenomas or hyperplasia, is more prevalent in the elderly due to the increased frequency of adrenal incidentalomas (56) and is associated with adverse outcomes such as hypertension, glucose intolerance, cardiovascular events, and osteoporosis (57). In contrast, aldosterone levels show a modest decline with aging, accompanied by a reduction in plasma renin activity, and these changes are thought to exert minimal physiological impact in the elderly (51). As for DHEAS secretion, levels peak at ~ age 25 and decline gradually with age, falling to childhood levels by age 80 in most adults (58) reflecting gradual atrophy of the zona reticularis (59). Men tend to have higher DHEAS concentrations than women (60). In women, more than half of circulating testosterone is derived from 19-carbon androgen precursors from the adrenal cortex, including DHEA, DHEAS, and androstenedione (61),

whereas the majority of testosterone in men is derived from the testes throughout adult life. Therefore, age-related decline in steroid production from the zona reticularis exerts a greater impact in women and in men with primary or secondary testicular dysfunction than in normal men. Additionally, the adrenal cortex also synthesizes 11-oxygenated androgens, notably 11β-hydroxyandrostenedione, which is metabolized into 11-ketotestosterone (62). In women, DHEA, DHEAS, androstenedione, and testosterone all decline from age 30 years onwards; however, 11β-hydroxyandrostenedione and 11-ketotestosterone increase slightly into the ninth decade and decline only slightly during this age window in men (63). In most women (63) and prepubertal children (64), 11-ketotestosterone is the most abundant bioactive circulating androgen and this adrenal androgen component is preserved throughout life. Because 11-ketotestosterone also provides negative feedback on the HPG axis, this contribution could become important in older men.

Hypothalamic-Pituitary-Thyroid (HPT) Axis

The HPT axis undergoes complex physiological changes with aging. However, direct age-related changes need to be distinguished from indirect alterations caused by simultaneous thyroid or non-thyroidal illness, or other physiological or pathophysiological states whose incidence increases with age. In an attempt to discriminate between effects of aging *per se* and those of thyroidal or nonthyroidal illness, Harman *et al*. (65) studied 74 healthy men from the Baltimore Longitudinal Study on Aging that were evenly distributed over the age range of 30-96 years. These investigators reported that aging is associated with subtle changes in thyroid function, including small decreases in total thyroxine (T4) primarily due to decreased thyroid hormone secretion and an increase in T4 binding to proteins leading to a lower free T4 index. Thyroid hormone clearance also decreases with aging resulting in longer half-lives of T4 and triiodothyronine (T3) and a compensatory decrease in the production of new thyroid hormones (66, 67), leading to unchanged net total and free serum T4 levels (68). The thyroid gland itself may also lose its responsiveness to TSH stimulation, resulting in the reduced production of T4 and T3 (69). A possible explanation for this observation is that the aging process itself results in decreased thyroid volume secondary to atrophy and fibrosis (70). Serum total and free T3 levels also decline with aging due to reduced peripheral conversion of T4 to T3 secondary to either the direct effect of aging itself or non-thyroidal illness (71), thus allowing for slower metabolism and maintenance of T4 levels at the expense of T3 levels (69). Conversely, TSH levels tend to increase in elderly apparently euthyroid patients, even in individuals without any history of thyroidal illness and with concurrently negative antithyroid antibody levels (72). While the exact mechanisms behind this age-related increase in TSH remains unknown, proposed age-related mechanisms for this change include increased production of TSH molecules with reduced biologic activity due to alterations in thyrotroph post-translational processing of TSH (69), decreased sensitivity of thyrotrophs to negative feedback from circulating thyroid hormone (73), and/or development of TSH resistance by the thyroid gland (73). Increased detection of thyroid autoantibodies have been reported with advancing age, which may explain the increased incidence of primary hypothyroidism in the elderly caused by chronic autoimmune thyroiditis (74). Additional factors complicating the relationship between thyroid hormone levels and aging include the presence of comorbid diseases in the elderly including hypertension, heart failure, liver failure, and kidney failure. As thyroid hormone metabolism relies in part on the liver and kidneys (75), if either of these organ systems are impaired, it can further affect the clearance of thyroid hormone. Decreased iodine intake from dietary salt restriction (76) and age-related decrease in gastrointestinal iodine absorption (77) predisposes elderly patients to iodine deficiency that can contribute to the development of hypothyroidism (78). Additionally, blunted circadian fluctuations in TSH levels and diminished TSH responses to TRH stimulation have been reported in elderly males (79, 80) suggesting the presence of an age-related

diminution in pituitary thyrotropic function.

Prolactin Regulation and Secretion

Prolactin regulation is primarily controlled by dopamine, which is tonically released by hypothalamic neurons and inhibits prolactin secretion via D2 receptors on the lactotrophs. The secretion of prolactin is approximately 50% in pulses and 50% tonically. Both modes of secretion show 24-hour rhythmicity with greater output at night than daytime (81). In individuals < 50 years, prolactin levels are higher in women than men (82). Across the menstrual cycle, prolactin levels vary slightly, with higher levels during the luteal phase and highest levels occurring during either the ovulatory or luteal phases (83). However, a distinct mid-cycle prolactin surge coinciding with the LH peak has not been consistently observed likely due to the pulsatile nature of prolactin release overshadowing any transient increases (84). Prolactin also plays a key inhibitory role in the HPG axis by suppressing kisspeptin-1 secretion with advancing age, which normally stimulates GnRH (85). Through this mechanism, elevated prolactin can impair fertility and reproductive hormone production. Following menopause, nocturnal prolactin secretion declines by approximately 40% because of decreased estrogen levels (86), whereas aging men experience more modest prolactin reductions (Figure 7) (87). Additionally, TRH-stimulated prolactin release diminishes with age (88, 89). Other mechanisms involved in the changes in prolactin secretion during aging include increased dopamine inhibition, reduced prolactin releasing-factor stimulation and/or increased adipokine inhibition of lactotropes (87).

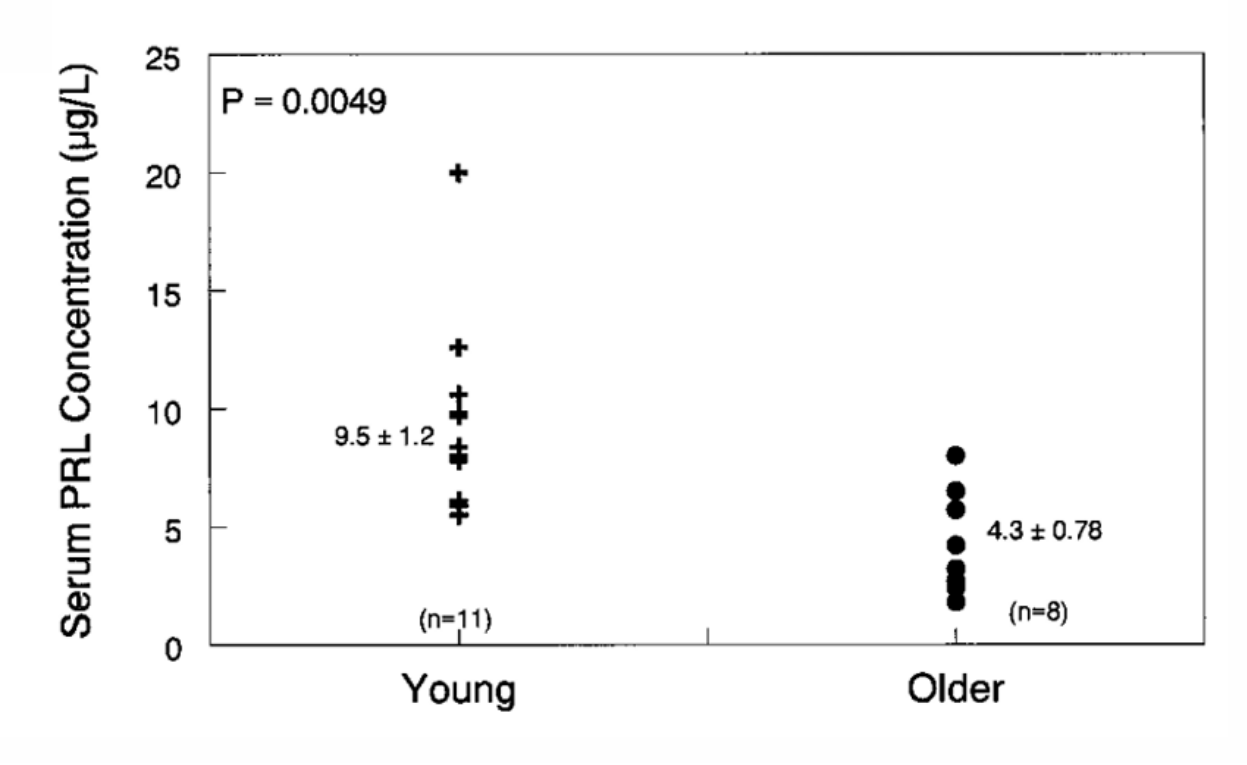

Figure 7. Serum prolactin levels determined by sampling every 2.5 min overnight in young and older healthy men. Reproduced with permission from Iranmanesh *et al.* (87).

In women with polycystic ovary syndrome, Albu *et al.* (90) demonstrated that lower prolactin levels correlated with insulin resistance and poorer metabolic profiles, implicating the role of prolactin in adiposity

and glucose regulation. In comparison, elevated prolactin levels are observed in individuals with depression and associated with anxiety, hostility, somatization, psychotic symptoms, and heart rate (91). Patients with Parkinson's disease treated with dopamine agonists exhibit reduced prolactin levels. Given the increased prevalence of Parkinson's disease with aging (92) and the frequent use of antipsychotic medications in older adults (93), careful medication history is essential when evaluating prolactin levels in these populations.

Sodium and Water Homeostasis

Aging causes distinct physiological changes that disrupt normal water homeostasis at multiple regulatory points. The net effect is a loss of homeostatic reserve, rendering older individuals susceptible to both pathological and iatrogenic disturbances in water homeostasis (94). Older individuals exhibit decreased thirst sensation and drinking response to thirst when plasma osmolality rises (Figure 8) (95). This deficit likely results from the reduced activity in the neural pathways that relay osmotic signals to higher cortical centers responsible for the thirst perception and from which the thirst-activated drinking responses arise (96). Some studies suggest this impairment may even be attributed to a higher osmotic threshold needed to trigger thirst in older individuals (97). Additionally, baroreceptor-mediated regulation of thirst is altered with age, whereby plasma volume expansion fails to generate sufficient suppression of thirst found in the young (98). The loss of appropriate thirst responses to both osmotic and volume stimuli hinder the critical compensatory mechanisms to trigger fluid intake in the face of hyperosmolality to replace lost body fluid, thus undermining a key physiological defense against dehydration.

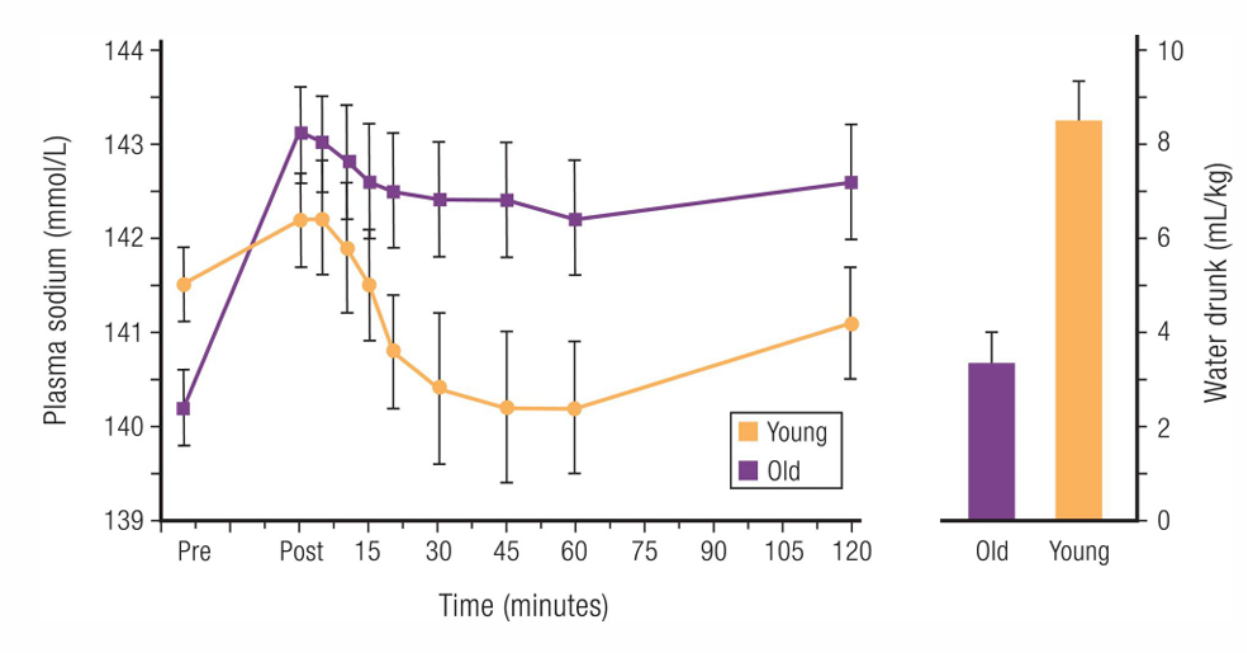

Figure 8. Plasma sodium and total water intake in healthy older and younger subjects following 24 hours of dehydration. Baseline sodium concentrations before and after dehydration are shown. Free access to water was allowed for 60 minutes following dehydration starting at time = 0 minutes. Cumulative 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 sodium, older participants drank less water with less correction of the elevated serum sodium. Reproduced with permission from Phillips *et al.* (95).

Renal function also declines with age, including a reduction in glomerular filtration rate and a loss of maximal urinary concentrating capacity (99). These changes impair the ability of the kidneys to conserve free water, increasing the risk of body water deficits, hyperosmolality, and hypovolemia. When coupled with an impaired thirst drive, this decline in renal function contributes to the increased incidence of hypernatremia observed in older adults (100).

Aging is also associated with a reduced ability to excrete excess water mainly attributed to reduced age-related glomerular filtration rate and decreased intrarenal generation of prostaglandins (101). Furthermore, a higher sensitivity to osmotic stimuli may be observed with advancing age given that the relatively rare idiopathic syndrome of inappropriate antidiuresis (SIAD) is more frequently observed in the elderly (101). The frequent reduction in protein intake in this population impairs water excretion that may contribute to the development of hyponatremia (102). This, in turn, increases the susceptibility to volume overload, especially in the context of pre-existing comorbidities like heart failure and cirrhosis, which are more prevalent in older populations. Their compromised ability to eliminate excess fluid places them at higher risk for developing hypo-osmolar hyponatremia.

Among the most intriguing aspects of age-related changes in water homeostasis is the regulation of arginine vasopressin (AVP) and its AVP-mediated effects on renal and vascular targets being more pronounced in males than in females (103). While many endocrine functions decline with aging, basal AVP secretion is maintained or even increased in older adults, with males tending to have higher AVP levels than females (104). Additionally, osmoreceptor sensitivity governing AVP secretion in response to plasma osmolality appears to be increased (105). It is likely that the enhanced secretion of AVP and inability to suppress AVP secretion during fluid intake (96), coupled with decreased free water excretion (106), increases the risk of hypo-osmolar hyponatremia in older individuals. Therefore, aging alters the regulation of water homeostasis through changes in thirst perception, renal concentrating and diluting ability, and AVP secretion that compromise the ability to respond appropriately to both fluid loss and fluid excess.

DISEASES OF THE HYPOTHALAMIC-PITUITARY AXIS IN THE ELDERLY

Non-Functioning Pituitary Adenomas (NFPAs)

The number of elderly patients detected with pituitary adenomas is now increasing (107) as the population is living to an older age (108) and the increasing accessibility of magnetic resonance imaging (MRI). Among these, NFPAs are the commonest subtype, accounting for up to 70% of cases in individuals aged ≥ 65 years (109, 110), and tend to be discovered as slow-growing micro-incidentalomas (111). Mass effect symptoms (e.g., headache and visual impairment) are the most frequently reported symptoms (112). Notably, elderly patients experience longer symptom duration and are more likely to be misdiagnosed at their initial visit (109). Older patients with NFPAs tend to present more frequently with chronic comorbidities, less frequently with hormone-secreting effects, and tumors that are larger in size without a significant increase in invasiveness compared to younger patients (112). Chronic comorbidities are more prevalent (109), and a higher Charlson index is observed in elderly patients associated with increased in-hospital mortality after undergoing pituitary surgery (113).

Despite concerns about age-related risks, studies have shown that tumor resection outcome rates in the elderly are comparable to those in younger patients (109, 114-118), with similar rates of postoperative visual improvement (71–100%) (115, 118-120). However, recovery from preoperative hypopituitarism

after pituitary surgery for NFPAs is less favorable in the elderly (34, 120, 121). Nonetheless, pituitary surgery in the elderly overall carries a low risk of morbidity and mortality (117, 120, 121), but the risk of complications (e.g., cerebrospinal fluid leakage, postoperative hematoma, and postoperative water and electrolyte disturbances) (115, 117, 122, 123), in-patient mortality, and hospital stay duration tends to increase with advancing age (109, 115, 123). Moreover, if frailty is present, postoperative elderly patients may experience higher rates of medical complications resulting in longer hospital stays, greater hospitalization costs, higher rates of unplanned readmission, and more discharges to a destination other than home (124), indicating that frailty is an important indicator of perioperative risk.

Intriguingly, the rate of tumor recurrence in elderly patients is lower than that in younger patients (118, 125). Zhan *et al.* demonstrated that the rate of recurrence in elderly patients (≥ 65 years of age) with NFPA (7.0%) was lower than in younger patients (40–55 years of age) (15.5%) (118), which may be attributed to the 2-fold greater tumor volume doubling time of residual NFPAs in elderly patients (≥61 years of age) than that in younger patients (<61 years of age) (126). Additionally, age is negatively associated with the immunohistochemical expression of pituitary tumor transforming gene in pituitary adenomas, a marker associated with tumor regrowth and recurrence (127).

The indications for either microscopic or endoscopic surgery for NFPAs are generally consistent across all age groups (117-119, 121, 125) and has been reported to be safe and effective (117, 128). However, due to the higher risk of perioperative complications and mortality in elderly patients, pituitary surgeries in the elderly should only be performed by experienced neurosurgeons at higher-volume centers (117, 128). Pituitary surgery should not be recommended for elderly patients with NFPAs and hypopituitarism alone, instead, should be reserved for patients presenting with symptoms due to mass effects (e.g., visual impairment) or evidence of rapid tumor growth (128). For elderly patients with high surgical risk or tumors with no mass effect on the optic chiasm, conservative management with regular MRI surveillance is plausible.

Hypopituitarism

Hypopituitarism in the elderly can be caused by “tumoral” causes, of which can be subdivided into pituitary and non-pituitary tumors (< 10% of cases), and “non-tumoral” causes (129) (Table 2). For tumoral causes, pituitary macroadenomas are the most frequent cause. Unlike younger patients, where prolactinomas make up the majority of pituitary tumors, the majority of pituitary tumors in the elderly are NFPAs with higher rates of compressive symptoms (e.g., headaches and visual field defects) and hypopituitarism before and after surgery (109, 110). The development of hypopituitarism related to macroadenomas are secondary to the local compressive effects on the pituitary stalk resulting in decreased availability of hypothalamic hormones, compression and/or destruction of functioning pituitary tissue, and hypothalamic involvement by the pituitary tumor. Hypopituitarism is manifested by the typical sequence of growth hormone deficiency (GHD) being affected first, followed by gonadotropin, ACTH, and thyrotropin (TSH) deficiencies. Mild to moderate hyperprolactinemia can also occur due to pituitary stalk compression (“the stalk effect”). However, the diagnosis of hyperprolactinemia may be under-recognized because of lack of menstrual periods in women and frequently low testosterone levels in men that may be misinterpreted as being age-related.

Table 2. Causes of Hypopituitarism in the Elderly	
Neoplastic Pituitary adenoma Metastases Meningioma Craniopharyngioma Glioma Chordoma Rathke's cleft cyst Germinoma Lymphoma	**Infiltrative/inflammatory diseases** Hypophysitis Hypothalamitis Sarcoidosis Hemochromatosis Granulomatosis with polyangiitis Langerhans cell histiocytosis
Iatrogenic Surgery Radiation Medications (immune checkpoint inhibitors, opioids)	**Vascular** Subarachnoid hemorrhage Pituitary apoplexy Ischemic stroke Intrasellar aneurysm
Infections Meningitis (bacterial, viral, fungal) Tuberculosis	**Traumatic brain injury** **Empty sella** **Idiopathic**

In elderly patients, the finding of a pituitary lesion on magnetic resonance imaging studies should alert for the possibility of a metastatic lesion from breast, lung, prostate, and colorectal cancers. In such patients, there may be a history of malignancy and symptoms of polydipsia and polyuria because of AVP-deficiency (130). Other less common "tumoral" causes of hypopituitarism in the elderly include meningiomas, craniopharyngiomas, gliomas, chordomas, germinomas, and Rathke's cleft cysts (131). Additionally, the associated treatment by surgery and/or radiation to the pituitary tumor can also cause hypopituitarism (131).

As for "non-tumoral" causes, empty sella, traumatic brain injury, ischemic stroke, and aneurysmal subarachnoid bleeding are some examples (131). Rarely autoimmune hypophysitis (including immune checkpoint inhibitor-induced hypophysitis) (132), pituitary apoplexy (especially in patients on anticoagulant therapy) (133), or previously undiagnosed pre-existing pituitary adenomas can also cause hypopituitarism. In the elderly, some medications are taken more frequently to treat acute or chronic diseases (e.g., opioids, glucocorticoids, and anti-depressants) that may result in hormonal alterations and thus interfere and pose diagnostic challenges in these patients.

Growth Hormone Deficiency

Adult GHD (AGHD) is a clinical entity characterized by pathologically lower GH levels than the physiological decline in GH and IGF-I levels associated with aging (134, 135). Because patients with AGHD often present with non-specific signs and symptoms that overlap with aging, including increased central adiposity, decreased physical and mental performance, decreased bone mineral density, impaired quality of life and social withdrawal (131), the diagnosis may be under-recognized. Previous studies have shown that GH replacement reverses many, but not all of these alterations (131), and that it is safe and durable in the short and long-term (131, 136). However, there is currently no accepted consensus on the identification

of elderly AGHD as an entity for which GH replacement is recommended, as data on the real impact of GH replacement in reducing cardiovascular morbidity and mortality in elderly AGHD patients is still lacking (137). Additionally, it is unclear whether GH therapy should be continued indefinitely in older patients already undergoing treatment, or if it should be discontinued upon reaching very old age (e.g. > 85 years). An important concern in older adults is the increased potential for adverse outcomes related to GH replacement, including risks of inducing malignancy, cellular senescence, telomere shortening, and the onset or worsening of DM.

DIAGNOSIS OF ELDERLY GHD

Low IGF-I levels support the diagnosis of GHD, whereas normal IGF-I levels do not reliably exclude the diagnosis in the elderly (131), as up to 40% of patients over 60 years with GHD present with normal IGF-I values compared with only 4% in those between 20 and 39 years (131, 138). The observed pattern is explained by the age-related decline of IGF-I in healthy individuals and the age-independent IGF-I levels in patients with GHD (131). Thus, the diagnosis of elderly AGHD often requires confirmation with GH stimulation tests (131). The exception is in patients with a structural brain defect, pre-existing hypopituitarism (coexistence of ≥ 3 pituitary hormone deficits), and low serum IGF-I SDS (< -2.0 SDS), where it is sufficient to confirm the diagnosis without undergoing GH stimulation testing (131). Other patients will require GH stimulation testing, with the need to proceed to one, sometimes two, GH stimulation tests (131). Current guidelines recommend first determining the probability of hypopituitarism and optimally treating any pituitary hormonal deficiencies first before testing for AGHD (131). For elderly GHD, the decision to perform diagnostic testing for AGHD should be corroborated by a strong pre-test probability to avoid false positive results (139). Furthermore, interpreting the results of GH stimulation tests may be challenging due to the variability in response of GH stimulation tests available (135), given the fact that these tests lack age-adjusted cut-offs (131). The two available tests for the diagnosis of GHD in the United States are the insulin tolerance test (ITT) and the glucagon stimulation test (GST). However, the ITT is contraindicated in the elderly (140), whereas the GST needs to be conducted with close medical supervision in the elderly. This test is not without its caveats in the elderly as Tavares *et al*. (141) demonstrated that 21.4% of elderly patients who underwent the GST reported adverse events, including 4 patients with severe symptomatic hypotension, dizziness, and sweating. The GHRH plus arginine stimulation test seems to offer the best accuracy/safety ratio in elderly patients, but the effect of body mass index (BMI) is unclear. Moreover, this test cannot be performed in the United States as because the sole manufacturer of the necessary recombinant GHRH analog (Geref[@]) discontinued its production in 2008 (142). Conversely, the utility of the macimorelin test, which is a simple, accurate, well-tolerated, reproducible, and safe test (143-145), has not been studied in patients > 66 years of age and should be used with caution in patients with pro-arrhythmic manifestations. Unfortunately, this test is also not available in many countries, including the United States, and when it was available in the United States, was limited in its use because of cost reasons (142).

TREATMENT OF ELDERLY GHD

Although GH replacement improves most metabolic and psychological abnormalities in adults with GHD (131), specific studies of these effects in elderly patients are lacking. From a pragmatic standpoint, we recommend starting GH at low doses of 0.1 to 0.2 mg/day in the elderly, and up titrating the dose based on clinical response and side-effects (131). Because elderly patients are more sensitive to GH effects, it is important to perform periodic monitoring of clinical benefits and adverse events. Side-effects in the elderly consist mainly of fluid retention and worsening of insulin resistance that must be closely monitored and generally resolve with dose reductions or discontinuation of GH therapy (131).

Similar to AGHD, the goals of treatment in elderly GHD are clinical response, attainment of IGF-I levels between -2 and +2 SD (146) and minimization or avoidance of side-effects (147). Toogood *et al.* reported that the majority of elderly GHD patients maintained IGF-I levels at goal on a dose of 0.33 mg/day (148). Follow-up intervals in treated patients are initially 1 or 2 months; the up-titration of GH dose is carried out with small increments of 0.1 to 0.2 mg/day, based on the clinical response, IGF-I levels, occurrence of side-effects, and individual considerations. Shorter follow-up intervals and smaller dose increments may be needed, especially for those patients with other comorbidities such as DM and prediabetes (131). Once maintenance GH dose is achieved, follow-up intervals can be increased to 6 to 12 months. During follow-up, the several parameters that need to be evaluated include IGF-I, fasting glucose, hemoglobin A1c, lipid profile, BMI, waist circumference and waist-to-hip ratio, while thyroid, glucocorticoid and sex hormone requirements may need to be adjusted due to possible effects of GH interactions with these hormones (131). Despite studies demonstrating the safety of long-term GH therapy in AGHD patients, the possibility of malignancy in the elderly should be borne in mind and the presence of any active neoplasia should prompt the discontinuation of GH replacement in this population. Potential adverse effects of long-term GH replacement therapy on senescence and telomere shortening are theoretical safety concerns in elderly individuals and have not been assessed after the eighth decade of life in any reported study. Reassuringly, current evidence have not shown an association between GH replacement and primary tumor or cancer recurrence; hence we propose considering GH therapy in the elderly to be based on each individual's circumstance (149, 150).

ACTH Deficiency

Undiagnosed central adrenal insufficiency (CAI) is a potentially life-threatening condition, and prompt diagnosis and replacement therapy is essential. In elderly patients, isolated ACTH deficiency is rare, unless caused by prolonged exposure to exogenous oral, parenteral, or even inhaled glucocorticoid therapies. Therefore, CAI in elderly patients is mainly caused by conditions that could result in the development of hypopituitarism (Table 2). Specifically, CAI has been reported in up to 30% in patients with pituitary adenoma undergoing surgery (151) and in 12-68% of patients after pituitary or cranial irradiation (152). The expansion of immune checkpoint inhibitors in treating various cancer subtypes (153) has led to an increase in immune-related adverse events, and is now recognized as an important cause of isolated ACTH deficiency in the elderly (154).

Glucocorticoid use is relatively common in the elderly due to the high prevalence of inflammatory, immune-mediated, pulmonology and neoplastic diseases (155, 156). These individuals are particularly susceptible to CAI, especially if the medication is stopped suddenly. Obtaining a careful history of use of synthetic glucocorticoids is helpful to arrive at the diagnosis, with high doses, longer duration of treatment, and use of long-acting glucocorticoids giving the highest risk. Diagnosis of CAI is based on laboratory evaluation, and the diagnostic approach is similar for both isolated and non-isolated forms. In elderly patients, the diagnosis of CAI is often challenging due to factors such as polypharmacy, the presence of multiple comorbidities, interferences related to the use of concurrent medical therapies, and the lack of cortisol or ACTH cut-offs specific to older adults or chronically ill populations. Under normal physiological conditions, severe stress such as that induced by critical illness should lead to an increase in ACTH and cortisol secretion due to central activation of the HPA axis (157). Nevertheless, in hospitalized patients with critical illness, studies have observed a transient suppression of the HPA axis that occurs independently of any organic pituitary disorder (158). For example, in patients with septic shock, a form of relative adrenal insufficiency has been described (159), with ACTH levels often found to be mostly low

to low-normal levels (160). If hepatic cirrhosis is present, this might further complicate the assessment of adrenal function. In these patients, adrenal cortisol secretion is impaired due to reduced levels of total cholesterol, and ACTH secretion is suppressed by elevated levels of circulating proinflammatory cytokines. Furthermore, serum cortisol measurements may appear falsely low due to decreased levels of albumin and cortisol-binding globulin (161).

The initial step in making the diagnosis of CAI involves measuring morning serum cortisol levels along with ACTH. A low morning cortisol level with an inappropriately low or normal ACTH level suggests CAI (147). Based on the Endocrine Society guidelines, a morning cortisol level < 3 mcg/ dL is suggestive for adrenal insufficiency, while levels > 15 mcg/dL exclude the diagnosis (147). Prete *et al.* (162) proposed to consider the diagnosis with morning cortisol levels < 3.6 mcg/dL and the diagnosis being less likely for morning cortisol levels > 12.7 mcg/dL. Giordano *et al.* (163) demonstrated that in normal elderly subjects (age 63–75 years), the cortisol response to ACTH was preserved after supramaximal (250 μg) and submaximal (0.5 μg) doses, but was absent after administration of a very low ACTH dose (0.06 μg), in agreement with other studies of a possible reduced sensitivity to ACTH stimulation of the adrenal fasciculata zone occurring with aging (164). Le *et al.* (52) investigated the cortisol response to ACTH 250 μg in a cohort of 51 women aged 85–96 years and demonstrated similar pre-ACTH stimulation levels of cortisol among frail, pre-frail, and non-frail participants, and after ACTH administration, a prolonged cortisol response to the stimulus was shown, suggesting an inadequate negative feedback. These data imply an exaggerated cortisol response to the ACTH stimulus in aging or, alternatively, mechanisms related to diminished ACTH metabolism or cortisol clearance. Additionally, it is important that clinicians are aware of the type of assay when interpreting serum cortisol results, given that modern monoclonal antibodies-based assays tend to read 20-30% lower than older assays (165). If the morning cortisol level alone is insufficient to make the diagnosis of adrenal insufficiency, then performing the ACTH stimulation test is required. While the standard 250 μg dose of synthetic ACTH (ACTH 1-24) is accepted for diagnosing adrenal insufficiency, the utility of the low-dose 1 μg ACTH test has been suggested as the more sensitive test by some investigators for assessing CAI. However, there is no clear consensus on which test is superior, and current guidelines do not provide definitive recommendations regarding which test to use (147). However, the low-dose ACTH stimulation test is difficult to perform due to the lack of commercially available low-dose Cosyntropin analogs, which makes accurate dilution and dosing challenging (166). The accuracy of the ACTH stimulation test is also influenced by the methods used to measure serum cortisol levels. Earlier studies were based on traditional immunoassays using polyclonal antibodies, which tended to overestimate cortisol concentrations. More recently, assays using liquid chromatography-tandem mass spectrometry (LC-MS/MS) and monoclonal antibodies have been developed, offering greater specificity and accuracy, and lower cortisol cut-offs have been proposed using these newer assays for both basal and stimulated cortisol levels (165). Another caveat about the ACTH stimulation test is that the diagnostic value of this test in patients with suspected CAI lies in the assumption that chronic ACTH deficiency has resulted in adrenal atrophy, and a consequent impaired response to stimulation by Cosyntropin analogs (147). Alternative but less frequently used provocative tests to the ACTH stimulation test have been utilized, including the insulin tolerance test, glucagon stimulation test and overnight metyrapone stimulation test. The insulin tolerance test can assess the HPA function as hypoglycemia is a potent stimulus for cortisol release. However, this test is unpleasant and contraindicated in the elderly and in individuals with a history of seizures or cardiovascular or cerebrovascular disease, for the risk-related hypoglycemia. The glucagon stimulation test is another provocative test that can be utilized but the side-effects reported in older individuals, such as nausea, vomiting, hypotension, sweating and dizziness (141), and

debatable cortisol cut-offs makes this test less attractive in the elderly. The metyrapone stimulation test can assess HPA function as the test is based upon the principle that metyrapone inhibits the conversion of 11-deoxycortisol to cortisol, with the resultant decrease in serum cortisol levels followed by an increase in ACTH secretion and the immediate precursor of cortisol, 11-deoxycortisol. If the HPA axis fails to respond appropriately to the decreased glucocorticoid feedback, then subnormal increases in 11-deoxycortisol will be observed (167). Compared with the insulin tolerance test, the metyrapone stimulation test is considered more physiological, with fewer adverse side-effects. However, the use of this test is limited as metyrapone is not accessible in many countries and measurements of 11-deoxycortisol in blood and urine are also not widely available.

Treatment of CAI involves glucocorticoid replacement therapy aimed at mimicking the natural circadian rhythm of cortisol secretion. Unlike primary adrenal insufficiency, fludrocortisone is not required in CAI because the renin-angiotensin-aldosterone axis is preserved. Short-acting glucocorticoids, such as hydrocortisone and cortisone acetate, are preferred due to better physiological alignment. Traditional replacement doses, such as 30 mg/day of hydrocortisone, are excessive (168) since patients with CAI retain some residual HPA axis function and hence, have lower cortisol needs than those with primary adrenal insufficiency. Other factors can also affect glucocorticoid dosing, including growth hormone deficiency, which can reduce cortisol clearance by upregulating 11β-HSD1 activity (169) and older age that is associated to increased expression of 11β-HSD1 in skin, brain, and muscle (170, 171), thus resulting in lower glucocorticoid requirements in older patients. While no specific recommendations have been provided for elderly patients by any consensus guidelines, it is reasonable to use the lowest possible glucocorticoid dose to maintain well-being and avoid overtreatment. The standard hydrocortisone regimen is 15–20 mg per day, split into two or three doses, with the highest dose (half or two-thirds of the total daily dose) taken in the morning and subsequent doses taken either in the early afternoon (2 h after lunch; two-dose regimen) or at lunch and afternoon (three-dose regimen) at least 6 hours before bedtime to reduce the risk of sleep disturbances (147). There are now two different extended-release hydrocortisone formulations (Plenadren once-daily dosing and Efmody twice-daily dosing) that have been developed, allowing closer mimicking of circadian secretion of cortisol serum profile to improve quality of life and metabolic profiles of patients with adrenal insufficiency (172). Plenadren and Efmody were approved for adrenal insufficiency in 2011 and congenital adrenal hyperplasia in 2021 in Europe (172); however neither formulation is currently approved in the United States.

In elderly patients with hypopituitarism with concurrent CAI, central hypothyroidism (CH) and GHD, these particular considerations should be made for these patients. In these patients, glucocorticoids should be started before levothyroxine therapy is commenced, and only when these two hormones are optimally replaced should GH replacement be considered. As CAI may mask the presence of partial AVP deficiency, it is important to monitor for the development of symptomatic polyuria after starting glucocorticoid replacement therapy (147). For patients with CAI on GH replacement therapy, higher glucocorticoid doses may be needed because of the inhibitory effects of GH on the 1l beta-HSDl activity (173). Polypharmacy in elderly patients is common and possible interference of other drugs on glucocorticoid metabolism must be considered. Co-administration of drugs acting on CYP3A activity can interfere with glucocorticoid metabolism, causing increased glucocorticoid requirement (e.g., carbamazepine, phenytoin and rifampicin) or, conversely, increased glucocorticoid exposure (e.g., the azole antimycotics ketoconazole and itraconazole, macrolide antibiotics and calcium-channel antagonists) leading to glucocorticoid excess toxicity. Patients with glucocorticoid-induced CAI

require the dosing to be tapered gradually to physiologic doses before further evaluation to test functional recovery of the HPA axis can be performed (162). Because there are no validated biomarkers to accurately assess the adequacy of glucocorticoid replacement, one must rely on evaluation of well-being, weight, physical examination to detect excess glucocorticoid features such as facial plethora, dorsocervical fat accumulation, skin thinning, and abdominal obesity. Fasting glucose and hemoglobin A1c levels can be used as indirect measures of adequate glucocorticoid replacement therapy. However, in elderly patients, evaluating these parameters can be difficult as the presence of age-related conditions like DM and hypertension may confound the interpretation of glucose and blood pressure readings, and physical examination findings may be subtle or masked. Additionally, clinicians should educate patients and caregivers about the importance of stress dosing with glucocorticoid administration during illness or surgery and ensure that they wear medical alert identification to inform healthcare providers of their dependence on glucocorticoid therapy in emergencies.

Adrenal crisis is the most severe acute manifestation of adrenal insufficiency resulting in hypotension and hypoglycemia, with increased risk of cardiovascular events, acute renal injury and possibly death. Adults > 60 years are at the highest risk of adrenal crises and infection, falls and fractures are the most common precipitating factors of adrenal crisis (174). Rarely, concomitant therapies with CYP3A4 inducers (e.g., carbamazepine, phenytoin and rifampicin) can also enhance the metabolism of synthetic glucocorticoids, causing the induction of adrenal crisis. Emergent treatment of an adrenal crisis in the elderly is similar to that of younger patients, with parenteral hydrocortisone 100 mg bolus, followed by intravenous (or intramuscular) boluses every 6 hours with subsequent dose reductions based on clinical response (174).

Gonadotropin Deficiency in Men

Central hypogonadism in aging men can present with symptoms such as low libido, erectile dysfunction, cognitive decline, depression, fatigue, osteoporosis, and loss of muscle mass and strength. Diagnostic work up starts with a morning, fasting serum testosterone measurement, considering that in elderly men, testosterone levels decrease between 15 and 20% over the course of 24 hours (175). Factors such as illness (acute and chronic), certain medications, food intake, weight gain and insufficient sleep can lower testosterone levels that potentially can be reversed when these factors are removed or resolved (176, 177). While LC-MS/MS is the most accurate testing method for total T, this method is not universally available, and many laboratories use standardized immunoassays, which can show high correlation with LC-MS/MS within the adult male testosterone range, although the accuracy is lower for the hypogonadal range (178).

In some cases, total testosterone may appear normal despite clinical signs of hypogonadism due to elevated sex hormone-binding globulin (SHBG), which increases with age and in conditions such as HIV, liver disease, hyperthyroidism, or use of anticonvulsants (phenobarbital, phenytoin, carbamazepine, valproate) (179). If testosterone is borderline low and symptoms are present, SHBG should be measured to calculate free testosterone. Direct measurements of free testosterone via equilibrium dialysis or ultrafiltration can be performed but are not widely available, while radioimmunoassays for free testosterone are unreliable. Nevertheless, hypogonadism is unlikely with total testosterone levels > 350 ng/dL, and more likely in patients with testosterone levels < 231 ng/dL (180).

Central hypogonadism in older men is established by inappropriately low or low-normal LH and FSH levels. Prolactin should also be assessed, as hyperprolactinemia can suppress gonadotropin-releasing hormone and testosterone pulsatility (181).

Differentiating between "andropause" and central hypogonadism can be challenging because both can present with similar hormonal profiles. However, the presence of additional pituitary hormone deficiencies or known hypothalamic-pituitary disease supports the diagnosis of central hypogonadism.

In elderly men, it is important to consider an appropriate risk-to-benefit ratio before starting testosterone treatment in symptomatic patients (182). Benefits of treatment in elderly men include improving well-being and sexual performance, maintaining bone mineral density, increasing muscle mass and improving quality of life and cognitive function (182). Although testosterone has been shown to produce anabolic effects in young and middle-aged men with hypogonadism, the data in elderly men remain limited. A significant increase in lean body mass in older people treated with testosterone for hypogonadism has been reported, despite biases in the selection of the patients (183, 184). The most important benefits of testosterone replacement therapy have been reported in mobility, increased bone mineral density and improvement of anthropometric measurements (182). Different testosterone formulations can be used, depending on the patient's preferences, local availability and insurance coverage. Transdermal systems of testosterone are potentially more appropriate for elderly men for quick adaption and avoidance of supraphysiological testosterone levels (180). An important side effect of testosterone gel treatment is the possibility of cross-transfer during contact with the skin's surface. Therefore, to limit this inconvenience, a higher testosterone concentration preparation (1.6%-2.0%) may be preferred, as these preparations may allow lesser amounts of gel applied, thereby limiting the transfer risk. The adequacy of the therapy is confirmed by the improvement of clinical symptoms and of serum testosterone levels. In elderly men, it is reasonable to maintain circulating testosterone levels in the lower quartile of the normal range (180), and to monitor safety aspects of therapy such as prostate-specific antigen (PSA) and hematocrit, as testosterone therapy may result in prostatic hyperplasia but no excess cases of prostate cancer have been detected, and can induce erythropoiesis (185, 186).

There has been some controversy regarding testosterone replacement therapy and cardiovascular safety in hypogonadal men. Some observational studies have shown that testosterone increases the risk, others have reported a neutral effect (187). In a large retrospective study (n = 544,115) by Layton *et al.* (188), those treated with intramuscular testosterone had higher risk of cardiovascular events (1.26) and death (1.34) but not in those treated with testosterone gel or patch. Randomized trials further complicate the picture. While the Testosterone in Older Men with Mobility Limitations trial (TOM trial) reported more cardiovascular events with high-dose testosterone gel in older men with pre-existing cardiovascular conditions (189), another similar trial using lower doses of testosterone gel found no such increase (190). In randomized trial by Basaria *et al.* (191), no significant difference in atherosclerosis markers after 3 years of testosterone gel were observed, yet another randomized trial by Budoff *et al.* (192) demonstrated a greater increase in noncalcified plaque volume with testosterone treatment but no differences in the progression of coronary calcium scores. Despite these varied individual study outcomes, most meta-analyses of randomized clinical trials generally conclude no statistically significant increase in cardiovascular events with testosterone replacement therapy (193-198). Notably, one meta-analysis did highlight a significant increase in cardiovascular risk specifically with oral testosterone, while intramuscular and transcutaneous (gel or patch) deliveries did not show this elevation (199). Therefore, while evidence regarding specific formulations and dosages warrants careful consideration, particularly concerning oral testosterone and high-dose testosterone regimens, the consensus from meta-analyses of diverse testosterone replacement therapy methods points towards a generally neutral effect on cardiovascular risk.

To further evaluate the effect of testosterone replacement therapy on cardiovascular disease, a large, randomized outcome trial like the Women's Health Initiative is required. To attempt to answer this question, the TRAVERSE study ("Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy ResponSE in Hypogonadal Men") was conducted that assessed hypogonadal men with pre-existing or a high risk of cardiovascular disease (200). This study found that testosterone therapy was non-inferior to placebo for the primary cardiovascular safety endpoint and no increased risk of prostate cancer, though some secondary endpoints showed increased rates of other events like atrial fibrillation, acute kidney injury, and pulmonary embolism in the testosterone-treated group (201). While these data are helpful and reassuring, it has several potential flaws that prevent it from being definitive, specifically its relatively small number of patients for a cardiovascular outcome study (n = 5,246 patients), the relatively short duration (mean treatment of 22 months), the large number of patients (61.4%) who discontinued testosterone, and modestly increased median testosterone levels of approximately 350 ng/dL. More recently, Lin *et al.* (202) demonstrated no statistically significant association between testosterone replacement therapy and cardiovascular risk in hypogonadal men in real-world clinical practice, whereas other real-world studies conducted using claims data and electronic health records data demonstrated reduced risk of cardiovascular events under long-term exposure to testosterone therapy (203, 204). While these studies are reassuring, overall, these studies have their individual limitations making it difficult to definitively rule out the association of testosterone replacement therapy on cardiovascular events in the elderly. However, if hypogonadism is caused by a prolactinoma, then dopamine agonist treatment can result in the recovery of gonadal function in about 60% (205). If hyperprolactinemia is related to the use of drugs, then withdrawal or the change to therapies without effects on prolactin levels will improve testosterone levels and sexual dysfunction (206).

In terms of clinical application, current clinical practice recommendations prioritize the identification of men with classical or pathological hypogonadism due to diseases of the hypothalamus, pituitary or testes (185). In such men, testosterone treatment resolves symptoms and signs of testosterone deficiency (185). In men with classical or pathological hypogonadism the benefits of testosterone treatment likely outweigh possible cardiovascular risks. In any case, individualized assessment and management of cardiovascular risk factors and disease should be part of routine clinical care. Until more evidence is available, it may be prudent to adopt a cautious approach in older men who are frail or who have pre-existing cardiovascular disease, and to optimize management of cardiovascular risk factors first before starting testosterone treatment. Treatment should aim for physiological replacement of testosterone using approved formulations and avoiding excessive testosterone doses (185), should not be used in older men with significant cardiovascular diseases and caution exercised in those with benign prostatic hyperplasia (182).

Gonadotropin Deficiency in Women

Aging in women is associated with progressive decline in fertility, reflecting the reduction in ovarian follicle number and quality, and the cessation of monthly menstrual cycles. Consequently, symptoms (e.g., vasomotor symptoms, genitourinary syndrome of menopause, disordered mood, sleep disruption, sexual disorders) and systemic effects (amenorrhea, bone loss, metabolic syndrome, increased cardiovascular risk, cognitive decline) may arise, and in some women, can be severe and debilitating (207). During menopause, women will also experience deterioration in lipid profiles, accelerated cardiovascular risk, adverse changes in body composition including more central (i.e. visceral) distribution of adipose tissue, accelerated lumbar spine BMD loss, and negative effects on sleep, cognition, and mood (208, 209). On the other hand,

vasomotor symptoms are caused by changes in hypothalamic thermoregulation (210).

Although formulations, routes of administration, and dosages of menopausal hormone therapy (MHT) have expanded in recent years, its primary indication for women experiencing natural menopause remains the management of symptoms (e.g., vasomotor symptoms and genitourinary syndrome of menopause). Specifically for vasomotor symptoms, evidence-based treatments include MHT, non-hormonal prescription medications and mind-body interventions such as cognitive behavioral therapy and hypnosis (211). Recently, there is emerging evidence that MHT initiated within a decade of the onset of perimenopause has been associated with several long-term health benefits, including reduced vasomotor symptoms, without significantly affecting cardiovascular disease amongst younger postmenopausal women aged 50 to 59 years (212). Menopausal hormone therapy has also been associated with a 25% to 50% reduction in fatal cardiovascular events (213), a 50% to 60% reduction in bone fractures (214), a 64% reduction in cognitive decline (215), and a 35% decreased risk of Alzheimer disease (216). With these recent developments, decisions regarding the optimal choice for an individual woman should incorporate her degree of symptom bother, personal preferences, pre-existing cardiovascular disease and breast cancer risk assessments and uterine status (217). Treatment of genitourinary syndrome of menopause includes over-the-counter moisturizers and lubricants, vaginal estrogens, DHEA, and oral ospemifene (211). Because testosterone therapy is not approved for women by the United States Food and Drug Administration (FDA), titration of approved therapies dosed for men has been recommended only for treatment of hypoactive sexual desire disorders in women (218). Prevention of osteoporosis is another approved indication of MHT for postmenopausal women at risk of osteoporosis for whom other approved therapies are neither tolerated nor appropriate. In contrast, the results of secondary coronary heart disease (CHD) prevention trials have been disappointing (219-221). In contrast to anticipated CHD benefit based upon myriad observational studies, trials revealed an increase in myocardial infarction within the first year of therapy, and failure to decrease CHD events or coronary atherosclerosis progression (222). While bone loss is accelerated during menopause, primarily affecting trabecular bone, estrogen therapy or alternatives like bisphosphonates and raloxifene can help preserve bone mineral density and decrease fracture risk (223, 224).

However, there has been considerable debate about the risk: benefit ratio of MHT after the publication of the results from the Women's Health Initiative study (225). The Women's Health Initiative clinical trials were initiated in 1992 to determine whether MHT (conjugated equine estrogens [CEE] ± medroxyprogesterone acetate [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) (226). 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 and DM) (227). 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 (220), dementia risk increased > age 65 (226), and CHD events increased > age 70 (220). All-cause mortality decreased by 21% in those ages 50 to 59 at enrollment in the CEE-alone arm (228), with maximal mortality benefit—a 40% decrease—for those with bilateral oophorectomy < age 45 (229). 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 (227). By contrast, a 21% decrease with CEE alone became statistically significant (227). 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 (230). These findings reflect the complexities of these specific hormone preparations on breast cancer incidence and mortality and should not be extrapolated to other MHT preparations. Observational studies do not suggest that estradiol administration inhibits breast cancer, whereas progesterone may have less breast cancer–stimulating effects than MPA (211). The paucity of randomized controlled trials safety evidence means that MHT is usually not prescribed for women with a history of breast cancer and symptom relief with non-hormonal options is recommended (211, 231).

Due to the lack of adequately powered randomized controlled trials, observational studies and meta-analyses provide some evidence that safety outcomes, particularly for venous thromboembolic disease and possibly stroke risks, improved with lower doses and transdermal estradiol preparations (211). After the initial reports of the Women's Health Initiative, limiting MHT to 3 to 5 years was recommended to minimize breast cancer risk. Both the North American Menopause Society and the American College of Obstetricians and Gynecologists subsequently issued statements allowing for longer duration of MHT in healthy women ≥ age 65 without contraindications, following an annual discussion of anticipated risks and benefits, and reevaluation of individual health status (232, 233). For women who prefer to continue MHT for an extended time, shared decision making, progressive dose reductions and switching to transdermal from oral preparations are recommended (211).

Nevertheless, the investigators of the Women's Health Initiative have recently reported subgroup analyses of the age-specific impact of MHT on atherosclerotic cardiovascular outcomes among women with moderate to severe vasomotor symptoms (212) who may have a higher underlying risk of cardiovascular disease but also the strongest clinical indication for MHT. These analyses indicated that MHT was associated with greatest cardiovascular disease risk in women with vasomotor symptoms in their 70s but did not detect any increased risk for cardiovascular events with MHT use in younger women with vasomotor symptoms. These data provide reassuring evidence that symptomatic younger postmenopausal women are at low risk of cardiovascular complications with MHT. Because menopause is not a simple estrogen deficiency state but a multisystem biological and psychological transition, no one medication or treatment, including MHT (234), can eliminate or prevent all menopausal manifestations or related health changes. Hence, there is a need to broaden menopause management beyond MHT that leverages a multidisciplinary care approach and incorporates other evidence-based treatments and behavioral strategies tailored to the individual woman's needs.

Thus, recent analyses and observational studies have highlighted the importance of initiating MHT within 10 years of onset of menopause or under 60 years for bothersome menopausal symptoms (235). Timing of initiation is critical in determining the risk-benefit ratio (230, 236). Compared with the 63-year-old average age in the Women's Health Initiative trials, women who present with new onset of moderate to severe vasomotor symptoms needing treatment tend to be younger than 60 years. Data from this cohort of younger women suggest that initiating hormone therapy within 10 years of menopause reduces all-cause mortality in the subsequent decade. This age-dependent differential risk has prompted renewed appraisal to support a more nuanced interpretation of MHT's benefit-risk balance. The FDA has acknowledged these developments by recognizing the need to revisit hormone therapy labeling and has removed the boxed warnings from all combined estrogen-progestogen, estrogen alone, other estrogen containing and progestogen only products. The

evidence basis for the labeling changes included a comprehensive FDA evaluation of Women's Health Initiative and post- Women's Health Initiative publications, with particular attention to evidence related to timing, duration, and risks associated with MHT use during the earlier postmenopausal years (230, 236).The FDA's hormone therapy label updates include removal of boxed warnings (cardiovascular disease, stroke, breast cancer, probable dementia), except for the boxed warning in systemic estrogen labels for endometrial cancer with unopposed estrogen in women with a uterus, removal of the recommendation to prescribe hormone therapy at the lowest effective dose for the shortest duration and treatment decisions are individualized after discussions with the patient, tailored safety information, emphasis on the safety findings most relevant to topical vaginal use and not the broader warnings associated with systemic exposure and timing information for systemic hormone therapy of including updated guidance on initiating treatment in women younger than 60 years or within 10 years of menopause onset to optimize the benefit-risk balance. These labeling revisions signal a shift towards more nuanced, evidence-based communication of hormone therapy risks; one that prioritizes clinical relevance, distinguishes between different formulations and patient populations, and balances the narrative to reflect both safety and therapeutic value. The goal of these changes is to guide appropriately tailored hormone therapy use and optimize individualized care.

TSH Deficiency

Hypothyroid symptoms are non-specific and often overlap with symptoms of aging, including tiredness, weight gain, depression, cold intolerance, constipation, and poor concentration that may be overlooked by both physicians and patients. Careful drug review should always be conducted in the elderly before the diagnosis of central hypothyroidism, as they often present with increased comorbidities and polypharmacy. A number of medications can affect the thyroid function tests by interfering with the synthesis, transport, and metabolism of TSH and thyroid hormones, and thyroid function immunoassays.

In the elderly, if central hypothyroidism is suspected based on clinical history, thyroid function tests, pituitary MRI and evaluation of other pituitary hormones are indicated. Detection of low free thyroxine levels with inappropriately normal or low TSH levels is sufficient to confirm the diagnosis. Circulating free triiodothyronine (FT3) levels are less useful, because they can be influenced by intercurrent diseases, which can cause the "low T3 syndrome", whereas for the interpretation of TSH levels, it is important to exclude possible interferences by drugs that can suppress TSH. Glucocorticoids are frequently prescribed to elderly patients and high cortisol levels reduce TRH expression and TSH secretion causing a pattern of central hypothyroidism (237). Other drugs that directly suppress TSH secretion are dopamine agonist and somatostatin analogues (44), while anti-epileptic medications carbamazepine and valproic acid can increase thyroid metabolism and suppress TSH. Acute, chronic and debilitating illnesses can affect thyroid function tests causing low thyroid hormones (total T3 and T3) and low/low-normal TSH, where "non-thyroidal illness" should be considered, and in such cases, thyroid hormone replacement is generally not recommended (238). It is important for physicians to inquire about biotin intake because an intake of 10 mg a day to interferes with measurements of T4, T3 and TSH (239). and can lead also to erroneous values that incorrectly indicate the presence of hyperthyroidism (240) prompting physicians to undertake inappropriate management decisions.

Levothyroxine is the treatment of choice for central hypothyroidism, and liothyronine (LT3), thyroid extracts and other thyroid hormone supplements are generally not recommended (147). However, before initiating levothyroxine treatment, it is important to treat with glucocorticoid replacement therapy first if CAI is present, to avoid precipitating adrenal crisis

(147). We recommend a more conservative treatment regimen of levothyroxine in the elderly, with lower doses at initiation and more gradual dose titration to minimize the risk of precipitating possible cardiac arrhythmias. Levothyroxine can be started at 0.25-0.5 mcg/kg/day and the dose gradually increased over 6-8 weeks to target fT4 levels between mid to the upper half of the reference range and guided by clinical symptoms (241). If overtreatment is suspected and fT4 levels are within the reference range, fT3 can be assessed (241). Other considerations pertinent to the elderly patient include increased levothyroxine dosing if the patient is also on GH and estrogen therapy, and therapies for other comorbidities that may affect levothyroxine absorption (e.g., calcium and iron supplements) and dose requirements (e.g., amiodarone and anti-epileptics).

Body Water Deficiency

HYPERNATREMIA WITH AGING

Hypernatremia reflects an increase in plasma osmolality. Hospitalized older patients and older residents of long-term care facilities show incidences of hypernatremia that vary between 0.3% and 8.9% (242). While hypernatremia is a common presenting diagnosis in older individuals, 60% to 80% of cases in older populations occur after hospital admission (243). 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 (104). Although renal water conservation can mitigate the development of severe hyperosmolality, only appropriate stimulation of thirst with subsequent increase in water ingestion can replace body fluid deficits thereby reversing hyperosmolality (244). This physiologic response is impaired with aging, whereby older patients have a decreased thirst perception (95), and blunted ability to maximally concentrate their urine in response to AVP (245). An additional factor that can cause or exacerbate hypernatremia in hospitalized older patients is osmotic diuresis from mobilization of urea following hydration for pre- renal azotemia, increased protein load from parenteral or enteral nutrition, and increased tissue catabolism (246). 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 (247, 248). The clinical implications of hypernatremia in hospitalized older individuals are significant. One hundred and sixty two hypernatremic older patients admitted for acute hospital care to a community teaching hospital had a serum [Na+] >148 mmol/L, and their all-cause mortality was 7 times greater in hypernatremic than age-matched normonatremic patients and 38% of the hypernatremic patients who survived to discharge had a significantly decreased ability to provide self-care (248). In intensive care units, hypernatremia is associated with increased mortality with adjusted odd ratios for mortality ranging between 2 to 3 (248).

Treatment of Hypernatremia

Adequate hydration is critical in 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 retrospective study of 449 patients hospitalized with a serum [Na+] >155 mmol/L showed 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 (249). Older patients with an established AVP deficiency should be treated with desmopressin, similarly to younger patients (250). Because of age-related decreases in glomerular filtration rate that increase the susceptibility of desmopressin-induced hyponatremia in the elderly, conservative desmopressin dosing is recommended. No recent clinical trials on the efficacy and safety of acute and chronic treatments for hypernatremia in older individuals have been

published. Only one study has been published on desmopressin treatment for nocturia (251), where older individuals are at higher risk for development of hyponatremia even with a single night-time low dose of desmopressin (252), especially in older females because of increased desmopressin response due to increased renal vasopressin V2 receptor expression (253).

PITUITARY HORMONE EXCESS STATES IN THE ELDERLY

Hyperprolactinemia and Prolactinomas

Prolactinomas in the elderly are rare (254), and usually present as macroadenomas with atypical features, thus posing a diagnostic challenge. Unlike prolactinomas diagnosed in the premenopausal period, which often present with symptoms such as menstrual irregularities, galactorrhea, or infertility, most women diagnosed with prolactinomas after menopause typically do not report specific complaints. Symptoms related to hyperprolactinemia in postmenopausal women are often absent due to the natural decline in estrogen,. The majority of prolactinomas after menopause are macroadenomas causing mass effects and infrequently galactorrhea (37.5%) (255), whereas microadenomas are more commonly reported in premenopausal women. The most common symptoms of macroprolactinomas in postmenopausal women are visual field disturbances and headache, but also other atypical presentations such as impaired hearing, hemiparesis, dementia, and new-onset epilepsy have been reported (256). In a study by Santharam *et al.* (257), acute pituitary apoplexy was diagnosed at presentation or during follow-up in 18% of 17 patients diagnosed with a prolactinoma in the postmenopausal period at a median age of 63 years. Most are asymptomatic (subclinical apoplexy) and resolve spontaneously (258). In men, macroprolactinomas are diagnosed at an older age than in women with microprolactinomas (255), and may represent the natural course of an untreated prolactinoma.

Cabergoline is the first-line therapy for macroprolactinomas diagnosed at menopause, and in most patients it is highly effective in terms of both hormonal and tumoral responses and with better outcomes with pituitary function (255). Cabergoline can achieve remission maintenance after cessation of 5 years of therapy in patients with macroprolactinomas (259), with factors favoring remission including absence of cavernous sinus invasion, lower serum prolactin levels before therapy, and low nadir serum prolactin on cabergoline therapy prior to withdrawal (260). Menopause facilitates the remission of hyperprolactinemia in women with prolactinoma and may be seen in about 50% of patients after dopamine agonist withdrawal (257).

The most commonly used definitions of dopamine agonist resistance include failure to normalize prolactin and/or to achieve at least 50% tumor shrinkage with maximal conventional doses of cabergoline (2 mg/week). In a retrospective study of a large cohort of patients with macroprolactinomas, 19.6% of the patients received doses of cabergoline > 2 mg/week (261). The dose of cabergoline increased to 8 mg/week in order to normalize prolactin, and 10% of the patients still had partial resistance to cabergoline where prolactin levels were not normalized. Even higher doses of cabergoline (11 mg/week) have been suggested in order to overcome resistance to treatment (262). In a study by Santharam *et al.* (257) on the long-term outcomes of discontinuation of dopamine agonist treatment in women with prolactinoma after menopause, residual adenoma regrowth was detected in 7% (2 out of 22) of the patients.

The role of surgery in patients with macroprolactinomas is difficult to establish, and indications include cerebrospinal fluid rhinorrhea, pituitary apoplexy, and tumor progression or regrowth despite medical treatment (263). Radiotherapy may be used postoperatively in proliferative tumors but is associated with hypopituitarism. In one meta-analysis,

recurrence of hyperprolactinemia after discontinuation of dopamine agonist treatment was observed in 32% of patients with idiopathic hyperprolactinemia, 21% of patients with microprolactinomas and 10-% of patients with macroprolactinomas (264). Recommendations from the Pituitary Society guidelines are that, after > 2 years of successful treatment (normal prolactin and disappearance of the tumor), dopamine agonist therapy can be tapered and discontinued (265) as menopause may facilitate normalization of prolactin. However, menopause does not ensure remission in tumor growth, particularly in invasive macroprolactinomas. As for patients with microprolactinomas, dopamine agonist therapy should proactively be withdrawn regardless of the possibility of recurrence of hyperprolactinemia. A major limitation of this strategy is the lack of published literature on outcomes in patients with prolactinomas after dopamine agonist treatment withdrawal.

Cushing's Disease and Syndrome

Cushing's disease (CD) is most commonly diagnosed in women in their 40s–50s, with a female-to-male ratio of 2.3–4:1 (266). However, due to increasing life expectancy in the general population (108), diagnoses in older individuals are becoming more evident. In women < 45 years, CD is more prevalent, whereas adrenal-dependent Cushing's syndrome (CS) has increasingly becomes more common in individuals > 65 years (266). Additionally, in older patients, the typical female predominance declines, likely due to reduced estrogen levels after menopause. These patients also more frequently present with pituitary macroadenomas (267).

The clinical presentation of CS differs in elderly in several aspects compared to younger patients. Advancing age is associated with increasing comorbidities (e.g., hypertension, DM, osteoporosis, obstructive sleep apnea, cognitive dysfunction, venous thromboembolism, and GHD), lower BMI but more visceral fat, frailty due to muscle weakness and wasting, all of which are exacerbated by sarcopenia, increased rates of postoperative thromboembolic disease, Knosp grade, tumor size, and postoperative cortisol and ACTH nadirs (267, 268). Depression and anxiety are underdiagnosed in the elderly due to its atypical presentation. In comparison, advancing age is associated with decreased hallmark CD features, preoperative 24-hour urinary free cortisol, Ki-67 indices, and AVP deficiency (267, 268), whereas younger patients present more frequently with weight gain, facial rounding/plethora, abdominal striae, hirsutism, menstrual irregularities, dorsocervical fat pad, and acne (269).

Hence, diagnosing CS in older adults is often more challenging as many symptoms overlap with normal aging (Table 3). Hormonal changes with age further complicate testing. Urinary free cortisol (UFC) and plasma cortisol production increase with age, but studies show mixed results regarding age-related differences in late-night salivary cortisol (LNSC) and other hormone levels. Age-related comorbidities, impaired kidney and liver function, smoking and medications can influence UFC and LNSC test accuracy. Furthermore, there is the apparent loss of feedback in elderly subjects, which may be due to alterations in the glucocorticoid receptor sensitivity in the hippocampus that is linked to age-related cell loss, the potential effect of interfering concomitant drugs (e.g., phenobarbital, phenytoin, and carbamazepine), malabsorption, and the underlying presence of depression and anxiety (269). To improve the diagnostic accuracy for CS, three clinical risk scoring systems have been proposed in Spanish (270), Italian (271) and United States cohorts (272); however, these scoring systems have not been formally validated in elderly patients.

Table 3. Challenges in the Management of Cushing Syndrome in the Elderly	
Diagnosis	Lack of typical Cushing syndrome symptoms (e.g., skin changes, weigh gain)
	Overlap of some symptoms/comorbidities that might be related to Cushing syndrome and aging (e.g., hypertension, diabetes mellitus, muscle weakness, cognitive impairment and catabolic state)
	Multiple factors influencing laboratory results in the diagnostic workup of hypercortisolism (age-related changes in the hypothalamic-pituitary adrenal axis, impaired renal function, poor nutrition intake, comorbidities, drugs)
Treatment	Greater pre- and postoperative risk and complications
	Lack of data concerning safety and efficacy of drugs in the elderly population
	Polypharmacy is common in the elderly with resulting greater risk of drug- drug interactions
Outcome	Higher morbidity and mortality rates
	Persistent impairment of quality of life despite achieving biochemical control of the disease

Transsphenoidal surgery is the first-line treatment for CD (268) and is generally safe and effective in elderly patients when performed in specialized centers (273). Complications such as delayed hyponatremia are more common in older adults, requiring careful postoperative management. Despite having more comorbidities and higher surgical risk, elderly patients achieve remission rates and complication profiles comparable to those in younger patients (125). However, younger individuals undergo surgery more frequently and show higher relapse rates, possibly due to more aggressive tumor behavior and longer follow-up duration (125).

Older patients are more frequently treated with medical therapy or radiotherapy, especially when surgery is not feasible. Medical treatments, including osilodrostat, ketoconazole, metyrapone, and mitotane, show varying levels of efficacy in the elderly, with some age-related limitations in data. Etomidate can be used in severe cases at lower doses. Radiotherapy is effective in about two-thirds of elderly patients but carries risks such as cognitive decline and cerebrovascular events. Age does not seem to impact the success of stereotactic radiosurgery, but more comparative studies are needed.

In terms of prognosis, older age is associated with increased mortality, particularly from cardiovascular causes, regardless of treatment outcomes. Factors such as male sex, pre-existing DM, and depression increase cardiovascular risk (267, 268). In the ERCUSYN cohort, mortality was independently associated with age (268). Quality of life remains impaired in many older patients due to ongoing comorbidities, residual symptoms, and the burden of multiple treatments. While younger patients report more concerns about physical appearance and social roles, older patients are more affected by fatigue, muscle weakness, cognitive issues, and depression, which often persist despite treatment (269).

Acromegaly

Due to increasing life expectancy in the general population (108), recent studies have shown an increase in the incidence and prevalence of

acromegaly in the elderly (274, 275). Essentially, elderly acromegaly patients can be divided into two groups: those with a new diagnosis > 65 years of age and those with early-onset acromegaly who have grown older over time (276, 277). In older acromegaly patients, IGF-I levels are usually lower, and the clinical phenotype is milder than in younger patients, making the diagnosis more challenging. In a series of 96 patients reported by Ceccato *et al.* (278), 13 (14%) of newly diagnosed cases of patients were > 65 years and had relatively low IGF-I levels. Among these patients, 11 (85%) of them were initially treated with medical therapy and half normalized their IGF-I levels after 6 months without undergoing pituitary surgery. Moreover, acromegaly is commonly associated with several complications, such as DM, renal impairment, and musculoskeletal disorders that may independently lower IGF-I levels (279-281). Consequently, an older patient with acromegaly may present with IGF-I values within the reference range or only marginally elevated. Consistent with this, previous studies have described older adults with acromegaly and normal or even low IGF-I levels (282, 283). Additionally, the characteristic facial changes, arthralgias, asthenia, paresthesia and sensation of enlargement of the lower limbs may be more subtle than younger patients (276, 277), which may lead to the confusion with features of normal aging and contribute to the delay in diagnosis. Visual abnormalities may also be confused with symptoms of age-related eye diseases such as cataracts, macular degeneration and vascular eye diseases (284, 285). Therefore, the clinical picture may be confounded with features associated with aging and clinicians will need to be aware of the nuances associated with elderly compared with younger acromegaly patients (Table 4).

Table 4. Clinical features, Complications and Response to Treatment of Elderly Patients with Acromegaly	
Clinical phenotype	Milder in elderly vs. younger patients
Tumor size	Smaller tumors in elderly vs younger patients
Basal GH and IGF-I levels and post-OGTT GH nadir levels	Lower in elderly vs. younger patients
Hypertension, glucose metabolism abnormalities and arthropathies	More frequent in elderly patients vs age-matched controls
Left ventricular hypertrophy	Characteristic of elderly patients
Risk of diabetes mellitus, hypertension and cancer	Age-related
Arthropathy and vertebral fracture risk	Not age-related
Surgery	Safe but increased comorbidity and anesthetic risk
Somatostatin receptor ligand treatment	Better treatment response in elderly vs younger patients, but close attention to blood glucose, especially with the use of pasireotide, and gastrointestinal symptoms due to higher prevalence of biliary tract disease, is essential
Pegvisomant treatment	In older patients, close monitoring of liver and renal function tests is recommended due to higher prevalence of pre-existing chronic liver and renal disease

Acromegaly-related comorbidities (e.g., colon polyps, thyroid cancer, obstructive sleep apnea, hypertension, and rheumatologic complications) are more prevalent in the elderly than in younger patients (278). In fact, changes in carbohydrate metabolism and hypertension in the elderly can be considered as related to aging itself, and therefore the diagnosis of acromegaly may be missed (285). The estimated prevalence of DM in acromegaly is higher in patients > 65 years than in younger patients (27%-86% *vs.* 19%-56%) (286), and the most characteristic predisposing factors for DM were older age, longer duration of acromegaly, and family history of DM (287, 288). In older patients, congestive heart failure as end-stage acromegalic cardiomyopathy occurs more frequently (287). It is suggested that aging and long duration of exposure to GH excess are key determinants of cardiac abnormalities (289, 290). Interestingly, in elderly acromegaly patients the frequency of rheumatologic complications (arthralgia, carpal tunnel or osteoarthritis) does not seem to be different from the elderly population without acromegaly (291). This finding may be explained by the prevalence of these complaints in the general elderly population, as well as by the inaccuracy of questionnaires addressing this issue. Elderly patients with acromegaly also exhibited a higher frequency of impaired cognitive functions, reduced mobility, difficulty in performing daily activities, and dementia, as compared with their age-matched counterparts without acromegaly (292). In terms of quality of life, Yamamoto *et al*. (293) reported different factors affected older vs younger patients, with arthropathy, higher BMI, treatment modalities and hydrocortisone replacement therapy being important factors in contributing to the impairment of disease-specific quality of life in older patients.

Given the appropriate clinical and neuroradiological context, the diagnosis of new or recurrent acromegaly is primarily based on the determination of circulating levels of IGF-I (294). Circulating IGF-I levels decline with increasing age in acromegaly (295, 296); therefore age-dependent IGF-I cutoffs are required to aid diagnosis in the elderly. Additionally, IGF-I levels are potentially influenced by DM, chronic kidney disease, liver diseases, insulin resistance and nutritional deficiencies (297), all of which are more prevalent in the elderly. However, some patients with acromegaly can show persistent or intermittent discordance between GH and IGF-I after undergoing pituitary surgery (298, 299), and age yields a highly significant effect on the serum GH/IGF-I relationship such that for a given serum GH value, older patients might show lower serum IGF-I values (296). Therefore, clinicians should proceed with caution in using solely IGF-I levels to diagnose acromegaly in the elderly, and evaluation of the GH suppression oral glucose tolerance test (OGTT) as a complementary laboratory investigation in doubtful cases is recommended (294). The introduction of ultrasensitive chemiluminescent assays for GH has led to the adoption of a lower GH threshold of 0.4 µg/L (300). However, an equivocal GH response to the OGTT can be seen in association with aging. Considering that basal GH levels are lower in the elderly and that this trend is maintained in acromegalic patients, numerous studies showed that post-OGTT nadir GH negatively correlates with age. In a cohort of naive acromegalic patients (19–77 years), baseline GH and IGF-I levels and GH nadir levels after OGTT were lower in patients with an age >60 years (285). A potential caveat to consider is that elderly patients show higher incidence of DM and cannot undergo the OGTT; in these cases, the diurnal GH profile could represent an alternative approach. In a cohort of patients undergoing pituitary surgery for acromegaly, the assessment of disease remission by the GH profile showed different cutoffs in older compared to middle-aged patients (1.4 vs. 2.3 µg/L) (301). Therefore, age appears to be a fundamental factor to be considered in the diagnosis and evaluation of acromegaly activity.

Following biochemical diagnosis, contrast enhanced magnetic resonance imaging (MRI) of the sellar region is required to assess tumor size, localization, and invasiveness (300). Gadolinium enhancement should

however be used with caution or be avoided in patients with renal impairment. If MRI is contraindicated or unavailable, pituitary computerized tomography can be performed (300). Despite some data pointing to smaller tumors in older acromegaly population (302), this finding has not been confirmed by most studies (276, 277, 284).

Although to date there are no published studies that have directly compared histopathological features of GH-secreting adenomas between elderly and non-elderly patients, several reports suggest age-related differences in tumor subtypes and clinical behavior. Additionally, previous studies also demonstrated a trend towards the diagnosis of sparsely granulated (SG) adenomas compared with densely granulated (DG) adenomas in younger acromegaly patients (303, 304). Cuevas-Ramos *et al*. (305) in a large retrospective study of 338 acromegaly patients, found a group of individuals with smaller, less aggressive DG tumors with a higher expression of SSTR2 and a higher mean age at diagnosis. These findings suggest a correlation between tumor granulation pattern and age, with SG tumors linked to younger age and more aggressive behavior, and DG tumors associated with older age and more favorable treatment responsiveness.

Transsphenoidal surgery has been shown to be a safe treatment modality for elderly patients with acromegaly (286). However, transsphenoidal surgery and radiotherapy tend to be performed less commonly, whereas primary medical treatment was offered more frequently in elderly compared to younger subjects. It is likely that elderly patients are poorer surgical candidates due to the increased age- and acromegaly-related comorbidities, and radiotherapy is not often considered because of its delayed effects over months to years in decreasing GH secretion. Increased cancer risk in acromegaly continues to be a matter of debate (306, 307), as the relationship between the oncological risk and excess GH exposure in acromegaly has yet to be fully elucidated. The utility of pegvisomant, a GH receptor antagonist approved by the FDA for the treatment of acromegaly, as a targeted intervention on GH action to improve the prognosis of cancer has recently been proposed but requires further clarification (308). Conversely, a recent study by Pascual-Corrales *et al.* (309) of 604 acromegaly patients (median age 48.5 years) having undergone transsphenoidal surgery demonstrated that remission of preoperative DM was more commonly seen in older patients, especially in those that did not develop postoperative hypopituitarism. These investigators postulated that because older patients tend to be more insulin resistant at muscle level, the decrease in insulin resistance after surgery as reported by Moller *et al.* (310) is an important factor in the improvement of postoperative glucose metabolism. Regarding cardiovascular comorbidities, the increased prevalence of hypertension with aging could also be a contributing factor (311) rather than the greater prevalence of hypertension in acromegaly (312). Hence, the prevalence of some of the more common acromegaly-related comorbidities is higher in elderly patients, especially when longer follow-up is performed.

Hyponatremia

Hyponatremia is the most common electrolyte disorder in clinical practice (313), especially when accompanied by plasma hypo- osmolality. 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, yet still significant, incidence of 1% to 4% (314). The incidence of hyponatremia in older populations varies between 0.2% and 29.8%, depending on the criteria used (242).

The most common causes of hyponatremia in older individuals are SIAD, drug therapy, and decreased solute intake. SIAD can be caused by many types of diseases and injuries more common in older

individuals, including central nervous system injury and degeneration, pulmonary diseases, paraneoplastic malignancy, nausea, pain, and an idiopathic form of SIAD. Studies have demonstrated that SIAD accounts for approximately 50% to 59% of the hyponatremia observed in some older populations, and 26% to 60% of older patients with SIAD appear to have the idiopathic form of this disorder (315, 316). Some drugs commonly used in the elderly have been associated with SIAD, including many antipsychotic, antidepressant, and antiepileptic drugs (317). The drug class most commonly implicated in causing hyponatremia is thiazide diuretics, which does not cause SIAD but rather secondary AVP secretion due to solute depletion and baroreceptor stimulation (318).

Hyponatremia in older individuals is frequently associated with multiple clinically significant outcomes including neurocognitive effects and falls (319), hospital readmission and need for long-term care (320), incidence of bone fractures (321), and osteoporosis (322). Hyponatremia is a strong independent predictor of mortality, reported to be as high as 60% in some series (323). In a study of the association between asymptomatic hyponatremia and gait instability, falls and attention deficits, a subset of 12 patients with hyponatremia secondary to SIAD with [Na+] in the range of 124 to 130 mmol/L demonstrated significant gait instability that normalized with correction of hyponatremia (324)). The effect of hyponatremia on bone quality has also been demonstrated between chronic hyponatremia and metabolic bone loss, with chronic hyponatremia associated with odds ratios of 4.0 for osteoporosis and 3.0 for fractures (325). Thus, hyponatremia-induced bone resorption and associated osteoporosis are unique in that they represent attempts of the body to preserve sodium homeostasis at the expense of bone structural integrity.

TREATMENT OF HYPONATREMIA

Treatment of hypo-osmolality and hyponatremia in the elderly generally should follow the same guidelines as in younger patients, particularly with regards to the 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 to 5 mmol/L in randomized controlled trials (326). If pharmacologic treatment is necessary, urea, furosemide in combination with sodium chloride tablets, demeclocycline and vasopressin receptor antagonist may be considered (327). Although each of these treatments can be effective in individual circumstances, vasopressin receptor antagonist is the only therapy currently FDA-approved for treatment of hyponatremia. Several randomized controlled clinical trials have been published on the efficacy and safety of vasopressin antagonist treatment for hyponatremia (328, 329); however these agents have not been utilized much in older individuals even though many older individuals were enrolled in the clinical trials, presumably due to cost reasons and the need for these agents to be only initiated as an in-patient. More recently, the therapeutic effect of empagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, in treating SIAD-induced hyponatremia was studied given that empagliflozin promotes osmotic diuresis via urinary glucose excretion, thereby causes increased electrolyte free water clearance (330, 331). Refardt *et al.* (332) demonstrated the efficacy of 4 days empagliflozin treatment in correcting hyponatremia in hospitalized patients with SIAD with a mean age 74 years. These investigators subsequently performed a randomized, double-blind, placebo-controlled, crossover study investigating 4 weeks of empagliflozin treatment and found a relevant increase in serum [Na+] levels compared with placebo in older outpatients with chronic SIAD who had a median age of 71.5 years and improvement in neurocognitive function (333). Overall, empagliflozin treatment was safe and well tolerated in both studies (332). However, larger studies in in- and out-patient settings are still needed to confirm these treatment effects in elderly patients before SGLT2 inhibitors can be recommended routinely to treat SIAD-induced hyponatremia in the elderly.

CONCLUSION

Aging is associated with complex physiological changes of the hypothalamic-pituitary axis, which occur independently of age-related diseases. Decreased levels of estrogen and testosterone occur universally in the elderly, accompanied by increased LH, FSH, and SHBG levels, and decreased GH, IGF-I, and DHEAS levels. By contrast, endocrine functions critical for survival, such as thyroid and adrenal function, show relatively minimal changes in basal hormone levels with aging, while intricate regulatory alterations still occur within the HPT and HPA axes. The clinical implications of these hormonal changes vary and remain an active area of investigation. In women, menopause leads to significant physiological changes, including disruptions in lipid metabolism, bone loss, vasomotor symptoms, cognitive changes, and elevated cardiovascular risk. In men, age-related decline in gonadal function has been linked to increased fat mass, reduced muscle and bone mass, fatigue, depression, anemia, sexual dysfunction, insulin resistance, and elevated cardiovascular risk. Similarly, the age-related decline in the GH–IGF-I axis contributes to reduced protein synthesis, loss of lean body and bone mass, and impaired immune function. When assessing elderly patients with AGHD and acromegaly, IGF-I levels may not be a reliable biomarker and should be carefully interpreted within a broader clinical context to define diagnosis and treatment efficacy. In comparison, changes in adrenal hormone production tend to have less clearly defined clinical consequences. Differentiating whether these changes are related to the aging process or whether they are due to other processes, such as intercurrent chronic diseases, inflammation, nutritional status, or a combination of these, is challenging. Over the past few years, numerous studies have explored hormone replacement strategies to restore hormone levels in the elderly to "youthful" ranges, aiming to counteract these age-related changes. However, despite these efforts, it remains unclear whether such interventions yield meaningful long-term health benefits, and may, in fact, increase potential risks and adverse side-effects. To date, no hormonal therapeutic interventions have been proven to be a definitive solution for reversing the aging process. On the other hand, management of conditions such as Cushing disease and acromegaly are more challenging in the older versus younger individuals due to many potential pitfalls in terms of symptom recognition and reliability of hormone testing, greater burden of concurrent comorbidities, increased tendency of polypharmacy and possible drug-to-drug interactions, and lack of information about safety and efficacy of treatment options. More studies are needed to establish effective approaches aimed at shortening the exposure time to excessive cortisol and GH and optimizing the diagnostic and therapeutic strategies specifically addressed at elderly patients with the primary goal of normalizing survival, managing comorbidities and promoting satisfactory, age-adjusted improvements in quality of life.

REFERENCES

1. Pataky MW, Young WF, Nair KS. Hormonal and Metabolic Changes of Aging and the Influence of Lifestyle Modifications. Mayo Clin Proc. 2021;96:788-814.
2. Veldhuis JD. Changes in pituitary function with ageing and implications for patient care. Nat Rev Endocrinol. 2013;9:205-215.
3. Chahal HS, Drake WM. The endocrine system and ageing. J Pathol. 2007;211:173-180.
4. Caputo M, Mele C, Ferrero A, et al. Dynamic Tests in Pituitary Endocrinology: Pitfalls in Interpretation during Aging. Neuroendocrinology. 2022;112:1-14.
5. Cappola AR, Auchus RJ, El-Hajj Fuleihan G, et al. Hormones and Aging: An Endocrine Society Scientific Statement. J Clin Endocrinol Metab. 2023;108:1835-1874.
6. Van Cauter E, Kerkhofs M, Caufriez A, Van Onderbergen A, Thorner MO, Copinschi G. A quantitative estimation of growth hormone secretion in normal man: reproducibility

and relation to sleep and time of day. J Clin Endocrinol Metab. 1992;74:1441-1450.

7. Zadik Z, Chalew SA, McCarter RJ, Jr., Meistas M, Kowarski AA. The influence of age on the 24-hour integrated concentration of growth hormone in normal individuals. J Clin Endocrinol Metab. 1985;60:513-516.

8. Iranmanesh A, Lizarralde G, Veldhuis JD. Age and relative adiposity are specific negative determinants of the frequency and amplitude of growth hormone (GH) secretory bursts and the half-life of endogenous GH in healthy men. J Clin Endocrinol Metab. 1991;73:1081-1088.

9. Ho KY, Evans WS, Blizzard RM, et al. Effects of sex and age on the 24-hour profile of growth hormone secretion in man: importance of endogenous estradiol concentrations. J Clin Endocrinol Metab. 1987;64:51-58.

10. Giustina A, Veldhuis JD. Pathophysiology of the neuroregulation of growth hormone secretion in experimental animals and the human. Endocr Rev. 1998;19:717-797.

11. Nass R, Pezzoli SS, Oliveri MC, et al. Effects of an oral ghrelin mimetic on body composition and clinical outcomes in healthy older adults: a randomized trial. Ann Intern Med. 2008;149:601-611.

12. Feldman HA, Longcope C, Derby CA, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab. 2002;87:589-598.

13. Arvat E, Ceda GP, Di Vito L, et al. Age-related variations in the neuroendocrine control, more than impaired receptor sensitivity, cause the reduction in the GH-releasing activity of GHRPs in human aging. Pituitary. 1998;1:51-58.

14. O'Connor KG, Tobin JD, Harman SM, et al. Serum levels of insulin-like growth factor-I are related to age and not to body composition in healthy women and men. J Gerontol A Biol Sci Med Sci. 1998;53:M176-182.

15. Aimaretti G, Fanciulli G, Bellone S, et al. Enhancement of the peripheral sensitivity to growth hormone in adults with GH deficiency. Eur J Endocrinol. 2001;145:267-272.

16. Cruz-Jentoft AJ, Volkert D. Malnutrition in Older Adults. N Engl J Med. 2025;392:2244-2255.

17. Georgieva M, Xenodochidis C, Krasteva N. Old age as a risk factor for liver diseases: Modern therapeutic approaches. Exp Gerontol. 2023;184:112334.

18. Mallappallil M, Friedman EA, Delano BG, McFarlane SI, Salifu MO. Chronic kidney disease in the elderly: evaluation and management. Clin Pract (Lond). 2014;11:525-535.

19. Sinclair A, Saeedi P, Kaundal A, Karuranga S, Malanda B, Williams R. Diabetes and global ageing among 65-99-year-old adults: Findings from the International Diabetes Federation Diabetes Atlas, 9(th) edition. Diabetes Res Clin Pract. 2020;162:108078.

20. Yuan S, Larsson SC. Epidemiology of sarcopenia: Prevalence, risk factors, and consequences. Metabolism. 2023;144:155533.

21. Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL. Trends in Obesity and Severe Obesity Prevalence in US Youth and Adults by Sex and Age, 2007-2008 to 2015-2016. JAMA. 2018;319:1723-1725.

22. Parekh N, Roberts CB, Vadiveloo M, Puvananayagam T, Albu JB, Lu-Yao GL. Lifestyle, anthropometric, and obesity-related physiologic determinants of insulin-like growth factor-1 in the Third National Health and Nutrition Examination Survey (1988-1994). Ann Epidemiol. 2010;20:182-193.

23. Tausendfreund O, Reif H, Bidlingmaier M, et al. Estimation of the biological variation of IGF-I in multimorbid geriatric patients and its clinical implications. Pituitary. 2025;28:59.

24. Leung KC, Johannsson G, Leong GM, Ho KK. Estrogen regulation of growth hormone action. Endocr Rev. 2004;25:693-721.

25. Leung KC, Doyle N, Ballesteros M, et al. Estrogen inhibits GH signaling by suppressing GH-induced JAK2 phosphorylation, an effect mediated by SOCS-2. Proc Natl Acad Sci U S A. 2003;100:1016-1021.

26. Weissberger AJ, Ho KK, Lazarus L. Contrasting effects of oral and transdermal routes of estrogen replacement therapy on 24-hour growth hormone (GH) secretion, insulin-like growth factor I, and GH-binding protein in postmenopausal women. J Clin Endocrinol Metab. 1991;72:374-381.

27. Brill KT, Weltman AL, Gentili A, et al. Single and combined effects of growth hormone and testosterone administration on measures of body composition, physical performance, mood, sexual function, bone turnover, and muscle gene expression in healthy older men. J Clin Endocrinol Metab. 2002;87:5649-5657.

28. Giannoulis MG, Sonksen PH, Umpleby M, et al. The effects of growth hormone and/or testosterone in healthy elderly

men: a randomized controlled trial. J Clin Endocrinol Metab. 2006;91:477-484.

29. Olarescu NC, Gunawardane K, Hanson TK, Moller N, Jorgensen JOL. Normal Physiology of Growth Hormone in Normal Adults. In: Feingold KR, Ahmed SF, Anawalt B, et al., eds. Endotext. South Dartmouth (MA)2000.

30. Broglio F, Benso A, Castiglioni C, et al. The endocrine response to ghrelin as a function of gender in humans in young and elderly subjects. J Clin Endocrinol Metab. 2003;88:1537-1542.

31. Ilich JZ, Kelly OJ, Inglis JE, Panton LB, Duque G, Ormsbee MJ. Interrelationship among muscle, fat, and bone: connecting the dots on cellular, hormonal, and whole body levels. Ageing Res Rev. 2014;15:51-60.

32. JafariNasabian P, Inglis JE, Reilly W, Kelly OJ, Ilich JZ. Aging human body: changes in bone, muscle and body fat with consequent changes in nutrient intake. J Endocrinol. 2017;234:R37-R51.

33. Blackman MR, Sorkin JD, Munzer T, et al. Growth hormone and sex steroid administration in healthy aged women and men: a randomized controlled trial. JAMA. 2002;288:2282-2292.

34. Liu H, Bravata DM, Olkin I, et al. Systematic review: the safety and efficacy of growth hormone in the healthy elderly. Ann Intern Med. 2007;146:104-115.

35. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR, Baltimore Longitudinal Study of A. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab. 2001;86:724-731.

36. Tenover JS, Matsumoto AM, Plymate SR, Bremner WJ. The effects of aging in normal men on bioavailable testosterone and luteinizing hormone secretion: response to clomiphene citrate. J Clin Endocrinol Metab. 1987;65:1118-1126.

37. Wu FC, Tajar A, Pye SR, et al. Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. J Clin Endocrinol Metab. 2008;93:2737-2745.

38. Mahmoud AM, Goemaere S, El-Garem Y, Van Pottelbergh I, Comhaire FH, Kaufman JM. Testicular volume in relation to hormonal indices of gonadal function in community-dwelling elderly men. J Clin Endocrinol Metab. 2003;88:179-184.

39. Liu PY, Iranmanesh A, Nehra AX, Keenan DM, Veldhuis JD. Mechanisms of hypoandrogenemia in healthy aging men. Endocrinol Metab Clin North Am. 2005;34:935-955, ix.

40. Xu P, Zeng R, Wan Q, et al. Aging-related increases in serum sex hormone-binding globulin levels in men might be related to increased synthesis. Exp Gerontol. 2023;179:112249.

41. Gray A, Feldman HA, McKinlay JB, Longcope C. Age, disease, and changing sex hormone levels in middle-aged men: results of the Massachusetts Male Aging Study. J Clin Endocrinol Metab. 1991;73:1016-1025.

42. Hak AE, Witteman JC, de Jong FH, Geerlings MI, Hofman A, Pols HA. Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: the Rotterdam study. J Clin Endocrinol Metab. 2002;87:3632-3639.

43. Wang C, Nieschlag E, Swerdloff R, et al. Investigation, treatment and monitoring of late-onset hypogonadism in males. Int J Androl. 2009;32:1-10.

44. Wu FC, Tajar A, Beynon JM, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med. 2010;363:123-135.

45. Broekmans FJ, Soules MR, Fauser BC. Ovarian aging: mechanisms and clinical consequences. Endocr Rev. 2009;30:465-493.

46. Santoro N, Randolph JF, Jr. Reproductive hormones and the menopause transition. Obstet Gynecol Clin North Am. 2011;38:455-466.

47. Clarke SA, Dhillo WS. Kisspeptin across the human lifespan:evidence from animal studies and beyond. J Endocrinol. 2016;229:R83-98.

48. Shaw ND, Srouji SS, Histed SN, McCurnin KE, Hall JE. Aging attenuates the pituitary response to gonadotropin-releasing hormone. J Clin Endocrinol Metab. 2009;94:3259-3264.

49. Kaminska MS, Schneider-Matyka D, Rachubinska K, Panczyk M, Grochans E, Cybulska AM. Menopause Predisposes Women to Increased Risk of Cardiovascular Disease. J Clin Med. 2023;12.

50. Lightman SL, Birnie MT, Conway-Campbell BL. Dynamics of ACTH and Cortisol Secretion and Implications for Disease. Endocr Rev. 2020;41.

51. Veldhuis JD, Sharma A, Roelfsema F. Age-dependent and gender-dependent regulation of hypothalamic-

adrenocorticotropic-adrenal axis. Endocrinol Metab Clin North Am. 2013;42:201-225.

52. Le NP, Varadhan R, Fried LP, Cappola AR. Cortisol and Dehydroepiandrosterone Response to Adrenocorticotropic Hormone and Frailty in Older Women. J Gerontol A Biol Sci Med Sci. 2021;76:901-905.

53. Morgan E, Schumm LP, McClintock M, Waite L, Lauderdale DS. Sleep Characteristics and Daytime Cortisol Levels in Older Adults. Sleep. 2017;40.

54. Tiganescu A, Walker EA, Hardy RS, Mayes AE, Stewart PM. Localization, age- and site-dependent expression, and regulation of 11beta-hydroxysteroid dehydrogenase type 1 in skin. J Invest Dermatol. 2011;131:30-36.

55. Kilgour AH, Gallagher IJ, MacLullich AM, et al. Increased skeletal muscle 11betaHSD1 mRNA is associated with lower muscle strength in ageing. PLoS One. 2013;8:e84057.

56. Fassnacht M, Tsagarakis S, Terzolo M, et al. European Society of Endocrinology clinical practice guidelines on the management of adrenal incidentalomas, in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2023;189:G1-G42.

57. Pelsma ICM, Fassnacht M, Tsagarakis S, et al. Comorbidities in mild autonomous cortisol secretion and the effect of treatment: systematic review and meta-analysis. Eur J Endocrinol. 2023;189:S88-S101.

58. Orentreich N, Brind JL, Rizer RL, Vogelman JH. Age changes and sex differences in serum dehydroepiandrosterone sulfate concentrations throughout adulthood. J Clin Endocrinol Metab. 1984;59:551-555.

59. Auchus RJ, Rainey WE. Adrenarche - physiology, biochemistry and human disease. Clin Endocrinol (Oxf). 2004;60:288-296.

60. Goldman N, Glei DA. Sex differences in the relationship between DHEAS and health. Exp Gerontol. 2007;42:979-987.

61. Burger HG. Androgen production in women. Fertil Steril. 2002;77 Suppl 4:S3-5.

62. Turcu AF, Rege J, Auchus RJ, Rainey WE. 11-Oxygenated androgens in health and disease. Nat Rev Endocrinol. 2020;16:284-296.

63. Davio A, Woolcock H, Nanba AT, et al. Sex Differences in 11-Oxygenated Androgen Patterns Across Adulthood. J Clin Endocrinol Metab. 2020;105:e2921-2929.

64. Rege J, Turcu AF, Kasa-Vubu JZ, et al. 11-Ketotestosterone Is the Dominant Circulating Bioactive Androgen During Normal and Premature Adrenarche. J Clin Endocrinol Metab. 2018;103:4589-4598.

65. Harman SM, Wehmann RE, Blackman MR. Pituitary-thyroid hormone economy in healthy aging men: basal indices of thyroid function and thyrotropin responses to constant infusions of thyrotropin releasing hormone. J Clin Endocrinol Metab. 1984;58:320-326.

66. Herrmann J, Heinen E, Kroll HJ, Rudorff KH, Kruskemper HL. Thyroid function and thyroid hormone metabolism in elderly people. Low T3-syndrome in old age? Klin Wochenschr. 1981;59:315-323.

67. van den Beld AW, Visser TJ, Feelders RA, Grobbee DE, Lamberts SW. Thyroid hormone concentrations, disease, physical function, and mortality in elderly men. J Clin Endocrinol Metab. 2005;90:6403-6409.

68. Oddie TH, Meade JH, Jr., Fisher DA. An analysis of published data on thyroxine turnover in human subjects. J Clin Endocrinol Metab. 1966;26:425-436.

69. Jasim S, Papaleontiou M. Considerations in the Diagnosis and Management of Thyroid Dysfunction in Older Adults. Thyroid. 2025;35:624-632.

70. Duarte GC, Araujo LMQ, Magalhaes FF, Almada CMF, Cendoroglo MS. Ultrasonographic assessment of thyroid volume in oldest-old individuals. Arch Endocrinol Metab. 2017;61:269-275.

71. Mariotti S, Franceschi C, Cossarizza A, Pinchera A. The aging thyroid. Endocr Rev. 1995;16:686-715.

72. Razvi SS, Wild H, Ingoe L, et al. Changes in Thyroid Function and Autoimmunity in Older Individuals: Longitudinal Analysis of the Whickham Cohort. J Clin Endocrinol Metab. 2025;110:e3078-e3084.

73. van Heemst D. The ageing thyroid: implications for longevity and patient care. Nat Rev Endocrinol. 2024;20:5-15.

74. Surks MI, Hollowell JG. Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. J Clin Endocrinol Metab. 2007;92:4575-4582.

75. Burch HB. Drug Effects on the Thyroid. N Engl J Med. 2019;381:749-761.

76. Niwattisaiwong S, Burman KD, Li-Ng M. Iodine deficiency: Clinical implications. Cleve Clin J Med. 2017;84:236-244.

77. Thiruvengadam S, Luthra P. Thyroid disorders in elderly: A comprehensive review. Dis Mon. 2021;67:101223.

78. Zimmermann MB, Boelaert K. Iodine deficiency and thyroid disorders. Lancet Diabetes Endocrinol. 2015;3:286-295.

79. Barreca T, Franceschini R, Messina V, Bottaro L, Rolandi E. 24-hour thyroid-stimulating hormone secretory pattern in elderly men. Gerontology. 1985;31:119-123.

80. van Coevorden A, Laurent E, Decoster C, et al. Decreased basal and stimulated thyrotropin secretion in healthy elderly men. J Clin Endocrinol Metab. 1989;69:177-185.

81. Veldhuis JD, Iranmanesh A, Johnson ML, Lizarralde G. Twenty-four-hour rhythms in plasma concentrations of adenohypophyseal hormones are generated by distinct amplitude and/or frequency modulation of underlying pituitary secretory bursts. J Clin Endocrinol Metab. 1990;71:1616-1623.

82. Roelfsema F, Pijl H, Keenan DM, Veldhuis JD. Prolactin secretion in healthy adults is determined by gender, age and body mass index. PLoS One. 2012;7:e31305.

83. Franchimont P, Dourcy C, Legros JJ, et al. Prolactin levels during the menstrual cycle. Clin Endocrinol (Oxf). 1976;5:643-650.

84. Freeman ME, Kanyicska B, Lerant A, Nagy G. Prolactin: structure, function, and regulation of secretion. Physiol Rev. 2000;80:1523-1631.

85. Xie Q, Kang Y, Zhang C, et al. The Role of Kisspeptin in the Control of the Hypothalamic-Pituitary-Gonadal Axis and Reproduction. Front Endocrinol (Lausanne). 2022;13:925206.

86. Kalleinen N, Polo-Kantola P, Irjala K, et al. 24-hour serum levels of growth hormone, prolactin, and cortisol in pre- and postmenopausal women: the effect of combined estrogen and progestin treatment. J Clin Endocrinol Metab. 2008;93:1655-1661.

87. Iranmanesh A, Mulligan T, Veldhuis JD. Mechanisms subserving the physiological nocturnal relative hypoprolactinemia of healthy older men: dual decline in prolactin secretory burst mass and basal release with preservation of pulse duration, frequency, and interpulse interval--a General Clinical Research Center study. J Clin Endocrinol Metab. 1999;84:1083-1090.

88. Arnetz BB, Lahnborg G, Eneroth P. Age-related differences in the pituitary prolactin response to thyrotropin-releasing hormone. Life Sci. 1986;39:135-139.

89. Blackman MR, Kowatch MA, Wehmann RE, Harman SM. Basal serum prolactin levels and prolactin responses to constant infusions of thyrotropin releasing hormone in healthy aging men. J Gerontol. 1986;41:699-705.

90. Albu A, Florea S, Fica S. Is prolactin the missing link in adipose tissue dysfunction of polycystic ovary syndrome patients? Endocrine. 2016;51:163-173.

91. Elgellaie A, Larkin T, Kaelle J, Mills J, Thomas S. Plasma prolactin is higher in major depressive disorder and females, and associated with anxiety, hostility, somatization, psychotic symptoms and heart rate. Compr Psychoneuroendocrinol. 2021;6:100049.

92. Marras C, Beck JC, Bower JH, et al. Prevalence of Parkinson's disease across North America. NPJ Parkinsons Dis. 2018;4:21.

93. Rapoport M, Mamdani M, Shulman KI, Herrmann N, Rochon PA. Antipsychotic use in the elderly: shifting trends and increasing costs. Int J Geriatr Psychiatry. 2005;20:749-753.

94. Cowen LE, Hodak SP, Verbalis JG. Age-associated abnormalities of water homeostasis. Endocrinol Metab Clin North Am. 2013;42:349-370.

95. Phillips PA, Rolls BJ, Ledingham JG, Forsling ML, Morton JJ. Osmotic thirst and vasopressin release in humans: a double-blind crossover study. Am J Physiol. 1985;248:R645-650.

96. Phillips PA, Johnston CI, Gray L. Disturbed fluid and electrolyte homoeostasis following dehydration in elderly people. Age Ageing. 1993;22:S26-33.

97. Mack GW, Weseman CA, Langhans GW, Scherzer H, Gillen CM, Nadel ER. Body fluid balance in dehydrated healthy older men: thirst and renal osmoregulation. J Appl Physiol (1985). 1994;76:1615-1623.

98. Stachenfeld NS, DiPietro L, Nadel ER, Mack GW. Mechanism of attenuated thirst in aging: role of central volume receptors. Am J Physiol. 1997;272:R148-157.

99. Lindeman RD. Assessment of renal function in the old. Special considerations. Clin Lab Med. 1993;13:269-277.

100. Brennan M, Mulkerrin L, O'Keeffe ST, O'Shea PM. Approach to the Management of Hypernatraemia in Older Hospitalised Patients. J Nutr Health Aging. 2021;25:1161-1166.

101. Clark BA, Shannon RP, Rosa RM, Epstein FH. Increased susceptibility to thiazide-induced hyponatremia in the elderly. J Am Soc Nephrol. 1994;5:1106-1111.

102. Filippatos TD, Makri A, Elisaf MS, Liamis G. Hyponatremia in the elderly: challenges and solutions. Clin Interv Aging. 2017;12:1957-1965.

103. Tamma G, Goswami N, Reichmuth J, De Santo NG, Valenti G. Aquaporins, vasopressin, and aging: current perspectives. Endocrinology. 2015;156:777-788.

104. Wong LL, Verbalis JG. Systemic diseases associated with disorders of water homeostasis. Endocrinol Metab Clin North Am. 2002;31:121-140.

105. Davies I, O'Neill PA, McLean KA, Catania J, Bennett D. Age-associated alterations in thirst and arginine vasopressin in response to a water or sodium load. Age Ageing. 1995;24:151-159.

106. Faull CM, Holmes C, Baylis PH. Water balance in elderly people: is there a deficiency of vasopressin? Age Ageing. 1993;22:114-120.

107. Kuratsu J, Ushio Y. Epidemiological study of primary intracranial tumours in elderly people. J Neurol Neurosurg Psychiatry. 1997;63:116-118.

108. Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. Lancet. 2009;374:1196-1208.

109. Liu J, Li C, Xiao Q, et al. Comparison of Pituitary Adenomas in Elderly and Younger Adults: Clinical Characteristics, Surgical Outcomes, and Prognosis. J Am Geriatr Soc. 2015;63:1924-1930.

110. Spina A, Losa M, Mortini P. Pituitary adenomas in elderly patients: clinical and surgical outcome analysis in a large series. Endocrine. 2019;65:637-645.

111. Kurosaki M, Saeger W, Ludecke DK. Pituitary tumors in the elderly. Pathol Res Pract. 2001;197:493-497.

112. Rosinha P, Fonseca L, Amaral C, Ribeiro I, Cardoso MH. Pituitary adenomas in the elderly: Retrospective comparative analysis of clinical/tumor features and surgical data by age group. Medicine (Baltimore). 2022;101:e30825.

113. Grossman R, Mukherjee D, Chaichana KL, et al. Complications and death among elderly patients undergoing pituitary tumour surgery. Clin Endocrinol (Oxf). 2010;73:361-368.

114. Chinezu R, Fomekong F, Lasolle H, et al. Risks and Benefits of Endoscopic Transsphenoidal Surgery for Nonfunctioning Pituitary Adenomas in Patients of the Ninth Decade. World Neurosurg. 2017;106:315-321.

115. Gondim JA, Almeida JP, de Albuquerque LA, Gomes E, Schops M, Mota JI. Endoscopic endonasal transsphenoidal surgery in elderly patients with pituitary adenomas. J Neurosurg. 2015;123:31-38.

116. Kinoshita Y, Kurisu K, Arita K. Nonfunctioning pituitary adenomas in elderly patients. J Clin Neurosci. 2018;53:127-131.

117. Pereira MP, Oh T, Joshi RS, et al. Clinical characteristics and outcomes in elderly patients undergoing transsphenoidal surgery for nonfunctioning pituitary adenoma. Neurosurg Focus. 2020;49:E19.

118. Zhan R, Ma Z, Wang D, Li X. Pure Endoscopic Endonasal Transsphenoidal Approach for Nonfunctioning Pituitary Adenomas in the Elderly: Surgical Outcomes and Complications in 158 Patients. World Neurosurg. 2015;84:1572-1578.

119. Marenco HA, Zymberg ST, Santos Rde P, Ramalho CO. Surgical treatment of non-functioning pituitary macroadenomas by the endoscopic endonasal approach in the elderly. Arq Neuropsiquiatr. 2015;73:764-769.

120. Yunoue S, Tokimura H, Tominaga A, et al. Transsphenoidal surgical treatment of pituitary adenomas in patients aged 80 years or older. Neurosurg Rev. 2014;37:269-276; discussion 276-267.

121. Locatelli M, Bertani G, Carrabba G, et al. The trans-sphenoidal resection of pituitary adenomas in elderly patients and surgical risk. Pituitary. 2013;16:146-151.

122. Kristof RA, Rother M, Neuloh G, Klingmuller D. Incidence, clinical manifestations, and course of water and electrolyte metabolism disturbances following transsphenoidal pituitary adenoma surgery: a prospective observational study. J Neurosurg. 2009;111:555-562.

123. Wilson PJ, Omay SB, Kacker A, Anand VK, Schwartz TH. Endonasal endoscopic pituitary surgery in the elderly. J Neurosurg. 2018;128:429-436.

124. Castle-Kirszbaum M, McCormack A, Ovenden C, et al. Frailty and pituitary surgery: a systematic review. Pituitary. 2025;28:43.

125. Tuleasca C, Ducos Y, Leroy HA, et al. Transsphenoidal resection for pituitary adenoma in elderly versus younger patients: a systematic review and meta-analysis. Acta Neurochir (Wien). 2020;162:1297-1308.

126. Tanaka Y, Hongo K, Tada T, Sakai K, Kakizawa Y, Kobayashi S. Growth pattern and rate in residual nonfunctioning pituitary adenomas: correlations among

tumor volume doubling time, patient age, and MIB-1 index. J Neurosurg. 2003;98:359-365.

127. Gruppetta M, Formosa R, Falzon S, et al. Expression of cell cycle regulators and biomarkers of proliferation and regrowth in human pituitary adenomas. Pituitary. 2017;20:358-371.

128. Chalif EJ, Morshed RA, Young JS, Haddad AF, Jain S, Aghi MK. Pituitary adenoma in the elderly: surgical outcomes and treatment trends in the United States. J Neurosurg. 2022;137:1687-1698.

129. Tanriverdi F, Dokmetas HS, Kebapci N, et al. Etiology of hypopituitarism in tertiary care institutions in Turkish population: analysis of 773 patients from Pituitary Study Group database. Endocrine. 2014;47:198-205.

130. Javanbakht A, D'Apuzzo M, Badie B, Salehian B. Pituitary metastasis: a rare condition. Endocr Connect. 2018;7:1049-1057.

131. Yuen KCJ, Biller BMK, Radovick S, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Growth Hormone Deficiency in Adults and Patients Transitioning from Pediatric to Adult Care. Endocr Pract. 2019;25:1191-1232.

132. Jacques JP, Valadares LP, Moura AC, Oliveira MRF, Naves LA. Frequency and clinical characteristics of hypophysitis and hypopituitarism in patients undergoing immunotherapy - A systematic review. Front Endocrinol (Lausanne). 2023;14:1091185.

133. Iglesias P. Pituitary Apoplexy: An Updated Review. J Clin Med. 2024;13.

134. Salomon F, Cuneo RC, Hesp R, Sonksen PH. The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. N Engl J Med. 1989;321:1797-1803.

135. Toogood AA, O'Neill PA, Shalet SM. Beyond the somatopause: growth hormone deficiency in adults over the age of 60 years. J Clin Endocrinol Metab. 1996;81:460-465.

136. Appelman-Dijkstra NM, Claessen KM, Roelfsema F, Pereira AM, Biermasz NR. Long-term effects of recombinant human GH replacement in adults with GH deficiency: a systematic review. Eur J Endocrinol. 2013;169:R1-14.

137. Kokshoorn NE, Biermasz NR, Roelfsema F, Smit JW, Pereira AM, Romijn JA. GH replacement therapy in elderly GH-deficient patients: a systematic review. Eur J Endocrinol. 2011;164:657-665.

138. Hilding A, Hall K, Wivall-Helleryd IL, Saaf M, Melin AL, Thoren M. Serum levels of insulin-like growth factor I in 152 patients with growth hormone deficiency, aged 19-82 years, in relation to those in healthy subjects. J Clin Endocrinol Metab. 1999;84:2013-2019.

139. Yuen KCJ, Birkegard AC, Blevins LS, et al. Development of a Novel Algorithm to Identify People with High Likelihood of Adult Growth Hormone Deficiency in a US Healthcare Claims Database. Int J Endocrinol. 2022;2022:7853786.

140. Yuen KCJ. Growth Hormone Stimulation Tests in Assessing Adult Growth Hormone Deficiency. In: Feingold KR, Ahmed SF, Anawalt B, et al., eds. Endotext. South Dartmouth (MA)2000.

141. Tavares AB, Seixas-da-Silva IA, Silvestre DH, Paixao CM, Jr., Vaisman M, Conceicao FL. Potential risks of glucagon stimulation test in elderly people. Growth Horm IGF Res. 2015;25:53-56.

142. Yuen KCJ, Johannsson G, Ho KKY, Miller BS, Bergada I, Rogol AD. Diagnosis and testing for growth hormone deficiency across the ages: a global view of the accuracy, caveats, and cut-offs for diagnosis. Endocr Connect. 2023;12.

143. Garcia JM, Biller BMK, Korbonits M, et al. Macimorelin as a Diagnostic Test for Adult GH Deficiency. J Clin Endocrinol Metab. 2018;103:3083-3093.

144. Garcia JM, Biller BMK, Korbonits M, et al. Sensitivity and specificity of the macimorelin test for diagnosis of AGHD. Endocr Connect. 2021;10:76-83.

145. Garcia JM, Swerdloff R, Wang C, et al. Macimorelin (AEZS-130)-stimulated growth hormone (GH) test: validation of a novel oral stimulation test for the diagnosis of adult GH deficiency. J Clin Endocrinol Metab. 2013;98:2422-2429.

146. van Bunderen CC, Lips P, Kramer MH, Drent ML. Comparison of low-normal and high-normal IGF-1 target levels during growth hormone replacement therapy: A randomized clinical trial in adult growth hormone deficiency. Eur J Intern Med. 2016;31:88-93.

147. Fleseriu M, Hashim IA, Karavitaki N, et al. Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101:3888-3921.

148. Toogood AA, Shalet SM. Growth hormone replacement therapy in the elderly with hypothalamic-pituitary disease:

a dose-finding study. J Clin Endocrinol Metab. 1999;84:131-136.

149. Boguszewski MCS, Boguszewski CL, Chemaitilly W, et al. Safety of growth hormone replacement in survivors of cancer and intracranial and pituitary tumours: a consensus statement. Eur J Endocrinol. 2022;186:P35-P52.

150. Yuen KC, Popovic V. Growth hormone replacement in patients with a history of malignancy: a review of the literature and best practice for offering treatment. Expert Rev Endocrinol Metab. 2015;10:319-326.

151. Webb SM, Rigla M, Wagner A, Oliver B, Bartumeus F. Recovery of hypopituitarism after neurosurgical treatment of pituitary adenomas. J Clin Endocrinol Metab. 1999;84:3696-3700.

152. Minniti G, Traish D, Ashley S, Gonsalves A, Brada M. Fractionated stereotactic conformal radiotherapy for secreting and nonsecreting pituitary adenomas. Clin Endocrinol (Oxf). 2006;64:542-548.

153. Kong X, Zhang J, Chen S, et al. Immune checkpoint inhibitors: breakthroughs in cancer treatment. Cancer Biol Med. 2024;21:451-472.

154. Wang F, Shi X, Yu X, Yang Y. Immune checkpoint inhibitor-induced isolated adrenocorticotropic hormone deficiency: a systematic review. Front Endocrinol (Lausanne). 2024;15:1326684.

155. Laugesen K, Jorgensen JOL, Sorensen HT, Petersen I. Systemic glucocorticoid use in Denmark: a population-based prevalence study. BMJ Open. 2017;7:e015237.

156. Overman RA, Yeh JY, Deal CL. Prevalence of oral glucocorticoid usage in the United States: a general population perspective. Arthritis Care Res (Hoboken). 2013;65:294-298.

157. Langouche L, Teblick A, Gunst J, Van den Berghe G. The Hypothalamus-pituitary-adrenocortical Response to Critical Illness: A Concept in Need of Revision. Endocr Rev. 2023;44:1096-1106.

158. Boonen E, Vervenne H, Meersseman P, et al. Reduced cortisol metabolism during critical illness. N Engl J Med. 2013;368:1477-1488.

159. Annane D, Sebille V, Troche G, Raphael JC, Gajdos P, Bellissant E. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. JAMA. 2000;283:1038-1045.

160. Vermes I, Beishuizen A, Hampsink RM, Haanen C. Dissociation of plasma adrenocorticotropin and cortisol levels in critically ill patients: possible role of endothelin and atrial natriuretic hormone. J Clin Endocrinol Metab. 1995;80:1238-1242.

161. Wentworth BJ, Geng CX, Novicoff WM, Siragy HM, Henry ZH. Adrenal Dysfunction in Outpatients with Decompensated Cirrhosis: Impairment in the Hypothalamic-Pituitary-Adrenal Axis. Dig Dis Sci. 2025.

162. Prete A, Bancos I. Glucocorticoid induced adrenal insufficiency. BMJ. 2021;374:n1380.

163. Giordano R, Di Vito L, Lanfranco F, et al. Elderly subjects show severe impairment of dehydroepiandrosterone sulphate and reduced sensitivity of cortisol and aldosterone response to the stimulatory effect of ACTH(1-24). Clin Endocrinol (Oxf). 2001;55:259-265.

164. Gupta D, Morley JE. Hypothalamic-pituitary-adrenal (HPA) axis and aging. Compr Physiol. 2014;4:1495-1510.

165. Javorsky BR, Raff H, Carroll TB, et al. New Cutoffs for the Biochemical Diagnosis of Adrenal Insufficiency after ACTH Stimulation using Specific Cortisol Assays. J Endocr Soc. 2021;5:bvab022.

166. Wade M, Baid S, Calis K, Raff H, Sinaii N, Nieman L. Technical details influence the diagnostic accuracy of the 1 microg ACTH stimulation test. Eur J Endocrinol. 2010;162:109-113.

167. Fiad TM, Kirby JM, Cunningham SK, McKenna TJ. The overnight single-dose metyrapone test is a simple and reliable index of the hypothalamic-pituitary-adrenal axis. Clin Endocrinol (Oxf). 1994;40:603-609.

168. Kraan GP, Dullaart RP, Pratt JJ, Wolthers BG, Drayer NM, De Bruin R. The daily cortisol production reinvestigated in healthy men. The serum and urinary cortisol production rates are not significantly different. J Clin Endocrinol Metab. 1998;83:1247-1252.

169. Morgan SA, Berryman DE, List EO, Lavery GG, Stewart PM, Kopchick JJ. Regulation of 11beta-HSD1 by GH/IGF-1 in key metabolic tissues may contribute to metabolic disease in GH deficient patients. Growth Horm IGF Res. 2022;62:101440.

170. Kim BJ, Lee NR, Lee CH, et al. Increased Expression of 11beta-Hydroxysteroid Dehydrogenase Type 1 Contributes to Epidermal Permeability Barrier Dysfunction in Aged Skin. Int J Mol Sci. 2021;22.

171. Wyrwoll CS, Holmes MC, Seckl JR. 11beta-hydroxysteroid dehydrogenases and the brain: from zero to hero, a decade of progress. Front Neuroendocrinol. 2011;32:265-286.

172. Steintorsdottir SD, Oksnes M, Jorgensen AP, Husebye ES. Extended-release Hydrocortisone Formulations-Is There a Clinically Meaningful Benefit? J Clin Endocrinol Metab. 2025;110:e566-e573.

173. Tomlinson JW, Crabtree N, Clark PM, et al. Low-dose growth hormone inhibits 11 beta-hydroxysteroid dehydrogenase type 1 but has no effect upon fat mass in patients with simple obesity. J Clin Endocrinol Metab. 2003;88:2113-2118.

174. Rushworth RL, Torpy DJ, Falhammar H. Adrenal crises in older patients. Lancet Diabetes Endocrinol. 2020;8:628-639.

175. Bremner WJ, Vitiello MV, Prinz PN. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. J Clin Endocrinol Metab. 1983;56:1278-1281.

176. Gagliano-Juca T, Li Z, Pencina KM, et al. Oral glucose load and mixed meal feeding lowers testosterone levels in healthy eugonadal men. Endocrine. 2019;63:149-156.

177. Spratt DI, Bigos ST, Beitins I, Cox P, Longcope C, Orav J. Both hyper- and hypogonadotropic hypogonadism occur transiently in acute illness: bio- and immunoactive gonadotropins. J Clin Endocrinol Metab. 1992;75:1562-1570.

178. Huhtaniemi IT, Tajar A, Lee DM, et al. Comparison of serum testosterone and estradiol measurements in 3174 European men using platform immunoassay and mass spectrometry; relevance for the diagnostics in aging men. Eur J Endocrinol. 2012;166:983-991.

179. Svalheim S, Sveberg L, Mochol M, Tauboll E. Interactions between antiepileptic drugs and hormones. Seizure. 2015;28:12-17.

180. Corona G, Goulis DG, Huhtaniemi I, et al. European Academy of Andrology (EAA) guidelines on investigation, treatment and monitoring of functional hypogonadism in males: Endorsing organization: European Society of Endocrinology. Andrology. 2020;8:970-987.

181. De Rosa M, Zarrilli S, Di Sarno A, et al. Hyperprolactinemia in men: clinical and biochemical features and response to treatment. Endocrine. 2003;20:75-82.

182. Yabluchanskiy A, Tsitouras PD. Is Testosterone Replacement Therapy in Older Men Effective and Safe? Drugs Aging. 2019;36:981-989.

183. Snyder PJ, Bhasin S, Cunningham GR, et al. Effects of Testosterone Treatment in Older Men. N Engl J Med. 2016;374:611-624.

184. Storer TW, Basaria S, Traustadottir T, et al. Effects of Testosterone Supplementation for 3 Years on Muscle Performance and Physical Function in Older Men. J Clin Endocrinol Metab. 2017;102:583-593.

185. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018;103:1715-1744.

186. Ponce OJ, Spencer-Bonilla G, Alvarez-Villalobos N, et al. The efficacy and adverse events of testosterone replacement therapy in hypogonadal men: A systematic review and meta-analysis of randomized, placebo-controlled trials. J Clin Endocrinol Metab. 2018.

187. Yeap BB, Dwivedi G. Androgens and Cardiovascular Disease in Men. In: Feingold KR, Ahmed SF, Anawalt B, et al., eds. Endotext. South Dartmouth (MA)2000.

188. Layton JB, Meier CR, Sharpless JL, Sturmer T, Jick SS, Brookhart MA. Comparative Safety of Testosterone Dosage Forms. JAMA Intern Med. 2015;175:1187-1196.

189. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. N Engl J Med. 2010;363:109-122.

190. Srinivas-Shankar U, Roberts SA, Connolly MJ, et al. Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab. 2010;95:639-650.

191. Basaria S, Harman SM, Travison TG, et al. Effects of Testosterone Administration for 3 Years on Subclinical Atherosclerosis Progression in Older Men With Low or Low-Normal Testosterone Levels: A Randomized Clinical Trial. JAMA. 2015;314:570-581.

192. Budoff MJ, Ellenberg SS, Lewis CE, et al. Testosterone Treatment and Coronary Artery Plaque Volume in Older Men With Low Testosterone. JAMA. 2017;317:708-716.

193. Alexander GC, Iyer G, Lucas E, Lin D, Singh S. Cardiovascular Risks of Exogenous Testosterone Use Among Men: A Systematic Review and Meta-Analysis. Am J Med. 2017;130:293-305.

194. Calof OM, Singh AB, Lee ML, et al. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. J Gerontol A Biol Sci Med Sci. 2005;60:1451-1457.

195. Corona G, Maseroli E, Rastrelli G, et al. Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis. Expert Opin Drug Saf. 2014;13:1327-1351.

196. Fernandez-Balsells MM, Murad MH, Lane M, et al. Clinical review 1: Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2010;95:2560-2575.

197. Hudson J, Cruickshank M, Quinton R, et al. Adverse cardiovascular events and mortality in men during testosterone treatment: an individual patient and aggregate data meta-analysis. Lancet Healthy Longev. 2022;3:e381-e393.

198. Marriott RJ, Harse J, Murray K, Yeap BB. Systematic review and meta-analyses on associations of endogenous testosterone concentration with health outcomes in community-dwelling men. BMJ Open. 2021;11:e048013.

199. Borst SE, Shuster JJ, Zou B, et al. Cardiovascular risks and elevation of serum DHT vary by route of testosterone administration: a systematic review and meta-analysis. BMC Med. 2014;12:211.

200. Bhasin S, Lincoff AM, Basaria S, et al. Effects of long-term testosterone treatment on cardiovascular outcomes in men with hypogonadism: Rationale and design of the TRAVERSE study. Am Heart J. 2022;245:41-50.

201. Lincoff AM, Bhasin S, Flevaris P, et al. Cardiovascular Safety of Testosterone-Replacement Therapy. N Engl J Med. 2023;389:107-117.

202. Lin Y, Gupta S, Shi L, Mauvais-Jarvis F, Fonseca V. Long-Term Testosterone Shows Cardiovascular Safety in Men With Testosterone Deficiency in Electronic Health Records. J Endocr Soc. 2025;9:bvaf074.

203. Cheetham TC, An J, Jacobsen SJ, et al. Association of Testosterone Replacement With Cardiovascular Outcomes Among Men With Androgen Deficiency. JAMA Intern Med. 2017;177:491-499.

204. Wallis CJ, Lo K, Lee Y, et al. Survival and cardiovascular events in men treated with testosterone replacement therapy: an intention-to-treat observational cohort study. Lancet Diabetes Endocrinol. 2016;4:498-506.

205. Colao A, Vitale G, Cappabianca P, et al. Outcome of cabergoline treatment in men with prolactinoma: effects of a 24-month treatment on prolactin levels, tumor mass, recovery of pituitary function, and semen analysis. J Clin Endocrinol Metab. 2004;89:1704-1711.

206. Kinon BJ, Ahl J, Liu-Seifert H, Maguire GA. Improvement in hyperprolactinemia and reproductive comorbidities in patients with schizophrenia switched from conventional antipsychotics or risperidone to olanzapine. Psychoneuroendocrinology. 2006;31:577-588.

207. Santoro N, Roeca C, Peters BA, Neal-Perry G. The Menopause Transition: Signs, Symptoms, and Management Options. J Clin Endocrinol Metab. 2021;106:1-15.

208. El Khoudary SR, Aggarwal B, Beckie TM, et al. Menopause Transition and Cardiovascular Disease Risk: Implications for Timing of Early Prevention: A Scientific Statement From the American Heart Association. Circulation. 2020;142:e506-e532.

209. Thurston RC, Karvonen-Gutierrez CA, Derby CA, El Khoudary SR, Kravitz HM, Manson JE. Menopause versus chronologic aging: their roles in women's health. Menopause. 2018;25:849-854.

210. Greendale GA, Reboussin BA, Hogan P, et al. Symptom relief and side effects of postmenopausal hormones: results from the Postmenopausal Estrogen/Progestin Interventions Trial. Obstet Gynecol. 1998;92:982-988.

211. Stuenkel CA, Davis SR, Gompel A, et al. Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015;100:3975-4011.

212. Rossouw JE, Aragaki AK, Manson JE, et al. Menopausal Hormone Therapy and Cardiovascular Diseases in Women With Vasomotor Symptoms: A Secondary Analysis of the Women's Health Initiative Randomized Clinical Trials. JAMA Intern Med. 2025;185:1330-1339.

213. Barrett-Connor E, Bush TL. Estrogen and coronary heart disease in women. JAMA. 1991;265:1861-1867.

214. Weiss NS, Ure CL, Ballard JH, Williams AR, Daling JR. Decreased risk of fractures of the hip and lower forearm with postmenopausal use of estrogen. N Engl J Med. 1980;303:1195-1198.

215. Bagger YZ, Tanko LB, Alexandersen P, Qin G, Christiansen C, Group PS. Early postmenopausal hormone therapy may prevent cognitive impairment later in life. Menopause. 2005;12:12-17.

216. Paganini-Hill A, Henderson VW. Estrogen replacement therapy and risk of Alzheimer disease. Arch Intern Med. 1996;156:2213-2217.

217. Santen RJ, Heitjan DF, Gompel A, et al. Approach to Managing a Postmenopausal Patient. J Clin Endocrinol Metab. 2020;105.

218. Parish SJ, Simon JA, Davis SR, et al. International Society for the Study of Women's Sexual Health Clinical Practice Guideline for the Use of Systemic Testosterone for Hypoactive Sexual Desire Disorder in Women. J Sex Med. 2021;18:849-867.

219. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA. 1998;280:605-613.

220. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA. 2007;297:1465-1477.

221. Shaywitz SE, Shaywitz BA, Pugh KR, et al. Effect of estrogen on brain activation patterns in postmenopausal women during working memory tasks. JAMA. 1999;281:1197-1202.

222. Stuenkel CA. Deciphering the complex relationship between menopause and heart disease: 25 years and counting. Menopause. 2018;25:955-962.

223. Delmas PD, Bjarnason NH, Mitlak BH, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. N Engl J Med. 1997;337:1641-1647.

224. Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med. 1995;333:1437-1443.

225. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002;288:321-333.

226. Manson JE, Bassuk SS, Kaunitz AM, Pinkerton JV. The Women's Health Initiative trials of menopausal hormone therapy: lessons learned. Menopause. 2020;27:918-928.

227. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA. 2013;310:1353-1368.

228. Manson JE, Aragaki AK, Rossouw JE, et al. Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women's Health Initiative Randomized Trials. JAMA. 2017;318:927-938.

229. Manson JE, Aragaki AK, Bassuk SS, et al. Menopausal Estrogen-Alone Therapy and Health Outcomes in Women With and Without Bilateral Oophorectomy: A Randomized Trial. Ann Intern Med. 2019;171:406-414.

230. Chlebowski RT, Anderson GL, Aragaki AK, et al. Association of Menopausal Hormone Therapy With Breast Cancer Incidence and Mortality During Long-term Follow-up of the Women's Health Initiative Randomized Clinical Trials. JAMA. 2020;324:369-380.

231. Santen RJ, Stuenkel CA, Davis SR, Pinkerton JV, Gompel A, Lumsden MA. Managing Menopausal Symptoms and Associated Clinical Issues in Breast Cancer Survivors. J Clin Endocrinol Metab. 2017;102:3647-3661.

232. ACOG Practice Bulletin No. 141: management of menopausal symptoms. Obstet Gynecol. 2014;123:202-216.

233. The NHTPSAP. The 2017 hormone therapy position statement of The North American Menopause Society. Menopause. 2017;24:728-753.

234. Hammar M, Christau S, Nathorst-Boos J, Rud T, Garre K. A double-blind, randomised trial comparing the effects of tibolone and continuous combined hormone replacement therapy in postmenopausal women with menopausal symptoms. Br J Obstet Gynaecol. 1998;105:904-911.

235. Lumsden MA, Dekkers OM, Faubion SS, et al. European society of endocrinology clinical practice guideline for evaluation and management of menopause and the perimenopause. Eur J Endocrinol. 2025;193:G49-G81.

236. Kim JE, Chang JH, Jeong MJ, et al. A systematic review and meta-analysis of effects of menopausal hormone therapy on cardiovascular diseases. Sci Rep. 2020;10:20631.

237. Brabant A, Brabant G, Schuermeyer T, et al. The role of glucocorticoids in the regulation of thyrotropin. Acta Endocrinol (Copenh). 1989;121:95-100.

238. Fliers E, Boelen A. An update on non-thyroidal illness syndrome. J Endocrinol Invest. 2021;44:1597-1607.

239. Ylli D, Soldin SJ, Stolze B, et al. Biotin Interference in Assays for Thyroid Hormones, Thyrotropin and Thyroglobulin. Thyroid. 2021;31:1160-1170.

240. Lim SK, Pilon A, Guechot J. Biotin interferes with free thyroid hormone and thyroglobulin, but not TSH measurements using Beckman-Access immunoassays. Ann Endocrinol (Paris). 2017;78:186-187.

241. Effraimidis G, Watt T, Feldt-Rasmussen U. Levothyroxine Therapy in Elderly Patients With Hypothyroidism. Front Endocrinol (Lausanne). 2021;12:641560.

242. Hawkins RC. Age and gender as risk factors for hyponatremia and hypernatremia. Clin Chim Acta. 2003;337:169-172.

243. Fried LF, Palevsky PM. Hyponatremia and hypernatremia. Med Clin North Am. 1997;81:585-609.

244. Palevsky PM. Hypernatremia. Semin Nephrol. 1998;18:20-30.

245. Beck LH. Changes in renal function with aging. Clin Geriatr Med. 1998;14:199-209.

246. Lindner G, Schwarz C, Funk GC. Osmotic diuresis due to urea as the cause of hypernatraemia in critically ill patients. Nephrol Dial Transplant. 2012;27:962-967.

247. Leung AA, McAlister FA, Finlayson SR, Bates DW. Preoperative hypernatremia predicts increased perioperative morbidity and mortality. Am J Med. 2013;126:877-886.

248. Snyder NA, Feigal DW, Arieff AI. Hypernatremia in elderly patients. A heterogeneous, morbid, and iatrogenic entity. Ann Intern Med. 1987;107:309-319.

249. Chauhan K, Pattharanitima P, Patel N, et al. Rate of Correction of Hypernatremia and Health Outcomes in Critically Ill Patients. Clin J Am Soc Nephrol. 2019;14:656-663.

250. Christ-Crain M, Bichet DG, Fenske WK, et al. Diabetes insipidus. Nat Rev Dis Primers. 2019;5:54.

251. Alford N, Hashim H. Desmopressin acetate the first sublingual tablet to treat nocturia due to nocturnal polyuria. Expert Rev Clin Pharmacol. 2021;14:939-954.

252. Juul KV, Malmberg A, van der Meulen E, Walle JV, Norgaard JP. Low-dose desmopressin combined with serum sodium monitoring can prevent clinically significant hyponatraemia in patients treated for nocturia. BJU Int. 2017;119:776-784.

253. Juul KV, Klein BM, Sandstrom R, Erichsen L, Norgaard JP. Gender difference in antidiuretic response to desmopressin. Am J Physiol Renal Physiol. 2011;300:F1116-1122.

254. Andereggen L, Tortora A, Schubert GA, et al. Prolactinomas in adolescent and elderly patients-A comparative long-term analysis. Front Surg. 2023;10:967407.

255. Green AI, Sherlock M, Stewart PM, Gittoes NJ, Toogood AA. Extensive experience in the management of macroprolactinomas. Clin Endocrinol (Oxf). 2014;81:85-92.

256. Delgrange E, Raverot G, Bex M, et al. Giant prolactinomas in women. Eur J Endocrinol. 2014;170:31-38.

257. Santharam S, Tampourlou M, Arlt W, et al. Prolactinomas diagnosed in the postmenopausal period: Clinical phenotype and outcomes. Clin Endocrinol (Oxf). 2017;87:508-514.

258. Briet C, Salenave S, Bonneville JF, Laws ER, Chanson P. Pituitary Apoplexy. Endocr Rev. 2015;36:622-645.

259. Watanabe S, Akutsu H, Takano S, et al. Long-term results of cabergoline therapy for macroprolactinomas and analyses of factors associated with remission after withdrawal. Clin Endocrinol (Oxf). 2017;86:207-213.

260. Yener S, Comlekci A, Arda N, Men S, Yesil S. Misdiagnosis due to the hook effect in prolactin assay. Med Princ Pract. 2008;17:429-431.

261. Paepegaey AC, Salenave S, Kamenicky P, et al. Cabergoline Tapering Is Almost Always Successful in Patients With Macroprolactinomas. J Endocr Soc. 2017;1:221-230.

262. Ono M, Miki N, Kawamata T, et al. Prospective study of high-dose cabergoline treatment of prolactinomas in 150 patients. J Clin Endocrinol Metab. 2008;93:4721-4727.

263. Maiter D, Delgrange E. Therapy of endocrine disease: the challenges in managing giant prolactinomas. Eur J Endocrinol. 2014;170:R213-227.

264. Dekkers OM, Lagro J, Burman P, Jorgensen JO, Romijn JA, Pereira AM. Recurrence of hyperprolactinemia after withdrawal of dopamine agonists: systematic review and meta-analysis. J Clin Endocrinol Metab. 2010;95:43-51.

265. Petersenn S, Fleseriu M, Casanueva FF, et al. Diagnosis and management of prolactin-secreting pituitary adenomas: a Pituitary Society international Consensus Statement. Nat Rev Endocrinol. 2023;19:722-740.

266. Wengander S, Trimpou P, Papakokkinou E, Ragnarsson O. The incidence of endogenous Cushing's syndrome in the modern era. Clin Endocrinol (Oxf). 2019;91:263-270.

267. Salcedo-Sifuentes JE, Shih R, Heaney AP, et al. Cushing Disease Clinical Phenotype and Tumor Behavior Vary With Age: Diagnostic and Perioperative Implications. J Clin Endocrinol Metab. 2025;110:2595-2604.

268. Amodru V, Ferriere A, Tabarin A, et al. Cushing's syndrome in the elderly: data from the European Registry on Cushing's syndrome. Eur J Endocrinol. 2023;188:395-406.

269. Zdrojowy-Welna A, Valassi E. Cushing's Syndrome in the Elderly. Exp Clin Endocrinol Diabetes. 2024;132:705-711.

270. Leon-Justel A, Madrazo-Atutxa A, Alvarez-Rios AI, et al. A Probabilistic Model for Cushing's Syndrome Screening in At-Risk Populations: A Prospective Multicenter Study. J Clin Endocrinol Metab. 2016;101:3747-3754.

271. Parasiliti-Caprino M, Bioletto F, Frigerio T, et al. A New Clinical Model to Estimate the Pre-Test Probability of Cushing's Syndrome: The Cushing Score. Front Endocrinol (Lausanne). 2021;12:747549.

272. Salcedo-Sifuentes JE, Mehta S, Suryadevara CM, et al. Development and validation of clinical screening systems for Cushing disease in the United States. Pituitary. 2025;28:108.

273. Couselo M, Frara S, Giustina A, Casanueva FF. Pituitary tumor centers of excellence for Cushing's disease. Pituitary. 2022;25:772-775.

274. Broder MS, Chang E, Cherepanov D, Neary MP, Ludlam WH. Incidence and Prevalence of Acromegaly in the United States: A Claims-Based Analysis. Endocr Pract. 2016;22:1327-1335.

275. Burton T, Le Nestour E, Neary M, Ludlam WH. Incidence and prevalence of acromegaly in a large US health plan database. Pituitary. 2016;19:262-267.

276. Minniti G, Jaffrain-Rea ML, Esposito V, et al. Surgical treatment and clinical outcome of GH-secreting adenomas in elderly patients. Acta Neurochir (Wien). 2001;143:1205-1211.

277. Puchner MJ, Knappe UJ, Ludecke DK. Pituitary surgery in elderly patients with acromegaly. Neurosurgery. 1995;36:677-683; discussion 683-674.

278. Ceccato F, Barbot M, Lizzul L, et al. Clinical presentation and management of acromegaly in elderly patients. Hormones (Athens). 2021;20:143-150.

279. Esposito D, Boguszewski CL, Colao A, et al. Diabetes mellitus in patients with acromegaly: pathophysiology, clinical challenges and management. Nat Rev Endocrinol. 2024;20:541-552.

280. Frystyk J, Ivarsen P, Skjaerbaek C, Flyvbjerg A, Pedersen EB, Orskov H. Serum-free insulin-like growth factor I correlates with clearance in patients with chronic renal failure. Kidney Int. 1999;56:2076-2084.

281. Gadelha MR, Kasuki L, Lim DST, Fleseriu M. Systemic Complications of Acromegaly and the Impact of the Current Treatment Landscape: An Update. Endocr Rev. 2019;40:268-332.

282. Moxey B, Sweet JM. Acromegaly with normal insulin-like growth factor I levels. Mayo Clin Proc. 2006;81:238.

283. Wijayaratne DR, Arambewela MH, Dalugama C, Wijesundera D, Somasundaram N, Katulanda P. Acromegaly presenting with low insulin-like growth factor-1 levels and diabetes: a case report. J Med Case Rep. 2015;9:241.

284. Arita K, Hirano H, Yunoue S, et al. Treatment of elderly acromegalics. Endocr J. 2008;55:895-903.

285. Tanimoto K, Hizuka N, Fukuda I, Takano K, Hanafusa T. The influence of age on the GH-IGF1 axis in patients with acromegaly. Eur J Endocrinol. 2008;159:375-379.

286. Sasagawa Y, Hayashi Y, Tachibana O, et al. Transsphenoidal Surgery for Elderly Patients with Acromegaly and Its Outcomes: Comparison with Younger Patients. World Neurosurg. 2018;118:e229-e234.

287. Colao A, Pivonello R, Spinelli L, et al. A retrospective analysis on biochemical parameters, cardiovascular risk and cardiomyopathy in elderly acromegalic patients. J Endocrinol Invest. 2007;30:497-506.

288. Fieffe S, Morange I, Petrossians P, et al. Diabetes in acromegaly, prevalence, risk factors, and evolution: data from the French Acromegaly Registry. Eur J Endocrinol. 2011;164:877-884.

289. Colao A, Grasso LFS, Di Somma C, Pivonello R. Acromegaly and Heart Failure. Heart Fail Clin. 2019;15:399-408.

290. Colao A, Pivonello R, Grasso LF, et al. Determinants of cardiac disease in newly diagnosed patients with acromegaly: results of a 10 year survey study. Eur J Endocrinol. 2011;165:713-721.

291. Dupuy O, Petrossians P, Brue T, et al. [Acromegaly in the elderly]. Ann Endocrinol (Paris). 2009;70:225-229.

292. Hatipoglu E, Yuruyen M, Keskin E, et al. Acromegaly and aging: a comparative cross-sectional study. Growth Horm IGF Res. 2015;25:47-52.

293. Yamamoto N, Urai S, Fukuoka H, et al. The Effect of Aging on Quality of Life in Acromegaly Patients Under Treatment. Front Endocrinol (Lausanne). 2022;13:819330.

294. Fleseriu M, Biller BMK, Freda PU, et al. A Pituitary Society update to acromegaly management guidelines. Pituitary. 2021;24:1-13.

295. Clemmons DR, Bidlingmaier M. IGF-I assay methods and biologic variability: evaluation of acromegaly treatment response. Eur J Endocrinol. 2024;191:R1-R8.

296. Parkinson C, Renehan AG, Ryder WD, O'Dwyer ST, Shalet SM, Trainer PJ. Gender and age influence the relationship between serum GH and IGF-I in patients with acromegaly. Clin Endocrinol (Oxf). 2002;57:59-64.

297. Junnila RK, Strasburger CJ, Bidlingmaier M. Pitfalls of insulin-like growth factor-i and growth hormone assays. Endocrinol Metab Clin North Am. 2015;44:27-34.

298. Brzana JA, Yedinak CG, Delashaw JB, Gultelkin HS, Cook D, Fleseriu M. Discordant growth hormone and IGF-1 levels post pituitary surgery in patients with acromegaly naive to medical therapy and radiation: what to follow, GH or IGF-1 values? Pituitary. 2012;15:562-570.

299. Zeinalizadeh M, Habibi Z, Fernandez-Miranda JC, Gardner PA, Hodak SP, Challinor SM. Discordance between growth hormone and insulin-like growth factor-1 after pituitary surgery for acromegaly: a stepwise approach and management. Pituitary. 2015;18:48-59.

300. Fleseriu M, Langlois F, Lim DST, Varlamov EV, Melmed S. Acromegaly: pathogenesis, diagnosis, and management. Lancet Diabetes Endocrinol. 2022;10:804-826.

301. Colao A, Pivonello R, Cavallo LM, et al. Age changes the diagnostic accuracy of mean profile and nadir growth hormone levels after oral glucose in postoperative patients with acromegaly. Clin Endocrinol (Oxf). 2006;65:250-256.

302. Lamberts SW, Reubi JC, Krenning EP. Somatostatin analogs in the treatment of acromegaly. Endocrinol Metab Clin North Am. 1992;21:737-752.

303. Akirov A, Asa SL, Amer L, Shimon I, Ezzat S. The Clinicopathological Spectrum of Acromegaly. J Clin Med. 2019;8.

304. Tomasik A, Stelmachowska-Banas M, Maksymowicz M, et al. Pathologic Characteristics of Somatotroph Pituitary Tumors-An Observational Single-Center Study. Biomedicines. 2023;11.

305. Cuevas-Ramos D, Carmichael JD, Cooper O, et al. A structural and functional acromegaly classification. J Clin Endocrinol Metab. 2015;100:122-131.

306. Terzolo M, Reimondo G, Berchialla P, et al. Acromegaly is associated with increased cancer risk: a survey in Italy. Endocr Relat Cancer. 2017;24:495-504.

307. Xiao Z, Xiao P, Wang Y, Fang C, Li Y. Risk of cancer in acromegaly patients: An updated meta-analysis and systematic review. PLoS One. 2023;18:e0285335.

308. Basu R, Boguszewski CL, Kopchick JJ. Growth Hormone Action as a Target in Cancer: Significance, Mechanisms, and Possible Therapies. Endocr Rev. 2025;46:224-280.

309. Pascual-Corrales E, Biagetti B, Marazuela M, et al. Glucose metabolism outcomes after pituitary surgery in patients with acromegaly. Pituitary. 2024;27:497-506.

310. Moller N, Schmitz O, Joorgensen JO, et al. Basal- and insulin-stimulated substrate metabolism in patients with active acromegaly before and after adenomectomy. J Clin Endocrinol Metab. 1992;74:1012-1019.

311. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Practice Guidelines for the Management of Arterial Hypertension. Blood Press. 2014;23:3-16.

312. Pivonello R, Auriemma RS, Grasso LF, et al. Complications of acromegaly: cardiovascular, respiratory and metabolic comorbidities. Pituitary. 2017;20:46-62.

313. Spasovski G, Vanholder R, Allolio B, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Eur J Endocrinol. 2014;170:G1-47.

314. Janicic N, Verbalis JG. Evaluation and management of hypo-osmolality in hospitalized patients. Endocrinol Metab Clin North Am. 2003;32:459-481, vii.

315. Anpalahan M. Chronic idiopathic hyponatremia in older people due to syndrome of inappropriate antidiuretic hormone secretion (SIADH) possibly related to aging. J Am Geriatr Soc. 2001;49:788-792.

316. Hirshberg B, Ben-Yehuda A. The syndrome of inappropriate antidiuretic hormone secretion in the elderly. Am J Med. 1997;103:270-273.

317. Liamis G, Milionis H, Elisaf M. A review of drug-induced hyponatremia. Am J Kidney Dis. 2008;52:144-153.

318. Cohen DL, Townsend RR. Hyponatremia and thiazides. J Clin Hypertens (Greenwich). 2012;14:653.

319. Rittenhouse KJ, To T, Rogers A, et al. Hyponatremia as a fall predictor in a geriatric trauma population. Injury. 2015;46:119-123.

320. Wald R, Jaber BL, Price LL, Upadhyay A, Madias NE. Impact of hospital-associated hyponatremia on selected outcomes. Arch Intern Med. 2010;170:294-302.

321. Murthy K, Ondrey GJ, Malkani N, et al. The Effects of Hyponatremia on Bone Density and Fractures: A Systematic Review and Meta-Analysis. Endocr Pract. 2019;25:366-378.

322. Upala S, Sanguankeo A. Association Between Hyponatremia, Osteoporosis, and Fracture: A Systematic Review and Meta-analysis. J Clin Endocrinol Metab. 2016;101:1880-1886.

323. Terzian C, Frye EB, Piotrowski ZH. Admission hyponatremia in the elderly: factors influencing prognosis. J Gen Intern Med. 1994;9:89-91.

324. Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. Am J Med. 2006;119:71 e71-78.

325. Verbalis JG, Barsony J, Sugimura Y, et al. Hyponatremia-induced osteoporosis. J Bone Miner Res. 2010;25:554-563.

326. Garrahy A, Galloway I, Hannon AM, et al. Fluid Restriction Therapy for Chronic SIAD; Results of a Prospective Randomized Controlled Trial. J Clin Endocrinol Metab. 2020;105.

327. Workeneh BT, Meena P, Christ-Crain M, Rondon-Berrios H. Hyponatremia Demystified: Integrating Physiology to Shape Clinical Practice. Adv Kidney Dis Health. 2023;30:85-101.

328. Schrier RW, Gross P, Gheorghiade M, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med. 2006;355:2099-2112.

329. Verbalis JG, Zeltser D, Smith N, Barve A, Andoh M. Assessment of the efficacy and safety of intravenous conivaptan in patients with euvolaemic hyponatraemia: subgroup analysis of a randomized, controlled study. Clin Endocrinol (Oxf). 2008;69:159-168.

330. Mordi NA, Mordi IR, Singh JS, McCrimmon RJ, Struthers AD, Lang CC. Renal and Cardiovascular Effects of SGLT2 Inhibition in Combination With Loop Diuretics in Patients With Type 2 Diabetes and Chronic Heart Failure: The RECEDE-CHF Trial. Circulation. 2020;142:1713-1724.

331. Refardt J, Winzeler B, Meienberg F, Vogt DR, Christ-Crain M. Empagliflozin Increases Short-Term Urinary Volume Output in Artificially Induced Syndrome of Inappropriate Antidiuresis. Int J Endocrinol. 2017;2017:7815690.

332. Refardt J, Imber C, Sailer CO, et al. A Randomized Trial of Empagliflozin to Increase Plasma Sodium Levels in Patients with the Syndrome of Inappropriate Antidiuresis. J Am Soc Nephrol. 2020;31:615-624.

333. Refardt J, Imber C, Nobbenhuis R, et al. Treatment Effect of the SGLT2 Inhibitor Empagliflozin on Chronic Syndrome of Inappropriate Antidiuresis: Results of a Randomized, Double-Blind, Placebo-Controlled, Crossover Trial. J Am Soc Nephrol. 2023;34:322-332.