Clinical Interventions in Aging

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REVIEW

Treating Hypopituitarism in the Over 65s: Review of Clinical Studies

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Abstract: The current increase of life expectancy is associated with the presence of endocrine diseases in the elderly. The management of hypopituitarism in this group of patients is a challenging task. A correct diagnosis, which represents an essential requisite for an appropriate medical treatment, can be difficult because of the physiological changes occurring in pituitary function with aging, which may lead to challenges in the interpretation of laboratory results. Furthermore, the treatment requires several careful considerations: the need to restore the hormonal physiology with replacement therapies must be balanced with the need to avoid the risks of the over-replacement, especially in the presence of concomitant cardiovascular and metabolic disease. Interactions with other drugs able to modify the absorption and/or the metabolism of hormonal replacement therapies should be considered, in particular for the treatment of hypoadrenalism and hypothyroidism. The most important challenges stem from the lack of specific studies focused on the management of hypopituitarism in older people.

Keywords: hypopituitarism, elderly, levothyroxine, glucocorticoid replacement therapy, recombinant GH, testosterone, central hypothyroidism, central hypoadrenalism, GH deficiency, central hypogonadism

Introduction

Hypopituitarism is characterized by a decreased secretion of one or more hormones produced by the pituitary, resulting in a functional deficiency of the target glands. In some cases, a defect of the posterior pituitary can occur, causing an impaired secretion of anti-diuretic hormone (ADH), with consequent diabetes insipidus.

Hypopituitarism is thought to be an uncommon condition with a prevalence of ~46 per 100,000[1] without differences related to sex. It can be due to a variety of tumoral, inflammatory, or infiltrative lesions or trauma or radiation of the hypothalamic–pituitary region, with the most common cause represented by non-functioning pituitary macroadenomas.[2] Hypopituitarism is associated with increased mortality,[3] even when pituitary hormonal defects are correctly replaced. A prompt and appropriate therapeutic approach is crucial in the management of this condition.

The increase in life expectancy in the general population is associated with a higher incidence and prevalence of many endocrine diseases, including hypopituitarism.[4] It has been recognized that hypopituitarism in the elderly is an underestimated condition,[5] which may have an insidious clinical presentation that can vary according to the severity of deficient hormones. Its symptoms can be attributed to aging or to associated comorbidities. Because of the physiological changes occurring in pituitary function with aging, the interpretation of laboratory results may lead to misinterpretations. Finally, the possible effects of drugs used for the treatment of comorbidities have to be considered. All these peculiarities must be considered for a correct diagnostic and therapeutic approach. Conventionally, ageing is commonly measured by chronological age and a person aged 65 years or more is often referred to as "elderly".[6] In this review we report the peculiarities related to the management of hypopituitarism in elderly people.

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Causes of Hypopituitarism in the Elderly

The causes of hypopituitarism in the elderly consist of pituitary or hypothalamic disease. Pituitary deficiency due to the loss of gland parenchyma causes more than 95% of the cases of hypopituitarism, and pituitary macroadenomas represent a frequent cause of pituitary deficiency associated to gland cells damage.[7] Unlike the younger population, where prolactinomas represent the most common pituitary adenomas, more than 80% of the pituitary tumors in the elderly are non-secreting. Furthermore, compared with younger subjects, patients >65 years have a higher frequency of macroadenomas, compressive symptoms and hypopituitarism, both before and after surgery.[8] Therefore, in the elderly visual deterioration and hypopituitarism remain the leading symptoms associated to the presence of pituitary macroadenomas.[9] Several mechanisms are involved in the development of hypopituitarism related to macroadenomas, including compression of the pituitary stalk resulting in decreased availability of hypothalamic stimulatory hormones, compression and/or destruction of functioning pituitary tissue, and hypothalamic involvement by the pituitary tumor.[10] In the majority of patients with macroadenomas pituitary insufficiency includes growth hormone (GH) deficiency (85% of cases), and gonadotropin deficiency (75% of cases), while adrenocorticotropin (ACTH) and thyrotropin (TSH) deficiencies are less frequent (~38% and ~32%, respectively).[10] Mild to moderate hyperprolactinemia can occur, as consequence of the compression of the pituitary stalk resulting in the lack of hypothalamic inhibitory effects on prolactin (PRL) secretion mediated by dopamine. In the elderly the clinical symptoms associated with hyperprolactinemia may be underestimated, because women do not have periods, and in men reduction in serum testosterone may be interpreted as being age-related. Therefore, biochemical evaluation is the most reliable criterium to confirm the presence of hyperprolactinemia. The degree of hyperprolactinemia due to stalk effect is in general mild (less than 100 ng/mL), and disproportionally low in relation to the size of the adenoma. Sometimes the differential diagnosis between prolactinoma and non-functioning mass is challenging, and the time of response to dopamine-agonist agent does not represent a useful criterion to help the differential diagnosis between prolactinoma and non-secreting adenoma.[11]

Both primary and secondary (caused by various processes causing injury to the pituitary gland) empty sella, detected in 3–35% of the general population, with frequency directly proportional to age, also represents a possible cause of hypopituitarism in older people. The prevalence of hypopituitarism in empty sella ranges from 10% to 40%.[12,13]

Hypopituitarism is a common complication of both traumatic brain injury and aneurysmal subarachnoid bleeding, occurring in about 19–36% of cases.[14] Other causes of hypopituitarism in the elderly include peri-pituitary tumors, surgical or radiation treatment of the pituitary or brain tumors as well as infiltrative lesions. Rarely autoimmune lymphocytic hypophysitis or pituitary apoplexy or often previously undiagnosed pre-existing adenomas (for example occurring during coronary artery bypass or spontaneously due to hypertension) can cause hypopituitarism. On the other hand, with the widespread use of immune checkpoint inhibitors for various malignancies[15] frequent cases of drug-induced hypophysitis are being detected, especially in older male patients with multiple comorbidities.[16] In these conditions, central hypoadrenalism is the most frequent abnormality, followed by central hypothyroidism and hypogonadism, often without MRI evidence of obvious pituitary enlargement.[17]

Establishing the Correct Diagnosis of Hypopituitarism in the Elderly

A correct therapeutic approach of hypopituitarism is based on an appropriate diagnosis of the pituitary hormone's deficiency. In the elderly hypopituitarism risks to remain underestimated, because the complex and unspecific clinical features are often ascribed to age comorbidities Additionally, the diagnosis may be challenging in older age, because several issues in the interpretation of the biochemical results have to be considered. Modifications in pituitary function have been documented in the elderly in both sexes, and some of them are considered physiological adaptations to aging.

Modification of Pituitary Function with Aging

Hypothalamus-Pituitary-Adrenal Axis (HPA)

The HPA axis shows a circadian rhythm characterized by higher activity in the early morning (acrophase), by a progressive decline during the day with a nadir around midnight, and then by a subsequent fast increase until the

early morning.[18] In older people, the nocturnal nadir of cortisol is less marked, and occurs approximately 2 hours earlier than in younger people. These changes are the consequence of a blunted negative feedback that results from a reduced expression of glucocorticoid and mineralocorticoid receptors in the hippocampus, and from the activation of hypothalamic neurons secreting corticotropin releasing hormone (CRH) and antidiuretic hormone (ADH).[19] Some conditions can alter the activity of the HPA axis: diabetes mellitus, inflammation, anxiety, trauma, stress, sleep loss and systemic disease can increase the release of ACTH and cortisol, while concomitants such as benzodiazepines, antidepressants, narcotics, and synthetic glucocorticoids can blunt the activity of the HPA axis.[20] The chronic effect of narcotics on the function of the HPA axis has been recognized as a common cause of suppression of the adrenal and gonadal axis.[21]

Hypothalamus-Pituitary-Thyroid Axis (HPT)

Several factors including sex, exercise, fasting, concomitant illness, medications, iodine availability, brief light exposure, sleep stage, and exercise are able to influence TSH levels. The Whickham survey showed that TSH levels increased markedly in women after the age of 45 years.[22] In a subsequent study, a decrease in baseline, overnight and thyrotropin releasing hormone (TRH)-stimulated TSH release with age has been demonstrated in men.[23] A more recent survey (Busselton survey) showed that TSH increases in both sexes in elderly subjects (mean increase of 0.32 mcU/mL over 13 years) with no significant change in free T4 concentrations.[24] Triiodothyronine (T3) levels fall, leading to a reduced free T3:free T4 ratio. The possibility of "non-thyroidal illness syndrome", characterized by reduced plasma T3 concentrations without a concomitant rise in TSH and with low-normal T4, must be considered in interpreting thyroid function tests in cases of acute and debilitating illness, as the hormonal pattern may be indistinguishable from central hypothyroidism.[25] This phenomenon, whose pathophysiological mechanisms remain incompletely understood, has been considered by some authors as a response of adaption.[26]

Hypothalamus-Pituitary-Gonadal Axis

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) rise gradually in ageing men as a consequence of the reduced secretion of androgen from Leydig cells and decreased secretion of inhibin B from Sertoli cells.[27] However, spermatogenesis can be preserved in ageing.[28] In women, an elevation of FSH may precede the clinical menopause by 5–10 years.[29] The underlying mechanism is an increased secretion of gonadotropin releasing hormone (GnRH), which in turn is regulated by several factors, including sex steroids and kisspeptin.[30] Additionally, ageing is associated with longer LH and FSH isoform's half-life.

Growth Hormone

The activity of the GH/insulin-like growth factor 1 (IGF-1) axis presents age-related modifications, and in general it declines with aging, starting from early adulthood ("somatopause"). Indeed, the response of GH secretion during fasting, exercise or sleep is blunted in the elderly. The mechanism of such a decrease is not completely understood, as the GH secretion during insulin-induced hypoglycemia or the triple combination of L-arginine plus GH-releasing hormone (GHRH) plus ghrelin is the same as for young individuals.[31] The reduction of GH secretion in older people is more marked in males than in females, probably due the role of sex hormones (estrogens cause GH resistance) and their age-related modifications.[32] Changes in lifestyle, such as reduced physical exercise, can contribute to decreased activity of the GH-IGF-1 axis in the elderly.[33] Somatopause has been proposed to have a role in the clinical alterations related to aging, including sarcopenia, osteopenia, and increased visceral adiposity.[19] Accordingly, serum IGF-1 levels decrease with age, and a correct interpretation of serum IGF-1 levels must be based on age-adjusted values. Because of the "physiological" occurrence of age-related reduction in GH secretion, it is mandatory to ask if the biochemical finding of a mild GH deficiency in older patients with pituitary disease does necessarily constitute a disease.[34]

Prolactin

Several factors can stimulate PRL secretion, both acutely (psychological and physical stress, breast stimulation, hypoglycemia, dopamine-2-receptor blockers, hyperthermia, food intake, sleep, exercise) and chronically (end-stage renal disease, and primary hypothyroidism).[35] In young individuals, PRL levels are higher in women, while they decrease after menopause, probably because of the effect of reduced estrogen levels. Several anti-dopaminergic drugs (such as

anti-psychotic and pro-motility agents) stimulate PRL secretion. Aripiprazole is the only anti-psychotic medication that frequently reduces PRL levels due to partial D2-receptor agonism. Conversely, low levels of PRL are observed in patients affected by Parkinson disease on treatment with dopamine-agonist agents. Given the high prevalence of Parkinson disease (with incidence that increases 5 to 10-fold from the sixth to the ninth decades of life)[36] and the common use of antipsychotic drugs in older subjects, a careful drug history must be conducted when interpreting PRL levels.

Anti-Diuretic Hormone (ADH)

The homeostatic adjustment of fluid and salt handling has been demonstrated to be impaired in the elderly, and older people are more susceptible to disorders of body volume and osmolality. Aging is a strong independent risk factor for both hypo- and hypernatremia, and these disorders are more common than in young people. The incidence of hyponatremia and hypernatremia in elderly populations has been reported to be between 0.2% and 29.8% and between 0.3% and 8.9% respectively.[37,38] A deficit in thirst and water intake in healthy elderly can occur, as compared with younger people.[39] Furthermore, a deficit of secretion of aldosterone has been reported,[40] as well as an impaired activity of baroreceptor reflexes and expression of the ADH receptor and aquaporin.[41]

Establishing the Diagnosis of Hypopituitarism in the Elderly

The biochemical diagnosis of hypopituitarism in the elderly is based on the same laboratory test used for the younger population. No specific cut-offs related to age have been reported for older people. The challenge is represented by the need of overriding possible pitfalls related to the above-mentioned modifications in pituitary activity, as well as on interferences related to the use of medical therapies.

For the evaluation of HPT axis, the detection of low free thyroxine (FT4) levels associated with inappropriately normal or low TSH levels is enough to confirm the diagnosis of central hypothyroidism. Circulating free triiodothyronine (FT3) levels are less useful, because they can be influenced by intercurrent diseases, which can cause the "low T3 syndrome".[26] For the interpretation of TSH levels, it is mandatory to consider the possible effects by drugs that can interfere with the HPT axis function. Corticosteroids regulate the diurnal variation of TSH secretion, and high levels of glucocorticoids (either exogenous or in Cushing syndrome) reduce TSH secretion by inhibiting the TRH activity, causing a pattern indistinguishable from central hypothyroidism.[42,43] The reduction of TSH has been reported in patients treated with dopamine agonist and with somatostatin analogues.[44] The administration of somatostatin decreases both the pulse amplitude and the pulse frequency of TSH, and can induce a transient subclinical hypothyroidism.

The assessment of basal serum cortisol in the morning (8–9 a.m.), associated with inappropriately normal or low ACTH levels, is the first diagnostic step to confirm central hypoadrenalism: Prete and co. proposed to consider the diagnosis for cortisol levels <3.6 mcg/dl, while the diagnosis is unlikely for cortisol levels >12.7 mcg/dl.[45] If cortisol levels are between 3.6 and 12.7 mcg/dL a dynamic test is mandatory to confirm or exclude diagnosis (see Table 1).[46] It is important to remember that newer, more specific (based on monoclonal antibodies) cortisol assays have results that are significantly (about 30%) lower than older assays.[47,48] Impairment of the HPA axis can cause hyponatremia, because glucocorticoid deficiency can produce altered water excretion. This mechanism is mediated by a non-suppressible release of ADH with enhanced expression of the aquaporin-2 water channel.[49] The diagnosis of central hypoadrenalism must be considered in older patients treated with synthetic glucocorticoids prescribed for anti-inflammatory and immunosuppressive activity for longer than 3 weeks (occurring in about 2.5% of the general population over 70 years).[50] This includes repeated intra-articular glucocorticoid injections, commonly performed in older patients with degenerative or inflammatory joint disease. These patients are at risk of developing tertiary adrenal insufficiency. Therefore, the differential diagnosis between a steroid-induced HPA axis impairment (tertiary hypoadrenalism) and secondary adrenal insufficiency related to organic damage to the pituitary or hypothalamus is sometimes difficult. Such differential diagnosis is important, as steroid-induced adrenal insufficiency may be reversible with weaning from exogenous glucocorticoid treatment. Such differential diagnosis is mainly based on the clinical history of use of synthetic glucocorticoid, with other causes of hypopituitarism being excluded. It has to be kept in mind that tertiary (steroid-induced) hypoadrenalism is the most frequent cause of central adrenal insufficiency.[51,52]

The diagnosis of GH deficiency (GHD) in older people may be challenging. Older patients affected by GHD may present signs and symptoms (increased abdominal fat mass, sarcopenia, low basal metabolic rate, decreased bone density, self-isolation, and a reduced quality of life) that are non-specific, and have significant overlaps with aging. IGF-1 levels are poorly sensitive in distinguishing normal subjects from GHD, especially in males and overweight and underweight populations, because IGF-1 production is influenced by sex (higher in males), nutritional factor and body mass index. Therefore (with the exception of subjects with panhypopituitarism and frankly low age-adjusted serum IGF-1), the diagnosis of GHD in older subjects is generally based on the demonstration of a reduced GH response to stimulation in the appropriate clinical context[53] (see Table 1). Several stimulation tests are available. The gold standard (insulin induced hypoglycemia) is contraindicated in elderly patients as it may trigger coronary artery events. Possible alternatives are glucagon, GHRH+ arginine and macimorelin test. For glucagon and GHRH+ arginine the cut-offs of peak GH after stimulation change are based on body mass index (BMI),[19] and a correct interpretation must be performed considering possible comorbidities, as diabetes or malnutrition. Conversely, macimorelin test seems to be independent from BMI, at least until the value of 36.9 kg/m^2.[54] The accuracy of the dynamic tests depends on the pre-test probability to find the disease. Therefore, the endocrine evaluation should be proposed only in subjects with a high clinical suspicion, as clinical history or signs and symptoms of hypothalamic-pituitary diseases.

Hypogonadotropic hypogonadism can be diagnosed in males by the detection of low serum testosterone associated with inappropriately normal or low FSH and LH levels. The lack of elevated FSH is suggestive of central hypogonadism in post-menopausal women who are not on estrogen replacement.

The diagnosis of diabetes insipidus (DI) is often challenging: a clinical history of nocturia, polyuria or polydipsia is crucial in establishing the diagnosis of diabetes insipidus, but the elderly often have urinary frequency or incontinence due to unrelated disorders.[14] It is important to note that pituitary adenomas that have not been operated on almost never cause DI, independently from their size. A 24 urine volume of hypo-osmolar urine exceeding 3 liters is suspicious for diabetes insipidus. The gold standard for diagnosis is the documentation of diluted urine simultaneously with increased serum osmolality. This may require a water deprivation test: urine remains hypo-osmolar despite dehydration. Measurement of serum copeptin (C-terminal fragment of the 164 amino ADH precursor pre-pro-vasopressin)

Table 1 Dynamic Test Used for the Diagnosis of Hypoadrenalism and GH Deficiency

Dynamic Test	Procedure	Normal Response
ACTH test 250 mcg	Administer ACTH 1–24 (Cosyntropin) 250 μg i.v. o i.m. Blood sample for cortisol at 0, 30, and 60 min	Cortisol peak >15 mcg/dL at 30 or 18 mcg/dL at 60 min
GHRH plus arginine*	Administer bolus of GHRH i.v. followed by arginine infusion i.v. over 30 min. GHRH dose: 1 μg/kg (max 100 μg) Arginine dose: 0.5 g/kg (max di 30 g) Blood sample for GH at 0, 30, 45, 60, 75, 90, 105, and 120 min	Cutoff BMI related: BMI <25 kg/mq: GH peak >11.5 ng/mL BMI between 25 and 30 GH peak:>8 ng/mL BMI >30 kg/mq: GH peak >4.2 ng/mL
Glucagon	Administer glucagon 1 mg (1.5 mg if body weight >90 kg) i.m. Blood sample for GH and glucose at 0, 30, 60, 90, 120, 150, 180, 210, and 240 min	GH peak >3 ng/mL (for normal-weight and overweight patients with a high pretest probability)GH peak >1 ng/mL (for obese and overweight patients with a low pretest probability)
Macimorelin	Administer oral macimorelin (0.5 mg/kg). Blood samples for GH at 30, 45, 60 and 90 min	GH peak > 5.1 ng/mL if BMI ≤ 37 kg/mq. No data available for BMI ≥ 37 kg/mq

Notes: *GHRH not currently available in the USA. Adapted from Caputo M, Mele C, Ferrero A, et al. Dynamic Tests in Pituitary Endocrinology: pitfalls in Interpretation during Aging. *Neuroendocrinology*. 2022;112(1):1–14 with permission from S. Karger AG, Basal.[19]

distinguishes central from nephrogenic DI.[55] The deprivation test should be performed with great caution in elderly patients, because of the risk of dehydration.

Treatment of Hypopituitarism in the Elderly

The treatment of hypopituitarism in the elderly requires several careful considerations. On the one hand the most important goal is the reduction of cardiovascular risk that can be associated with hypopituitarism. On the other hand the dogma that the main goal of the hormone replacement therapy is to restore the hormonal physiology as close as possible, and to avoid the symptoms associated with its deficiency, should be applied very carefully in older people, considering the physiological changes associated with aging, and the possible risks associated to the over-replacement, avoiding worsening of intercurrent diseases (diabetes, hypertension, osteoporosis, risk of malignancy). Additionally, the presence of concomitant therapies that may modify the clearance and effects of replacement therapies must be considered.

In general, the hormonal requirements in older people are lower than young adults. A recent retrospective study showed that in older patients (>70 years-old) affected by hypopituitarism hormone replacement with low-dose glucocorticoids, levothyroxine (and androgens in men) resulted in the reduction in estimated cardiovascular risk.[56]

Treatment of Central Hypoadrenalism

In patients affected by ACTH deficiency glucocorticoid replacement is essential to avoid life-threatening adrenal crises. The cortisol circadian rhythm follows the activity of a circadian clock sited in the suprachiasmatic nucleus of the hypothalamus, but also of other brain areas.[57] Therefore, a residual circadian rhythm function is still present in central adrenal insufficiency, while it is lost in primary adrenal insufficiency. This, together with the knowledge that the physiological daily production of cortisol is lower than previously commonly believed, suggests the possibility of using a lower replacement dose of glucocorticoids than used in the past in central adrenal insufficiency to avoid overtreatment, which poses the risk of loss of bone and of metabolic derangements.

The replacement of glucocorticoid should be started before the levothyroxine (LT4) therapy because the Initiation of LT4 can enhance the clearance of cortisol and exacerbate underlying adrenal insufficiency, increasing the risk of adrenal crisis.[46]

The gold standard therapy is represented by hydrocortisone (HC), which is administered in 2 or 3 divided daily doses arranged to mimic the circadian rhythm (more on this below). Possible alternatives include cortisone acetate (which is no longer available in the US), prednisone and dexamethasone. Hydrocortisone is an active glucocorticoid, whereas cortisone acetate and prednisone require activation via hepatic 11 beta-hydroxysteroid dehydrogenase type 1 (HSD1). Prednisone has an intermediate duration of action, and can generally be administered in a single morning dose. Longer acting glucocorticoids, such as dexamethasone, present a more potent glucocorticoid activity, but we recommend against their use due to the lack of a "glucocorticoid-free" period during 24 hours (see Table 2).

Supplementation of mineralocorticoid by 9alpha fludrocortisone is not necessary in secondary adrenal insufficiency, because the renin-angiotensin-aldosterone axis is preserved.

Generally, patients with central adrenal insufficiency require lower daily glucocorticoid doses than those with primary, probably because of the effect of GH deficiency on 11beta-HSD1 activity resulting in reduced cortisol clearance.[58] Indeed, 11beta-HSD1 is negatively regulated by GH, and the elevated 11beta-HSD1 within key metabolic tissues leads to an increased

Table 2 Glucocorticoids Used in Replacement Therapy and Their Characteristics

Synthetic Glucocorticoids	Equivalent Dose (mg)	Anti-Inflammatory Activity (Related to Hydrocortisone)	Biological Half-Life (Hours)
Hydrocortisone	20	1	8–12
Cortisone Acetate	25	0.8	8–12
Prednisone	5	4	12–36
Prednisolone	5	4	12–36
Dexamethasone	0.75	30	36–72

cortisol availability.[59] Additionally, the expression of 11beta-HSD1 in several tissues (skin, brain, muscle) is increased both in aging rodents and humans.[60–62] Based on the above-mentioned considerations, it is reasonable to reason that older patients need lower glucocorticoid replacement doses than young patients. However, no specific recommendations have been provided for this group of patients by guidelines. The current literature suggests replacement in adults of 15–20 mg of HC as a total daily dose, in two or three divided oral doses. The highest dose (half or two-thirds of the total daily dose) should be given in the morning at awakening, the next either in the early afternoon (2 hours after lunch; two-dose regimen) or at lunch and afternoon (three-dose regimen).[46] The last dose should be given no less than 6 hours prior to bedtime, to avoid sleep disorders or metabolic side-effects[63] that can be more pronounced in older people. Cortisone acetate is considered comparable to HC. As an alternative, oral prednisolone or prednisone (3–5 mg/day), once daily can be used, while the use of dexamethasone should be avoided because of risk of Cushingoid effects and difficulties in dose titration. In attempting to mimic the normal circadian rhythm, the combination of immediate and delayed-release HC (dual-release) forms can be considered (not available in the USA), with possible advantages in metabolic profile. Dual-release HC (DR-HC) can be administered as an oral once daily dose (20–25 mg/day). Compared to conventional tablets given three times daily, once daily DR-HC tablets results in an increased cortisol exposure during the first four hours after intake, but reduced exposure in the late afternoon/evening and over the 24-hour period.[64] A recent study confirms that DR-HC appears safe in patients with central adrenal insufficiency. A significant reduction of waist circumference and BMI have been reported after switching to DR-HC, while no significant changes were observed in fasting glucose, insulin, HbA1c, total cholesterol, triglycerides, LDL cholesterol, electrolytes, and blood pressure.[65] Although there are no specific studies on the treatment of central hypoadrenalism in the elderly patient, our recommendation is to use the lowest possible dose that maintains a good level of energy while minimizing comorbidities related to overtreatment. It is important to note that there are no standardized biochemical evaluations to assess the adequacy of glucocorticoid replacement. Urinary free cortisol (UFC) measurement is not useful, because the saturation of corticosteroid-binding globulin (CBG) following oral HC results in supraphysiological UFC excretion.[66] Well-being and electrolytes measurement represent useful tools. Hyponatremia and gastrointestinal symptoms are common in elderly affected by hypopituitarism and reflect low cortisol bioavailability.[67] However, the interpretation of sodium levels in older patients affected by hypopituitarism must consider the possible presence of a concomitant syndrome of inappropriate ADH secretion due to illness, medications, or ageing itself,[68] or an over-replacement of desmopressin (DDAPV) in patients with concomitant diabetes insipidus. Hyperkalemia, which represents a common symptom of primary adrenal insufficiency, is less common in patients with central adrenal insufficiency because lack of ACTH does not cause aldosterone deficiency. However, in the interpretation of serum potassium levels the possible effects of potassium-sparing drugs (spironolactone, potassium canrenoate) or with potassium losing effects (furosemide, hydrochlorothiazide) must be considered.

Dehydroepiandrosterone (DHEA) is another adrenal hormone which declines with aging. Its regulation is under the control of ACTH. Therefore, a great interest has risen in the literature concerning the effects of DHEA replacement therapy in older (not hypopituitary) patients. However, a systematic review showed that DHEA treatment is not associated with benefits in physical function or performance.[69] As expected, DHEA replacement can improve hip bone mineral density (BMD) in both sexes and spine BMD in females.[70] A randomized, double-blind, placebo-controlled trial conducted in older people (65–78 years) with age-related decrease in DHEA level (measured as DHEA sulfated form, DHEAS) of both sexes, showed that DHEA treatment (50 mg/day) is associated with a significant decreases in visceral fat area and subcutaneous fat, as well as with increased insulin sensitivity.[71] However, it is not clear if the same results would be observed in elderly patients with hypopituitarism. Therefore, currently, routine DHEA replacement is not recommended in older hypopituitary patients.

Treating Hypoadrenalism in Special Groups of Patients

An important problem in the treatment of central hypoadrenalism is related to the presence of comorbidities and to the possible interference of other drugs on glucocorticoid's metabolism. This problem is more pronounced in older people, who are often in poly-pharmacological therapy for concomitant disease. Increases in synthetic glucocorticoid doses may need to be considered when enzyme-inducing drugs are co-administered since they increase glucocorticoids metabolism. Conversely, the co-administration of drugs that are enzyme-inhibitors may increase glucocorticoid exposure and toxicity (see Table 3).

Table 3 Inducers and Inhibitors of CYP3A

Inducers of CYP3A	
Interacting drug classes	**Drugs**
Anti-epileptic drugs	Carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone
Antimicrobials	Efavirenz, etravirine, nafcillin, rifampin, rifabutin, Rifapentine
Inhibitors of CYP3A	
Interacting drug classes	**Drugs**
Antimicrobials	Clarithromycin, telithromycin
Antifungal	Itraconazole, ketoconazole, posaconazole, Voriconazole
Antiviral (HIV and anti HCV)	Boceprevir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir, Atazanavir,
Immunosuppressant	Cyclosporine, tacrolimus, everolimus

Elderly patients are more prone to develop spontaneous hypoglycemia, both for the polypharmacy and for concomitant conditions, such as frailty, multiple organ failure, malnutrition, malignancies, and underlying dementia. The proposed pathogenic mechanisms for increased hypoglycemia risks are the impaired glucagon and epinephrine release in response to hypoglycemia, and the reduced awareness of the autonomic symptoms of hypoglycemia,[72] compared with younger people. This phenomenon is further enhanced in the presence of hypoadrenalism, because of the lack of a counter-regulatory effect mediated by cortisol. In diabetic patients taking insulin and/or other anti-diabetic medications, the possibility of the so-called "Houssay phenomenon", caused by the failure of counter-regulatory hormones produced by the anterior pituitary gland to correct hypoglycemia,[73] should be considered. Despite this, the association of recurrent hypoglycemia in diabetic patients with hypopituitarism has been rarely described. Few cases have been reported and in particular in a geriatric population.[74–76]

Patients with central hypoadrenalism treated with recombinant human GH (rGH) may need a higher glucocorticoid dose as compared to patients in whom GHD is not replaced, because of the above mentioned effect of GH on 11beta-HSD1 activity.[77]

If a patient with central hypoadrenalism needs synthetic glucocorticoids for immunosuppressive or anti-inflammatory purpose at a dose particularly higher than the equivalent replacement daily HC doses, the replacement therapy should be halted. Interestingly, no data have been reported on hypopituitary patients treated with abiraterone for prostate cancer, whose incidence is strongly correlated with age, with the highest rates seen >65 years.[78] Abiraterone acetate, the precursor of the CYP17A1 inhibitor abiraterone, blocks androgen biosynthesis, and is approved for the treatment of patients with metastatic castration-resistant prostate cancer.[79] However, it also blocks cortisol secretion, and is therefore administered in combination with prednisone. The association with prednisone compensates the abiraterone-induced reductions in serum cortisol and blocks the compensatory increase in ACTH, which can increase the risk of mineralocorticoid-related adverse events.[80]

Adrenal Crisis in the Elderly

Adrenal crisis is the most severe acute manifestation of adrenal insufficiency, resulting in severe hypotension, with increased risk of cardiovascular events, acute renal injury, and possibly death. Evidence from population-based studies indicate that adults older than 60 have the highest age-specific incidence of adrenal crisis, which doubles between the age 60–69 years and 80 years or older. This is likely due to the higher prevalence of comorbidities, such as diabetes or cardiac and respiratory diseases. Therefore, even if adrenal crises are slightly more frequent in primary than in secondary adrenal insufficiency (5.2 and 3.6 adrenal crises per 100 patient-years, respectively),[81] a prompt diagnosis and treatment is mandatory in older patients affected by hypopituitarism. Possible precipitating factors include infections, falls and fractures, myocardial infarction or cerebrovascular accidents.[68] Concomitant therapies with

CYP3A4 inducers (see Table 3), which can enhance the metabolism of synthetic glucocorticoids, might induce an adrenal crisis.[82] Undiagnosed coexisting hyperthyroidism as well as initiation of LT4 therapy might precipitate an adrenal crisis in a patient with undiagnosed hypoadrenalism.[83] The treatment of an adrenal crisis in older patients is similar to that proposed for other ages. It is recommended the administration of parenteral HC as a 100 mg bolus, followed by frequent intravenous (or intramuscular) boluses every 6 h, with subsequent doses reduced on the basis of the clinical response.[68] In cases of hypoglycemia intravenous dextrose (5% or 10% concentration) in normal saline can be administered, but in the presence of concomitant diabetes insipidus, both on and without treatment with desmopressin (DDAVP or AVP-D), an accurate assessment of the balance of fluid intake and output must be performed to avoid hyponatremia or hypernatremia.[83]

Treatment of Central Hypothyroidism

LT4 is the treatment of choice, as in primary hypothyroidism. The Endocrine Society guidelines suggest avoiding the treatment of central hypothyroidism with LT3 as well as with thyroid extracts.[46] However, the treatment of secondary hypothyroidism often represents a challenge, because of the impossibility of using TSH levels as a reliable marker both of the severity of the hypothyroidism and of the appropriate replacement doses. Limited data are available to guide treatment of central hypothyroidism in older patients, but a reasonable approach can be proposed by the evaluation of those provided for primary hypothyroidism. Some authors state that, if cardiac co-morbidities have been ruled out, it is possible to start LT4 therapy with a full dose, similarly as in younger patients.[84] However, we recommend a more prudent approach, starting with lower dose (around 0.25–0.5 mcg/kg body weight), with gradual increases every 3–4 weeks, if well tolerated.[14] In adults the average LT4 requirement in central hypothyroidism is about 1.6 mcg/kg/day, with dose adjustments based on clinical context, age, and FT4 levels.[46] In people over 60 years, the target dose has been proposed to be around 1.1 mcg/kg/day.[85] This derives from several considerations related to aging: first of all, different factors that can interfere with LT4 metabolism, such as the reduced metabolic clearance and the reduced body mass. Additionally, LT4 overtreatment can results in tachyarrhythmias (in particular atrial fibrillation) and reduced bone density and fractures.[86,87]

In general, the adequacy of LT4 replacement is monitored by measuring serum FT4 at least 4 hours after oral intake, which should be maintained in the mid-upper normal range. However, while in primary hypothyroidism specific age-related TSH target have been proposed, no evidence is available about the optimal FT4 levels in older people. It seems reasonable, to avoid the risk related to overtreatment, to maintain FT4 in the lower half of the normal reference range, paying attention to clinical status and to other markers of adequacy of therapy, in particular lipids and body mass. In central hypothyroidism FT4 levels are negatively associated with BMI and waist and hip circumference,[88] even if these associations are less studied than in primary hypothyroidism.[89] However, it is very difficult to correctly perform this kind of assessment due to confounding variables. While an increased cardiovascular morbidity and mortality have been reported in hypopituitarism,[90] the impact of central hypothyroidism, which is rarely isolated, is difficult to assess. The interpretation of FT4 levels must consider the possible interferences by other drugs or supplements, particularly by anti-seizure medications, which (in addition to increasing LT4 catabolism) may falsely reduce the reading when measured by routine assays.[91]

LT4 has a peak concentration 2–4 h after ingestion. It is therefore recommended to perform blood tests before the ingestion of LT4 tablets.[92] Importantly, despite the lack of reliability of TSH in titrating therapy in central hypothyroidism, TSH levels are low (<0.5 mIU/L) in more than 80% of hypopituitary patients receiving LT4.[93] Therefore, insufficient replacement can be suspected if TSH levels are "inappropriately elevated" (>1 mIU/L). In patients with high-normal FT4 and high FT3 levels, the risk of overtreatment should be considered.[92] The effects of concomitant drugs must be considered. In patients taking amiodarone, the T4/T3 ratio can be increased because of the inhibitory effect of amiodarone on hepatic type 1 iodothyronine deiodinase (D1) activity.[94] On the contrary, GH increases T4 to T3 conversion through type 2 deiodinase (D2) activation, and therefore FT4 levels usually drop in patients with central hypothyroidism after starting rGH replacement therapy.[92] Reduced FT3 and FT4 levels have been reported in patients on enzyme-inducing anti-epileptic drugs therapy, such as phenobarbital, phenytoin and carbamazepine.[91]

Interestingly, Cappelli et al demonstrate that in elderly patients with primary hypothyroidism the use of liquid LT4 guaranteed a better stability in thyroid profile compared with tablets, with a significant reduction of cases of

overtreatment.[95] However, no similar study has been conducted in patients with central hypothyroidism. Therefore, we recommend the use of routine LT4 tablets.

Treatment of Hypogonadism

Treatment of hypogonadism in older females should follow the criteria used in any woman of a similar age. Here we will discuss testosterone replacement therapy in male patients. It is reasonable to treat with replacement therapy symptomatic male patients in the presence of serum total testosterone levels <250 ng/dl.[96,97] An adequate level of testosterone could play an important role in regulating several tissue's functions in geriatric age. Most studies in this area are generated in older males with mild to moderate low testosterone, not specifically related to organic pituitary disease. While it is difficult to compare the results of the different studies because the population samples are inhomogeneous, in older individuals with low serum testosterone replacement therapy showed an improvement of well-being and sexual performance,[98,99] while its effects on cognitive functions are still debated.[100] A recent clinical trial showed a possible improvement of cognitive function in a group of older men on testosterone replacement therapy (and lifestyle intervention) from a specific population of obese hypogonadal men.[101]

Testosterone produces a substantial anabolic effect in young and middle-aged men with hypogonadism, but data in older people are limited. The majority of the studies found a significant increase in lean body mass in older people treated with testosterone for hypogonadism,[98,102,103] but some bias of interpretation can be present (patients with increased cardiovascular morbidity have been excluded in some studies and included in others, and the clinical status of the participants has not always been reported). The effects of the treatment on mobility have been shown by a study involving a large group of elderly men with limitation of mobility and a total testosterone level between 100 and 350 ng/dL. In this study, a 6-month testosterone treatment allowed a significant improvement in mobility (leg-press and chest-press strength and in stair climbing while carrying a load).[104] Testosterone therapy has positive effects on bone health in older patients, with a significant increase of bone mineral density at the lumbar spine.[105] Beneficial effects on anthropometric measurements and lipids have also been reported.[106,107] Data concerning the impact of testosterone therapy on insulin sensitivity are conflicting: some authors reported a favorable effect in glycemic control both in type 2 diabetes[107] and in healthy older men,[108] while other studies did not find changes in insulin sensitivity in elderly men.[109]

For testosterone replacement therapy, different formulations can be used (Table 4), depending on the patient's preferences and compliance.

Table 4 Preparations Used for Testosterone Replacement Therapy

Administration Route	Preparation	Usual Dose Range
Intra-muscular	Solution (testosterone enanthate, testosterone cypionate)	50 to 100 mg once weekly, **or** 100 to 200 mg every 2 weeks
	Solution (testosterone undecanoate)	750 mg; repeat 750 mg dose after 4 weeks, and then every 10 weeks thereafter
Intranasal	Gel	11 mg (2 pump actuations; 1 actuation per nostril) 3 times daily (6 to 8 hours apart)
Oral	Capsules	158 to 396 mg twice daily
Sub cutaneous (injection)	Solution	50 to 100 mg once weekly
Sub cutanenous (implantation)	Pellet	150 to 450 mg every 3 to 6 months
Topical	1% Gel	50 to 100 mg/day (maximum: 100 mg/day)
	1.62% Gel	20.25 to 81 mg/day (maximum: 81 mg/day)
	2% Gel	10 to 70 mg/day (1 to 7 pump actuations; maximum: 70 mg/day)
	Transdermal solution	30 to 120 mg/day (1 to 4 pump actuations)

The adequacy of the therapy is confirmed by the improvement of clinical symptoms and by the serum testosterone levels, checking testosterone levels 1–2 months after starting therapy and then annually to assess the efficacy and adverse events. It is reasonable to maintain circulating testosterone levels in the lower quartile of the normal range.[14] To this end, transdermal or transmucosal systems of testosterone are potentially more appropriate, to assure a quick adaption and avoidance of supraphysiological peak levels. The patient's evaluation includes the monitoring of prostate-specific antigen (PSA), hematocrit, and lipid levels during treatment, for a prompt diagnosis of the possible side effects related to testosterone replacement therapy (as prostate disease and increased hematocrit levels). In particular, a careful urological follow-up is recommended, considering the frequency of prostatic diseases in this age group[110]. Indeed testosterone is crucial for the development of prostatic hyperplasia. Although if some studies failed to show complications associated with benign prostatic hyperplasia during testosterone supplementation in older men with low to normal-low baseline testosterone levels,[100] another study reported a significantly increased serum PSA levels after a 3-yr replacement period.[111] No excess cases of prostate cancer were detected. Therefore, data confirming the causal relationship between testosterone replacement therapy and prostate cancer in older man do not exist. Nevertheless, a reasonable caution is mandatory and a urological consultation and a careful follow-up is recommended. Testosterone replacement therapy is usually not recommended in patients with metastatic prostate cancer, breast cancer, unevaluated prostate nodule or induration, PSA >4 ng/mL (or >3 ng/mL in high risk population such men with first-degree relatives with prostate cancer).[14]

Testosterone is also known to induce erythropoiesis and in older men with low to normal-low baseline testosterone levels, which may result in increased hemoglobin and hematocrit levels.[111] This effect could be helpful in the presence of anemia, but elevation above normal levels may result in increased blood viscosity and coronary and cerebrovascular events, suggesting the need for a careful monitoring of hematocrit and hemoglobin levels.[112] Testosterone therapy is not recommended when hematocrit is >50%.[14] Testosterone therapy may also be associated with increased risk of venous thromboembolism in men with and without hypogonadism, with a risk that seems lower after 65 years.[113] Venous thromboembolism can be mediated by several mechanisms, including the above-mentioned increase of hematocrit levels and consequent increase blood viscosity. Other common adverse events include rash, acne, oily skin, and breast tenderness. Less common side effects include gynecomastia and sleep apnea.

The cardiovascular safety of testosterone replacement therapy is debated. A study including older men over 65 years affected by hypogonadism was stopped early due to increased incidence of cardiovascular events in the treated group,[104] However, several clinical trials and meta-analyses have not confirmed any significant adverse cardiovascular outcomes in older men treated with testosterone.[114,115] Due to the current lack of long-term safety studies, testosterone replacement therapy in older men with cardiovascular diseases should be used with caution, and uncontrolled or poorly controlled congestive heart failure represents a contraindication.[116] The rationale and the design of a Phase 4, randomized, double-blind, placebo-controlled study ("Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy ResponSE in Hypogonadal Men", TRAVERSE study) has been recently published. This clinical trial will hopefully determine the cardiovascular safety and long-term efficacy of testosterone treatment in middle-aged and older men with hypogonadism with or at increased risk of cardiovascular disease.[117]

Treatment of GH Deficiency

GHD in adults can lead to decreased cognitive function and quality of life (QoL) and can cause muscle weakness and decreased bone mass, leading to frequent falls and fractures,[118] which may increase morbidity and mortality in the elderly. GHD is associated with increased triglycerides, total and LDL cholesterol, body fat, and liver steatosis. These metabolic alterations have been demonstrated in both familial congenital[119] and adult-onset GHD.[120] A recent cross-sectional study demonstrated that although the occurrence of dyslipidemia is higher in patients affected by panhypopituitarism who did not receive therapy with recombinant GH, the frequency of metabolic syndrome is similar to that detected in control group.[121] Data derived from patients affected by lifetime untreated severe isolated GHD due to a homozygous inactivating mutation in the GHRH receptor gene showed a deleterious effect of suboptimal GH replacement on atherosclerosis.[119] The authors hypothesized that IGF-1 might have a dual action, promoting (by the increase of vascular smooth muscle cells proliferation), or preventing (by the increase in nitric oxide formation and

vascular compliance) atherogenesis. Therefore, the degree of the GHD could play a role: persistent very low IGF-1 levels might have a protective role, whereas a milder decrease could be deleterious. While many "physiological" changes that occur with aging are similar to those detected in young GHD subjects, no causative role has been established between GHD and aging. While restoring a youthful GH level in normal aging adults is not recommended, the situation is different in elderly patients with demonstrated GHD due to pituitary failure, in whom GH insufficiency could give a further contribution to frailty.[122] Indeed, elderly patients aged 60–80 years with panhypopituitarism have even lower GH and IGF-1 levels compared to age-matched controls.[123]

A large systematic review that included 543 GHD patients >60 years and treated with rGH for 6 or 12 months showed that rGH replacement therapy reduced the waist circumference and decreased LDL cholesterol levels and improved quality of life, but no relevant effects were observed on bone mineral density or blood pressure. There was no data for subjects >80 years.[124] The beneficial effects of long-term rGH therapy (7 years of follow-up) in GHD patients on body composition and lipid profile have been confirmed by a recent study involving 125 GHD adult patients (including 10 elderly patients), while glucose metabolism was not different compared with a control group (hypopituitary patients without GHD).[122] Compared with adults affected by GHD and despite a lower dose of rGH, elderly patients showed a more pronounced reduction in waist-to-hip ratio and LDL cholesterol levels.[125] In summary, considering the limitations and heterogeneity in the studies designs, the real impact of rGH replacement in reducing cardiovascular morbidity and mortality in older GHD subjects is still controversial.

The effects of rGH in the elderly with GHD on cognitive performance are still not well studied. A double blind, randomized, placebo-controlled study found that cognitive function improves in elderly patients affected by GHD during rGH treatment,[126] but data need to be confirmed by larger studies. In elderly adults GHD replacement therapy results in a progressive increase in lumbar and spine bone mass and density,[127] but there is not no clear evidence of a direct impact on the risk of fracture.

Improvement of the quality of life has been reported in elderly GHD patients during rGH replacement therapy[128] and this parameter seems to represent an important determinant, together with clinical parameters, to evaluate the replacement therapy.

In summary, despite favorable evidence, the choice to start or not rGH therapy in older hypopituitary subjects is still debated. In our opinion the evidence provided by literature supports replacing GH in GHD elderly patients in subjects less than 80 yrs of age. An initial dose of rGH of 0.1 mg/day is recommended[53] as it is crucial to avoid excessive IGF-1 levels above the upper normal range for age.[129] Doses between 0.2 mg/day and 0.33 mg/day are in general able to maintain IGF-1 levels in this range.[130,131] Fasting glucose, hemoglobin A1C levels, lipid profile, BMI, waist circumference and waist-to-hip ratio should be monitored. Even if studies revising the safety of the long-term therapy with rGH did not show an increased incidence of cancer,[132] the presence of an active neoplasia contraindicates the use of the rGH.[133] Finally, in women oral estrogen causes liver resistance to rGH therapy, and therefore use of transdermal estrogen is recommended if GH replacement is prescribed.[43]

Treatment of Diabetes Insipidus

Patients with ADH deficiency may be treated with adequate oral fluid intake in mild cases, while severe cases require DDAVP, a longer-acting analog of ADH acting mostly on the V2 receptor, and thus with only minimal vasopressor activity. The available formulations include oral, nasal or parenteral.[134] Oral DDAVP absorption rate is very low (<1%), while intranasal is about 6%.[46] Oral DDAVP is available in 0.1 mg and 0.2 mg tablets. Sublingual melts and nasal preparations include a spray (usually 10 mcg per squirt) and a rhinal tube (dose range, 1–10 mcg). In patients with an intact thirst mechanism, the lowest dose of DDAVP able to allow adequate rest during the night and minimal alterations of the normal activities during the day should be used. Treatment must be carefully individualized, and the most important aim is to prevent overtreatment resulting in potentially dangerous hyponatremia.[135] This is particularly important in the elderly, who may have increased renal sensitivity to DDAVP and abnormalities in osmoregulation.[136] Furthermore, older people can present an increased risk of hyponatremia related to other drugs (particularly carbamazepine).[137] Therefore, serum sodium should be monitored especially after a dose change. Sometimes the presence of hypothalamic pathology may cause damage in the regulation of the thirst mechanism. In these cases

("adipsic DI"), patients are at risk of both hypernatremia and hyponatremia because they are not able to judge the fluid intake according to thirst.[138]

Conclusion

The management of hypopituitarism in elderly patients has many challenges. The presence of comorbidities (and their treatment) prevalent in aging may raise concerns about accuracy of diagnosis and possible complications of replacement therapy. For this reason, a correct diagnosis of the hormonal defects must be established, and the optimization of the individual hormone dosage and long-term monitoring remain a primary goal. However, the diagnosis can be difficult because hypopituitarism in the elderly can mimic symptoms of normal aging, and no specific age-adjusted cut-offs for the biochemical diagnosis of hypopituitarism are established. Studies focused on replacement therapy in the geriatric population are still sparse, especially concerning the treatment of central hypoadrenalism and central hypothyroidism. Long term studies evaluating the benefits and risks of sex hormones and rGH are needed, to further assist physicians and patients in the therapeutic decision making.

Disclosure

Dr. Salvatori reports personal fees and is a member of the NovoNordisk advisory board. The authors report no other conflicts of interest in this work.

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