



Hypopituitarism in Adults: Rational Approaches to Diagnosis and Treatment

Mussa H. AlMalki¹

¹ Obesity, Endocrine, and Metabolism Center, King Fahad Medical City, Riyadh, Saudi Arabia

Address for correspondence: Mussa Hussain AlMalki, MD, FACE, Obesity, Endocrine and Metabolism Center, King Fahad Medical City, Riyadh, Kingdom of Saudi Arabia (e-mail: m2malki@yahoo.com).

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Abstract

Pituitary hormones are responsible for the regulation of growth, development, metabolism, reproduction, and homeostasis. Hypopituitarism is a condition that is defined as partial or complete insufficiency of anterior pituitary hormone secretion, and rarely, posterior pituitary hormone secretion. This condition can result from diseases of the pituitary gland or the hypothalamus. The annual incidence of hypopituitarism has been estimated to be 4.2 per 100,000 yearly, and the prevalence has been estimated at 45.5 per 100,000. The symptoms of hypopituitarism vary. The onset is insidious and depends on the number of hormone deficiencies and their degree of severity. Pituitary hormone deficiency can result in substantial clinical changes that increase the risk of morbidity and mortality. People commonly report persistent symptoms and a decline in their quality of life, both of which can be explained, at least in part, by the inherent shortcomings of hormone replacement strategies in their ability to imitate the normal hormone secretion processes. The diagnosis of hypopituitarism can be straightforward by measuring the lowered basal hormone levels. In cases where the basal hormone levels are uncertain or partial hormone deficiencies have been identified, it may be necessary to perform provocative testing of the hypothalamic–pituitary axis. The hypothalamus and pituitary region can be imaged using magnetic resonance imaging, which provides useful anatomical information. When necessary, genetic studies may be added to the diagnostic approach. The treatment consists of physiological replacement of the individual end-organ hormone deficiencies, and careful monitoring is required throughout the patient's entire life. Individualized hormone replacement therapy that considers potential interactions is recommended. This article provides an overview of the pathophysiology, clinical presentation, general diagnostic guidelines, and treatment options of hypopituitarism.

Keywords

- hypopituitarism
- hypothyroidism
- hypoadrenalism
- hypogonadism
- pituitary
- diagnosis
- hormone replacement therapy
- quality of life

Introduction

The pituitary gland (or “master gland”) is situated in the sella turcica, which is located in the anterior midline of the brain.

It is the most important endocrine gland in the body, consisting of the adenohypophysis (anterior pituitary) that secretes gonadotropins (follicle-stimulating hormone [FSH])

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and luteinizing hormone [LH]), thyroid-stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), growth hormone (GH), prolactin (PRL), and the neurohypophysis (posterior pituitary) which stores and secretes antidiuretic hormone (ADH) and oxytocin produced by the hypothalamus. These hormones can either have a direct growth effect on the target tissue (trophic effects) or induce the target tissue to secrete hormones with effects on adjacent tissues (tropic effects).¹ These hormones are involved in numerous physiological processes, including metabolism, growth, development, and reproduction.¹ Hypopituitarism is characterized by inadequate secretion of one or more pituitary hormones due to genetic or acquired causes.² It is an uncommon, lifelong condition.³ The clinical manifestations of hypopituitarism vary considerably based on the underlying etiology, patient's age and rate of onset, the affected pituitary hormones, and the severity of hormone insufficiency. The symptoms are typically nonspecific and develop insidiously in adults up to several years before diagnosis.³ Most patients with hypopituitarism have numerous pituitary hormone abnormalities, and it is difficult to attribute specific signs and symptoms to a single hormone shortage.

Moreover, hypopituitarism has been linked to an increased mortality risk, mainly from cardiovascular and cerebrovascular disorders.⁴ Nevertheless, if appropriately managed with regular medication, the condition exhibits a favorable prognosis.¹ The goal of treatment is to replace the target hormone of the disrupted hypothalamic-pituitary-endocrine gland axis. The absence or insufficiency of pituitary hormone replacement therapy may be incompatible with life, especially in ACTH deficiency. The aim of this article is to provide a practical guide for the diagnosis and management of individuals with hypopituitarism.

Epidemiology

According to epidemiological data in the adult population derived from a Spanish study, hypopituitarism is a rare condition, with an estimated annual incidence rate of 4.2 cases per 100,000 population and a prevalence rate of 45.5/100,000.⁵

Furthermore, hypopituitarism is thought to affect approximately 100,000 Brazilians, with approximately 8,500 new cases annually.⁶ The frequency of hypopituitarism has increased in recent years because of the recognition of new etiologies, such as head trauma and drug-induced hypophysitis.²

Etiology

Hypopituitarism is caused by diseases that impair the anterior pituitary secretory function or inhibit hypothalamic anterior pituitary-releasing hormone secretion. Hypopituitarism may result from genetic mutations, congenital abnormalities, or acquired diseases.⁶ The primary etiology of hypopituitarism in children is genetic or congenital disorders. Acquired conditions are frequently observed among adults.⁶

The majority of cases of hypopituitarism are caused by pituitary adenoma and their treatment with surgery and/or radiotherapy, comprising approximately two-thirds of cases. Nonpituitary lesions account for 9% of cases, while nontumoral causes make up 30%, including Sheehan's syndrome, which continues to be a prevalent cause of hypopituitarism among women in developing countries.^{5,7} Nontumoral causes of hypopituitarism can also be linked to subarachnoid hemorrhage as well. The incidence of hypopituitarism following traumatic brain injury (TBI) varies significantly across various studies, with reported rates ranging from 16% to 69%.^{8–10}

Hypophysitis, another frequently underdiagnosed cause of hypopituitarism, is related to an inflammatory process of the pituitary and may be classified as primary or secondary, which is either related to inflammatory (sarcoidosis and granulomatosis), infectious (tuberculosis, syphilis, and fungal infections), or infiltrative (hemochromatosis, amyloidosis, and Langerhans-cell histiocytosis) diseases, or drug-related, as observed with two classes of immune checkpoint inhibitors.⁶ ► **Table 1** summarizes the causes of hypopituitarism.

Clinical Features

The clinical manifestations of hypopituitarism are variable and nonspecific, frequently develop subtly, and depend on the underlying cause, affected pituitary hormones, and the degree of hormone deficiency.¹¹ ► **Table 2.** When pituitary tumors cause hypopituitarism, patients may exhibit symptoms attributable to mass effects, such as headache, visual impairment (typically bitemporal hemianopia), or cerebrospinal fluid rhinorrhea, and symptoms of hypothalamic dysfunction, such as autonomic nervous system disorders.¹¹ In addition, the patient may acquire endocrinopathy due to specific hormone deficiencies in isolation or in combination; however, some basal hormone secretion can be preserved in patients with pituitary involvement compared with patients with target organ damage, resulting in milder symptoms. It is challenging to attribute particular signs and symptoms to a single hormone deficiency^{12,13} in most patients with hypopituitarism who have multiple pituitary hormone deficiencies. Deficiencies in pituitary hormones may result from hormone excess produced by functional pituitary tumors or tumor-induced compression of normal pituitary cells, as elevated PRL would lead to a decrease in gonadotropin-releasing hormone (GnRH) secretion and, consequently, leading to hypogonadism.¹⁴ Hypopituitarism has a variable course and severity. It is defined by a complete or partial loss of pituitary function that is frequently permanent, but transient deficiencies with recovery years after the original event are possible.^{9,13} The pattern of endocrine failure varies according to the underlying pituitary pathology. The typical sequential pattern is loss of GH secretion followed by gonadotropins, TSH, and ACTH, which is primarily observed in patients with tumors, and after radiation therapy, whereas hypopituitarism due to other causes may present with a different sequence of deficiency, for example, ACTH deficiency may be the initial manifestation of hypophysitis.^{13,15}

Table 1 Causes of hypopituitarism

| | |
|-----------------|--|
| Childhood-onset | Genetic disorders, including familial hypopituitarism with isolated or multiple hormone deficiencies Perinatal insult (abnormal delivery, asphyxia) Pituitary hypoplasia or aplasia Craniopharyngiomas and other para-sellar tumors Craniospinal irradiation Head trauma |
| Adult onset | Pituitary defect as result of adenomas, neurosurgery, irradiation, and infarction. Non-pituitary tumors, including meningiomas, gliomas, chordomas, ependymomas and metastases. Infections including abscess, meningitis, encephalitis Autoimmune disorders; lymphocytic hypophysitis Postpartum hemorrhage (Sheehan's syndrome) Internal carotid artery aneurysm, subarachnoid hemorrhage Head trauma Infiltrative diseases; hemochromatosis, granulomatous diseases, histiocytosis Empty sella Idiopathic cause |

Table 2 Clinical manifestations of hypopituitarism

| Hormone deficiency | Symptoms |
|---------------------------------|---|
| Corticotroph deficiency | Acute: weakness, fatigue, dizziness, nausea, vomiting, hypotension, shock, hypoglycemia Chronic: fatigue, pallor, anorexia, weight loss, hypoglycemia Children: failure to thrive, hypoglycemia |
| Thyrotropin deficiency | Tiredness, cold intolerance, constipation, hair loss, weight gain, dry skin, bradycardia, hoarseness, cognitive slowing |
| Gonadotropin deficiency | Children: delayed puberty Women: in the short term; amenorrhea, oligomenorrhea, infertility, loss of libido, dyspareunia, while in the long term; osteoporosis, premature atherosclerosis. Men: loss of libido, impaired sexual function, mood impairment, decreased muscle and bone mass, loss of facial hair. |
| Growth hormone deficiency | Children: growth retardation Adults: decreased muscle mass and strength, visceral obesity, fatigue, memory impairment, premature atherosclerosis, decreased quality of life |
| Antidiuretic hormone deficiency | Polyuria, polydipsia |

Notably, some individuals may initially manifest with an acute onset of pituitary hormone deficiency, as in the case of a patient with pituitary apoplexy and a sudden onset of ACTH deficiency.

In contrast, hyperprolactinemia is prevalent in patients with hypopituitarism due to compression of the pituitary stalk or a macroprolactinoma. In addition, hypopituitarism is associated with various metabolic and cardiovascular comorbidities, including hypertension, unfavorable changes in body composition, and diminished exercise capacity, which may be accompanied by dyslipidemia, insulin resistance, dysglycemia, premature atherosclerosis, and cardiac dysfunction.^{2,16} In the case of functioning pituitary tumors, symptoms arising from increased hormone secretion can coexist and prevail in the clinical presentation.²

Diagnosis

Patients with nonspecific symptoms should be evaluated with a high index of suspicion for hypopituitarism, especially those with a history of hypothalamic–pituitary disease, those

at risk for pituitary dysfunction, or those who have undergone radiotherapy. A comprehensive medical history and physical assessment should elicit additional diagnostic features. Hypopituitarism is ultimately diagnosed by measuring baseline and stimulated secretion of anterior pituitary hormones and their target hormones.

Growth Hormone Deficiency

In adulthood, GH deficiency (GHD) differs from that in childhood. In children, the decreased growth velocity is the most noticeable symptom. In contrast, in adults, the symptoms are diverse and nonspecific, including, but not limited to increased fat mass, decreased muscle mass, poor energy, and decreased quality of life.¹ Therefore, biochemical testing is required for diagnosis.

Patients with a history of structural pituitary lesions, surgery, cranial radiation, TBI, or other pituitary hormone deficiencies should be evaluated for GHD. The deficiency of three or more pituitary hormones, combined with low insulin-like growth factor-I (IGF-I), is highly predictive of

GHD and warrants no further testing.^{17,18} Dynamic pituitary function tests are required in less clear-cut situations.

However, it is imperative to ensure the adequate replacement of other pituitary hormones before conducting GH stimulation tests. The insulin tolerance test (ITT) is the gold standard test for adult GHD, with a diagnostic threshold of less than 5.1 µg/L.¹⁸ However, ITT is not appropriate for all patients and is contraindicated in those with a history of seizures or ischemic heart disease. It also requires close monitoring and physician attendance, even in healthy adults. Adequate hypoglycemia (2.2 mmol/L) is not always achieved; therefore, larger insulin doses of up to 0.3 U/kg may be required in obese patients and those with fasting blood glucose levels above 5.5 mmol/L.¹⁹ As a result, alternative tests, such as the glucagon stimulation test and growth hormone-releasing hormone (GHRH)-arginine, can be used to stimulate GH release. Thus, the GHRH-arginine assay is reliable and accurate. This combined test is not influenced by sex or age, has few adverse effects, and does not cause hypoglycemia. Nonetheless, because GHRH directly stimulates the pituitary, individuals with hypothalamic GHD, particularly after radiotherapy, may exhibit a falsely normal GH response.²⁰ The diagnostic threshold should be adjusted for body mass index (BMI): 11.5 µg/L for individuals with BMI <25 kg/m; 8.0 µg/L for those between 25 and 30 kg/m; and 4.2 µg/L for those >30 kg/m.²¹ However, the GHRH is no longer available in some countries, necessitating other stimulation tests. In contrast, the glucagon stimulation test can be used to evaluate both the GH and cortisol axes with a few side effects, including nausea, vomiting, diaphoresis, and headaches, which occur in 10 to 30% of patients. It consists of administering 1 mg of glucagon intramuscularly (IM; or 1.5 mg for those weighing >90 kg) and monitoring the GH level every 30 minutes for 4 hours. The cutoff value for GHD is <3 µg/L,¹⁸ while a cutoff of less than 1 µg/L is recommended for overweight or obese patients to avoid overdiagnosis.²²

Macimorelin, a synthetic oral ghrelin agonist that stimulates GH in a dose-dependent manner,²³ has recently been approved by the FDA for the diagnosis of GHD. The accuracy of the macimorelin test was comparable to that of the GHRH-arginine test. It is conducted by administering 5 mg/kg orally and measuring GH at 0, 30, 45, 60, 75, 90, 120, and 150 minutes with the proposed cut-off points for GHD of <6.9 µg/L for nonobese subjects and 2.8 µg/L for obese subjects to reduce the misclassification rate.²⁴

Gonadotropin Deficiency

Gonadotropin deficiency is diagnosed in postmenopausal women when FSH and LH levels are low or undetectable. In younger women, oligo-/amenorrhea with low estradiol levels and low or normal gonadotropin levels is adequate to diagnose secondary hypogonadism.¹ Low or abnormally normal FSH and LH levels and low serum testosterone levels are diagnostic indicators of secondary hypogonadism in males. Sperm analysis is necessary when contemplating fertility and may reveal oligospermia or azospermia.¹ In adults, it is not advisable to conduct stimulation tests such as

the GnRH test because they provide no additional information.²⁵

Thyrotropin Deficiency

Central hypothyroidism is diagnosed when the serum TSH level is low or normal and the serum free thyroxine (FT4) level is low. In patients with concomitant GH and TSH deficiencies, serum FT4 concentrations may be normal and decrease only after GH replacement.²⁶ Measurement of serum tri-iodothyronine (FT3) is not required but may be low or normal. The thyrotropin-releasing hormone (TRH) stimulation test has been utilized less frequently in the past and is not recommended owing to a lack of availability and accuracy.²⁷

Adrenocorticotropin Deficiency

The hypothalamic-pituitary-adrenal (HPA) axis exhibits a diurnal rhythm, causing serum cortisol levels to peak at 5:00 AM and steadily decline throughout the day, often becoming undetectable at midnight during sleep.¹ Basal cortisol 09:00 hour more than 15 µg/dL (414 nmol/L) or less than 3 µg/dL (83 nmol/L) usually confirm sufficiency or deficiency.^{13,28} However, a stimulation test is needed in individuals with intermediate cortisol levels (>3 and <15 µg/dL at 0900 hours).¹³

Hypoglycemia is a potent stimulant of the HPA axis, and ITT is the gold standard for evaluating the HPA axis, with the additional benefit of assessing the GH status of patients simultaneously. A peak cortisol response to hypoglycemia (blood glucose 2.2 mmol/L) >18.1 to 20 µg/dL (500–550 nmol/L) is considered normal.²⁸ ITT is contraindicated in patients with ischemic cardiac disease and epilepsy.³ The short synacthen test (SST), which assesses the serum cortisol response to an intramuscular injection of cosyntropin (synacthen) (ACTH1–24), is a commonly used diagnostic tool with a dose of 250 µg.²⁹ It is a less labor-intensive alternative to ITT. It can be performed in an ambulatory setting at any time of the day and has been validated for detecting ACTH deficiency using peak cortisol levels.¹ In subjects in whom the onset of corticotropin deficiency is acute because of pituitary apoplexy or after pituitary surgery, SST may be less sensitive and provide a false-negative result, as the adrenal cortex remains responsive to exogenous corticotropin while it atrophies gradually; therefore, it should not be performed until at least 4 to 6 weeks after surgery or apoplectic event.³⁰ It is debatable whether a low-dose (1 µg) cosyntropin test (LDSS) would provide a more physiological stimulus for maximum adrenal stimulation than the 250 µg corticotropin dose (SST). A recent meta-analysis of studies demonstrated that both tests are equally effective and that there is no advantage to using the LDSST over the SST.³¹

As synacthen is only commercially available in 250 µg ampules, it is impractical to produce the necessary dilution because of the potential binding of the hormone to the surface of injection devices; therefore, it is recommended

that the standard SST be used in clinical practice.³¹ A serum cortisol level of 18.1 µg/dL (500 nmol/L) or higher at 30 or 60 minutes after synacthen administration was consistent with the normal corticotropin reserve. This has been shown to correlate well with peak cortisol levels during ITT.²⁹ A recent study suggested using a cutoff value of 14 to 15 µg/dL with liquid chromatography with tandem mass spectrometry or monoclonal antibody assays, as opposed to the historical value of 18 to 20 µg/dL derived from polyclonal antibody assays, which reduces the likelihood of overlooking secondary adrenal insufficiency.³² It is crucial for clinicians evaluating patients for adrenal insufficiency to be aware of the new assay-specific cut-off method available at their institution.³²

An alternative diagnostic test involves the administration of metyrapone, which acts by inhibiting 11-β-hydroxylase. This inhibition prevents the conversion of 11-deoxycortisol (11-DOC) to cortisol, leading to a decrease in the serum cortisol concentration. Because of the lack of cortisol-negative feedback inhibition, there was an increase in ACTH secretion.

The metyrapone test can be performed by administering a single oral dose (30 mg/kg body weight) overnight, followed by measurement of serum 11-deoxycortisol and cortisol the following morning (at 08:00).³ A serum cortisol concentration of <5 µg/dL (138 nmol/L) indicates adequate blocking of enzyme inhibition.³ An increase in serum 11-deoxycortisol concentration of 7 to 22 µg/dL (200–635 nmol/L) indicates adequate activation of the adrenal axis.³³

Compared with ITT, it is less cumbersome and appears to be safely performed on an outpatient basis³⁴; however, it is not frequently performed because of the limited drug supply. Furthermore, CRH has been used to distinguish between hypothalamic and pituitary disorders in patients with secondary adrenal insufficiency. Because exogenous CRH responses vary greatly, CRH stimulation does not help diagnose secondary adrenal insufficiency.³⁵

Prolactin Deficiency

It is rare and is defined as a serum PRL level that is consistently below the detection limit of the assay and is marked by the inability of women to lactate. Severe hypoprolactinemia (serum PRL 50 mU/L [normal range: 85–444 for men, 85–530 for women]) can be an indication of severe

hypopituitarism.³⁶ Basal PRL levels are low and do not increase after intravenous TRH administration.¹¹ However, PRL levels are increased in patients with hypopituitarism caused by pituitary mass lesions.¹¹

Desmopressin Deficiency

Diabetes insipidus (DI) may be diagnosed in a proper clinical setting in the presence of polyuria (>3 L per day) and concomitant polydipsia after excluding other causes of polyuria, such as hyperglycemia.³⁷ Providing the thirst sensation is intact and fluid intake is adequate, it helps to maintain normal serum sodium concentrations and osmolality.³⁷ When the diagnosis is uncertain, a water deprivation test should be performed. However, when this test was used alone, only 70% of the patients were classified into the correct diagnostic group.³⁸ A maximum urine osmolality of >800 mOsm/kg after fluid deprivation excludes DI. Simultaneously, a urine osmolality of <300 mOsm/kg H₂O with subsequent response to arginine vasopressin (AVP) suggests central DI.³⁸ An alternative option includes the direct measurement of AVP concentrations, but this is limited by the challenges of accurate AVP measurement and the need for clarity concerning the normal range for AVP to plasma osmolality.³⁹ Copeptin, the C-terminal moiety of AVP, has been proposed as a stable and alternative marker for AVP.³⁹ In a recent study, combining a fluid deprivation test and a hypertonic saline challenge using copeptin measurements provided an accurate diagnosis in 96% of patients presenting with polyuria and polydipsia.⁴⁰ Further studies are needed in symptomatic patients with a clear underlying cause of DI.⁴¹ These include magnetic resonance imaging (MRI) of the hypothalamic-pituitary region and or a therapeutic trial with desmopressin.

Neuro-ophthalmic Evaluation

Patients with hypopituitarism should be screened for sellar lesions and chiasm-optic nerve compression. The frequency of radiological assessment and visual evaluation depends on the tumor size and its proximity to vital structures.

Imaging

The MRI is the preferred imaging modality for patients with suspected of having pituitary diseases. ► **Fig. 1** illustrates the

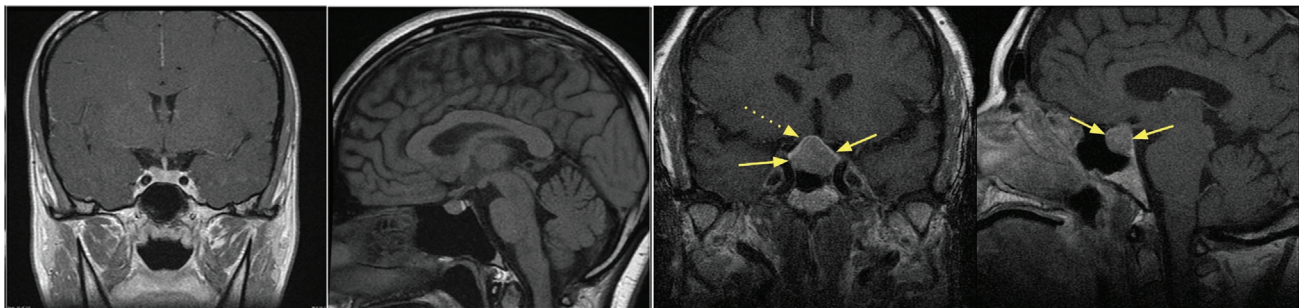


Fig. 1 MRI pituitary showing a normal pituitary gland in the left two panels and a pituitary macroadenoma in the right two panels.

normal appearance of the pituitary region and the typical appearance of a macroadenoma. The benefits of MRI include the absence of ionizing radiation and the ability to differentiate anatomical tissues without contrast agents. The disadvantages of MRI are its relative insensitivity to pathological calcifications and lack of cortical bone signals. CT scan is a suitable alternative when MRI is contraindicated. On nonenhanced images, a CT scan may generate images of adequate quality that depict the sellar anatomy and can detect skeletal changes more readily.

Ophthalmological Evaluation

All patients with pituitary lesions close to or compressing the optic chiasm on MRI must be evaluated by an ophthalmologist. This serves as a baseline and assists in subsequent monitoring. The evaluation involved a visual acuity test, a visual field test (by confrontation, along with the Goldmann or Humphrey perimetry test), and fundoscopy to identify papilledema, retinal vein engorgement, and optic atrophy. Vision loss usually occurs gradually, except in cases in which pituitary apoplexy may cause it to occur suddenly. **Fig. 2**

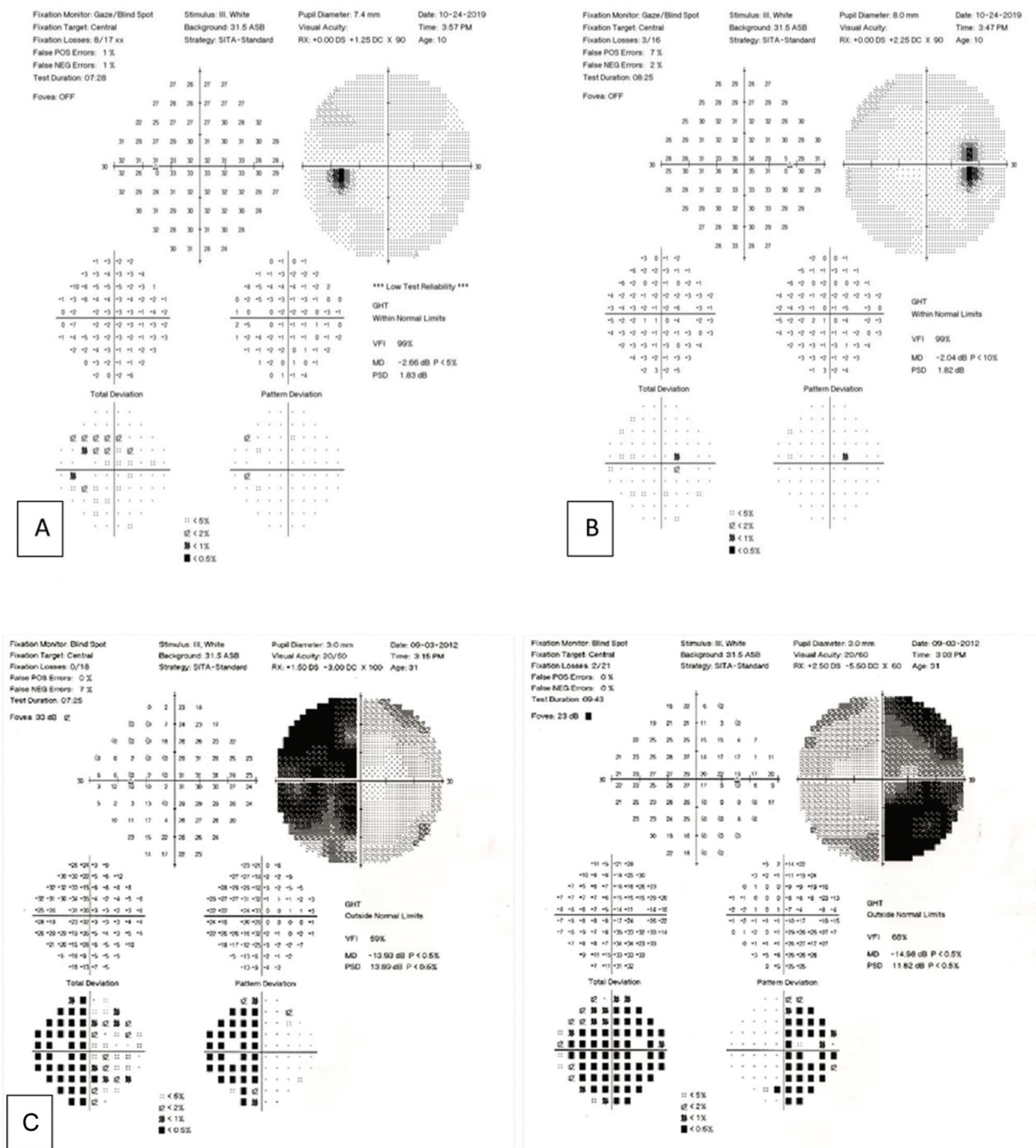


Fig. 2 Humphrey visual field analysis revealing normal visual field in the upper panel and the classic bitemporal hemianopia in the lower panel.

illustrates the normal visual fields and the classical pituitary-tumor-induced bitemporal hemianopia associated with hypopituitarism.

Management

Management of patients with hypopituitarism should focus on understanding the underlying pathophysiology in each patient and recognizing the likelihood of recovery of function.²⁵ Treatment of pituitary insufficiency is dependent on the etiology of the condition.

Hormone replacement therapy aims to alleviate the symptoms of hormone deficiency and avoid the long-term consequences of hormone deficits with minimal side effects by increasing circulating hormone concentrations within the normal range, considering the typical diurnal variation.²⁵ Nevertheless, the pharmacological and pharmacokinetic properties of the available hormone preparations currently fall short of these objectives. Hormone replacement therapy should be administered as soon as hypopituitarism is diagnosed. ► **Table 3** summarizes the replacement and monitoring of the various pituitary axes. It is critical to determine whether hypopituitarism is reversible or permanent and requires lifelong hormone replacement treatment.

Growth Hormone Replacement

Early detection and treatment of GHD in children are critical for achieving the best growth response, which is widely accepted. GH replacement therapy is currently approved for adults with proven severe GHD if no contraindications exist.¹⁷ Several studies have been conducted to assess the impact of GH replacement on a variety of parameters in adults, with positive results in improved body composition, lean body mass, bone density, cardiovascular risk markers (diastolic blood pressure, total cholesterol, and low-density lipoprotein-cholesterol [LDL]), and increased exercise capacity.^{42,43} However, research has not consistently reported improvements in QoL. Yet, sustained improvement in QoL scores toward normal values has been demonstrated in cohorts of adult GHD followed up for up to 10 years, particularly in women and patients with low QoL at baseline.^{44–46} Once the diagnosis has been confirmed and the decision to treat has been made, the usual initial recommended dose is 0.2 mg for young men, 0.3 mg for young women, and 0.1 mg for older individuals, which should be administered subcutaneously at bedtime to imitate physiologic GH release.¹³ Unlike in children, adult GH replacement doses are not based on body weight because this approach produces a high frequency of adverse events mainly related to fluid retention.¹³ However, for patients transitioning from pediatric treatment, initial doses can be as high as 0.5 to 0.7 mg daily.⁶ The dose of GH is then increased gradually, by 0.1 mg every 1 to 2 months, guided by clinical assessments, side effects, and serum IGF-I levels with the objective being to attain and maintain serum IGF-I levels in the upper range of normal, preferably using the same IGF-I assay during the follow-up visit.¹⁸ The effects of appropriate GH replacement usually

manifest within 6 weeks of starting therapy, but for maximum benefit, a longer time may be required.¹³ Once the maintenance dose of GH is achieved, IGF-I levels should be measured every 6 months to ensure that the levels are maintained within the target range and below the upper limit to avoid over-treatment.¹³ GH replacement is generally considered a safe and well-tolerated treatment option for individuals with hypopituitarism. It is imperative to carefully consider the potential adverse effects, particularly during the titration phase, such as peripheral edema, arthralgia, and headaches. In such instances, it is advisable to either reduce the dosage of GH or discontinue treatment in the event of significant adverse reactions.¹⁶ Moreover, patients should be monitored for hypothyroidism, and adrenal insufficiency because GH treatment increases thyroid hormone and cortisol metabolism, which may unmask these conditions.⁴⁷ Furthermore, because GH inhibits insulin action, glycemic control should be monitored by measuring blood glucose and glycosylated hemoglobin (HbA1c) concentrations at baseline and 6 months after treatment. Despite the potential role of GH and IGF-I in cell proliferation,⁴⁸ there is no evidence that GH replacement therapy affects the progression of pituitary tumors in adults. Furthermore, there is no evidence of tumor recurrence or an increased risk of neoplasia.^{49,50} Additionally, the recent consensus does not support an association between GH replacement and cancer relapse or progression in patients with pituitary tumors or craniopharyngiomas.⁵¹ GH replacement may be considered in GHD adult cancer survivors' patients (either with childhood- or adult-onset cancer) in remission after careful individual risk/benefit analysis.⁵¹ Good clinical practice predicts that patients with residual tumors should be monitored regularly, and GH replacement therapy does not require intensive follow-up.⁵¹ However, GH should not be administered to patients with an active malignancy, uncontrolled diabetes, diabetic retinopathy, or intracranial hypertension.

Adherence to daily injections can be difficult; thus, long-acting GH preparations that require GH administration once a week are approved for both children and adults with GHD and are currently commercially available.⁵² Of note, there is currently minimal data regarding the use of long-acting GH in cancer survivors.⁵¹

Gonadotropin Deficiency

Androgen replacement therapy (ART) in adult men aims to maintain secondary sexual characteristics; improve sexual motivation and sexual function, libido, bone, muscle mass, and strength; restore a sense of well-being and concentration; prevent loss of and optimize bone mass; and recover from anemia related to hypogonadism.¹³ ART is available in numerous forms, including injectable testosterone; oral formulations; transdermal patches; and sublingual, buccal, and implantable formulations.⁵³ The choice between the various formulations is determined by various factors, including the potential for adverse effects, expense, convenience for the patient, preferences, and availability.⁵⁴

Table 3 Replacement and monitoring of various pituitary axes^{12,13}

| Pituitary-axis | Treatment | Monitoring | Dose adjustment |
|----------------|--|--|---|
| GH | Daily subcutaneous injection Starting dose Age <60 y 0.2–0.4 mg/d Age >60 y 0.1–0.2 mg/d | IGF-1 level. | Increase dose by 0.1–0.2 mg/d Check IGF-1 6 wk after initiating GH replacement therapy, after dose increases, and every 6 mo thereafter. Further adjustment if side effects occur. |
| LH/FSH | Men Testosterone enanthate 250 mg IM every 2–4 wk or Testosterone undecanoate 1,000 mg intramuscularly every 12 wk or Testosterone gel 25–50 mg/d or buccal testosterone 30 mg twice a day Induction of fertility: Pulsatile GnRH or hCG with or without rFSH or HMG Women Estradiol valerate 2–4 mg/d or conjugated estrogens 0.626–1.25 mg/d or transdermal estradiol patch or gel Additional progesterone replacement is necessary unless hysterectomized or Use oral contraceptive (20–35 µg ethinyl oestradiol) as single pill. Induction of fertility: Pulsatile GnRH or rFSH | Testosterone Hematocrit PSA if age > 40 y Prostate exam | Adjust dose to normal testosterone concentrations. Evaluate symptoms and monitor for side effects. Use the minimum effective dose for improving clinical symptoms. Discontinue replacement therapy upon reaching menopause, if feasible. |
| ACTH | Oral hydrocortisone 15–20 mg per day (2–3 doses per day) with the highest dose in the morning at awakening and the second in the afternoon (two-dose regimen or the second and third at lunch and late afternoon, respectively (three-dose regime). Longer-acting glucocorticoid such as Prednisolone 2.5–5 mg or Dexamethasone 0.25–0.5 mg, may be considered in selected cases (e.g., non-availability, poor compliance, and convenience). | Clinical status as no reliable biochemical marker | May need to increase the dose to relieve clinical symptoms. Further dose increases might be necessary during pregnancy. GH replacement might unmask ACTH deficiency and require dose adjustment. Additional dose should be considered during stress (surgery, infection, etc.) |
| TSH | L-thyroxine 1.6 µg/kg/d | FT4 level | Adjust to FT4 middle-upper normal range. Further increase might be necessary during pregnancy or new estrogen or GH replacement. Additional considerations for age, comorbidities, and clinical context, including potential overtreatment risks. |
| ADH | Desmopressin oral tablet (0.3–1.2 mg/d) or intranasal (10–40 µg/d) or sublingual melts (60–240 µg/d) in 1–4 doses per day. | Clinical status, serum sodium level | Adjust dose to normalization of fluid intake. Patients should experience a phase of polyuria at least weekly Drink to thirst |

Abbreviations: ACTH, adrenocorticotrophic hormone; ADH, antidiuretic hormone; FSH, follicle-stimulating hormone; GnRH, pulsatile gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; HMG, human menopausal gonadotropin; LH, luteinizing hormone; rFSH, recombinant follicle-stimulating hormone; TSH, thyrotrophic hormone.

The intramuscular version of the long-acting depot testosterone esters is often favored because of its ease of use.⁵⁴ The testosterone levels in the blood can swing wildly from supraphysiological levels immediately after injection to subtherapeutic levels before the next one is scheduled.⁵⁵ Therefore, patients may complain of symptoms of androgen deficiency, which can be alleviated by increasing the fre-

quency of the injections or using a longer-acting depot preparation of testosterone undecanoate administered as an IM injection, given initially at 6 weeks and subsequently every 3 months which provides stable plasma testosterone levels. The main disadvantage is that it needs to be administered in a large volume (4 mL IM), and a small number of patients have reported coughing episodes after the

injection.^{1,56} Testosterone levels are monitored before the next injection and should be in the low-normal range. Oral preparations of testosterone undecanoate are administered as 80 or 120 mg two to three times daily with fatty meals, which is well tolerated but is not frequently used because it is less effective, fluctuates significantly, requires multiple daily doses, and is more likely than other formulations to induce hepatotoxicity.^{12,57} However, it may benefit patients with partial hypogonadism or intolerance to depot injection. Transdermal preparations, such as patches, gels, and buccal tablets, offer a viable alternative to oral preparations and noninvasive testosterone replacement that promptly normalizes testosterone levels and maintain them within the normal range.¹¹ Testosterone pellets containing 600 to 1,200 mg testosterone are implanted subcutaneously and provide a sustained level of physiologic testosterone for 3 to 6 months, depending on the formulation.⁵⁸ They necessitate a minor surgical procedure, which can leave the abdomen disfigured, especially in younger men who require two procedures annually. There is also a chance that the pellet will tumble out and there is a possibility of infection.⁵⁸ Testosterone level is measured at the end of the dosing interval, and the dosing interval is modified accordingly.

The efficacy of testosterone is determined clinically and biochemically, with the aim of treatment being the resolution of symptoms of hypogonadism. Before starting testosterone, all males should be screened for prostate cancer, polycythemia, and sleep apnea and regularly during follow-up. Screening involves prostatic symptoms, serum prostate-specific antigen (PSA) measurement, and annual digital rectal examination. Patients should be referred to a urologist if they have severe prostatic symptoms, a serum PSA level higher than 1.4 ng/mL or one that has increased considerably

in the previous 12 months, or if an abnormality is discovered during a digital rectal examination. It is also critical to determine the hematocrit levels. In the case of polycythemia, testosterone withdrawal is advised until the hematocrit level returns to normal, after which therapy can be resumed at a reduced dosage.⁵⁹ In males, there is no consensus on the optimal therapy to induce pubertal development; however, puberty can be induced by monthly injections of testosterone esters or exogenous gonadotropins depending on the size of the testicles. ►**Fig. 3** summarizes our suggested treatment approach for inducing puberty in male patients with central hypogonadotropic hypogonadism (CHH).⁶⁰ Fertility can be induced in men with hypopituitarism using GnRH pulse therapy, human chorionic gonadotropin (hCG), recombinant follicle-stimulating hormone, or both, but the process can take anywhere months to years. Initial testicular volumes < 4 mL are negative indicators of success. If fertility is desired, treatment must be maintained.¹¹

Adult females with gonadotropin deficiency require sex steroid replacement to alleviate symptoms of estrogen deficiency and optimize bone health.¹² All women with an intact uterus must undergo cyclical replacement with consistent withdrawal bleeding.¹² The most common replacement regimen consists of oral estrogen with cyclical additions of progesterone to simulate the natural menstrual cycle, administered for approximately 3 weeks each month, with a progestogen added in the third week. One week after drug withdrawal, during which menstruation occurs, therapy is resumed.¹¹ As an alternative to oral administration, estrogens can be administered transdermally through patches that are changed every 2 weeks.¹¹ It is recommended that steroid replacement therapy be continued until menopause onset. In girls, puberty can be induced by conjugated

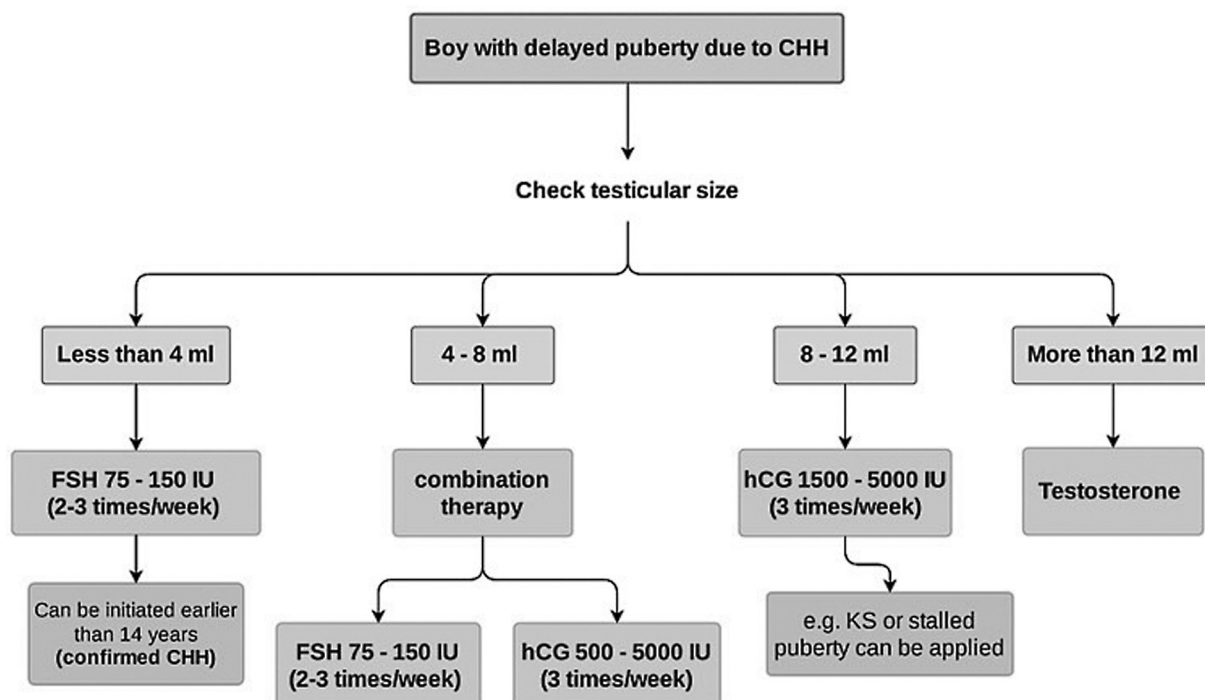


Fig. 3 Suggested treatment approach for inducing puberty in male patients.

estrogens or ethinyl estradiol.¹¹ The initial dose should be modest to maximize growth and prevent abnormal breast development. The estrogen dosage is increased every 6 to 12 months until the adult dose is reached. When young women take this medication for 2 years or if breakthrough bleeding occurs, cyclical progesterone must be added.¹¹ Fertility can be induced in females with hypopituitarism by using pulsatile GnRH or exogenous gonadotropins.⁶⁰ Multiple protocols have been developed to induce fertility. However, a more detailed description is beyond the scope of this article.

Thyroid Hormone Replacement

Typically, levothyroxine (L-T4) is used to treat central hypothyroidism.¹³ Alternative forms of thyroid hormones, such as liothyronine (L-T3) or other formulations, are currently not recommended because of the lack of evidence demonstrating that these treatments are better than L-T4 and potential safety concerns.¹³ The average adult dose is 1.6 µg/kg/d; however, this differs depending on the patient's age, comorbidities, and concomitant replacement with GH or estrogen.¹³

In most cases, L-T4 can be started at full dose, except in older individuals or patients with cardiac or neurological diseases, in whom therapy should be initiated at reduced doses and titrated up gradually.¹¹ The targeted FT4 level should be within the upper limit of the reference range. However, TSH measurement is not recommended for therapy monitoring, as this may be misleading. Almost all patients with central hypothyroidism who are adequately treated with L-T4 to maintain serum FT4 levels in the mid-to-high-normal range will have undetectable TSH levels, which may be interpreted as a sign of overtreatment.³ It is unclear whether the timing of blood samples in relation to L-T4 administration affects decisions regarding L-T4 dose adjustment in central hypothyroidism; however, the Endocrine Society Clinical Practice Guideline recommends measuring FT4 prior to L-T4 administration.¹³

Notably, the adrenal axis should be evaluated, and if concomitant ACTH deficiency is present, glucocorticoid replacement should be initiated before L-T4 replacement because of the risk of adrenal crisis.³ The dosage could be adjusted at 6 to 8 weeks intervals during titration and every 6 to 12 months thereafter. In addition, it may be necessary to modify the L-T4 dose during concurrent GH and L-T4 treatment, as GH replacement increases T4 to T3 conversion.¹³

Glucocorticoid Replacement

Most patients with secondary adrenal insufficiency have other pituitary hormone deficiencies.¹² Glucocorticoid replacement is of the utmost importance because its deficiency is potentially life-threatening. Replacement therapy should be instituted before the beginning of L-T4 and or GH replacement, as either could contribute to an adrenal crisis.¹³ Replacement treatment for cortisol deficiency must meet the day-to-day basic maintenance requirements and include

emergency treatment to prevent adrenal crisis.¹² Replacement therapy aims to obtain an appropriate daily dose for each patient and to imitate the diurnal serum cortisol profile. There is no consensus exists regarding the optimal glucocorticoid replacement regimen.⁶¹ The patients with secondary adrenal insufficiency are most treated with hydrocortisone. Clinical judgment should be used to determine whether to start with lower than conventional replacement doses (5–10 mg/d) or to use a higher dose. Hydrocortisone is commonly administered in divided doses, with a higher dose in the morning and a lower dose in the early afternoon to simulate the normal circadian variation in cortisol secretion, often with an additional 5 mg later in the day (before 1800 hours) to combat fatigue.¹² In our experience, a solitary morning dose (10–15 mg) is sufficient for most patients with central adrenal insufficiency. Once-daily modified hydrocortisone preparations are being developed and commercially approved in Europe as combined immediate and extended-release formulations to achieve a more physiological plasma cortisol profile. However, the physiological increase in early morning cortisol levels is not well mimicked. It has not been proven whether their use will result in more favorable clinical outcomes in patients with central hypoadrenalism.¹³ Other glucocorticoid preparations (cortisone acetate, prednisolone, or dexamethasone) have also been used with equivalent doses of 20 mg of hydrocortisone, including cortisone acetate (25 mg), prednisolone (5 mg), and dexamethasone (0.75 mg), which are occasionally used in some patients with adrenal insufficiency. According to the most current guidelines, dexamethasone should be avoided in the context of a longer duration of action. However, prednisolone can be administered to patients with reduced compliance or the nonavailability of hydrocortisone, and it may be significantly cheaper.¹³

The dose must be adequate to prevent a patient from developing symptoms of cortisol deficiency or adrenal crisis while avoiding the potential adverse effects of glucocorticoid excess. Monitoring glucocorticoid replacement is based solely on clinical grounds because no reliable parameters are available to allow endocrinologists to determine the appropriateness of the glucocorticoid dose.¹ The need for glucocorticoids increases during periods of stress caused by injury, surgery, infection, or concurrent illness to prevent adrenal crisis. Patients must be instructed to inform health care personnel that they are receiving long-term glucocorticoid replacement therapy whenever they require treatment. They should be advised to increase their daily glucocorticoid dose twice or thrice throughout their illness for at least three days or until they recover, if necessary.¹ Patients should have a kit for self-administering parenteral glucocorticoids in the event of an abrupt, severe illness when additional oral glucocorticoid doses are less likely to be effective. If the patient cannot take oral glucocorticoids or has a severe illness, 100 mg of hydrocortisone should be administered intravenously, followed by intravenously or IM administration of 50 mg three times daily.¹³ Patients should carry a steroid card containing information about glucocorticoid replacement and concurrent illness treatment and be encouraged to wear a bracelet

or necklace.¹ As the renin-angiotensin system governs mineralocorticoid secretion, ACTH-deficient patients do not require mineralocorticoids. Adult women with hypopituitarism are also deficient in dehydroepiandrosterone (DHEA), in addition to lacking corticotropin. Some, but not all, studies on the effects of DHEA replacement (25–50 mg/d) on these patients have demonstrated a positive impact on well-being and enhanced mood and sexual function.¹ A meta-analysis of the effect of DHEA replacement therapy on the quality of life of patients with primary or secondary adrenal insufficiency revealed a slight improvement in the quality of life and depression.

Nevertheless, there was no effect on anxiety or sexual health.⁶² Currently, there are insufficient data to recommend routine DHEA supplementation for these patients.¹³ However, women with hypopituitarism and low serum levels of DHEA who report decreased well-being and libido may benefit from the addition of DHEA. The most frequently reported adverse effects of DHEA include greasy skin, hirsutism, acne, scalp itching, increased apocrine sweat secretion and odor, increased body hair growth, and in rare cases, hair loss, which may be temporary or persistent.⁶² When DHEA is substituted, clinical effects are not observed for several weeks and the dosage may be reduced by 50% if side effects are observed.

Antidiuretic Hormone Replacement

Desmopressin (DDAVP), a vasopressin derivative, is used to treat central DI. The goal of therapy for patients with intact thirst is to avoid polyuria and polydipsia, allowing the individual to sleep through the night without nocturia and engage in everyday activities without excessive interruption.¹² To avoid nocturia, desmopressin should ideally be initiated at a single dose at bedtime. The duration of antidiuresis after nasal administration ranges from 6 to 12 hours, whereas the duration of antidiuresis after oral administration can be shorter. Most patients require dosing twice daily and sometimes three times daily to achieve sufficient urine output control. Desmopressin is typically administered as a nasal spray, with one puff providing 10 µg. Oral preparations include tablets (dose range 100, 200, and 400 µg) and sublingual (usually 60, 120, and 240 µg). ▶ **Table 4** lists dose comparisons.¹³ When oral or nasal administration is not feasible and in the inpatient setting, the parenteral form is available for emergency use and can be administered intravenously or subcutaneously at 1 to 4 µg /d divided into two doses.¹³ Patients should be educated about the signs and

symptoms of reduced medication efficacy, such as increased thirst and urinary output, and the signs of hyponatremia due to treatment overdoses, such as headache, fatigue, and decreased urinary output. In addition, desmopressin should be discontinued at least once per week to allow breakthrough polyuria to facilitate diuresis and reduce the risk of hyponatremia.¹³ On the contrary, individuals with compromised thirst due to hypothalamic injury, unconscious, or patients unable to regulate their intake are at risk of developing severe hypertonic hypernatremia, initially requiring an inpatient stay with careful monitoring of intake and output, as well as daily weighing and frequent monitoring of serum sodium.^{12,13} The standard practice of administering a constant dose of desmopressin daily and prescribing fluids replaces urine output and insensible losses.^{12,13}

Interactions between Replacement Hormones

The interaction between the different types of replacement therapy is a crucial aspect of hypopituitarism care. GH enhances the conversion of cortisol to biologically inactive cortisone; consequently, patients on glucocorticoid replacement might need higher doses once GH is initiated, and those with a limited adrenal reserve may become hypoadrenal.⁶³ This effect has been observed in patients with multiple pituitary defects but not in patients with GH deficiency alone.^{64,65} In contrast, patients with combined and untreated GH and TSH deficiencies may exhibit normal serum FT4 levels, which masks the diagnosis of central hypothyroidism and serum FT4 levels below the normal range are observed only after GH replacement.⁶⁶ These patients should be started on thyroid hormone therapy. If they are already receiving thyroid hormones, they may require increased doses when they begin GH therapy to maintain FT4 levels within target ranges.¹³ In addition, the hypothalamic–pituitary–thyroid axis influences GH dynamics. To avoid overdiagnosis of GHD, clinicians should treat central hypothyroidism before GH stimulation testing, as untreated central hypothyroidism reduces IGF-1 levels and may attenuate GH response to stimulation with insulin or GHRH.¹³ Oral estrogen replacement affects GH dosage by reducing the action of GH on hepatic tissue, which in turn reduces circulating IGF-I levels.

Consequently, patients taking estrogen orally should have increased their GH dosages.⁶⁷ Since this effect is not observed in patients receiving transdermal estrogen working to lower estrogen concentrations in the liver, indicating a first-pass effect of estrogen and the inhibition of hepatic GH actions, this mode of administration is typically preferred for patients with GH deficiency.¹³ Additionally, increased serum estrogen levels, whether endogenous as in pregnancy or exogenous from estrogen replacement therapy or oral contraceptives, lead to increased thyroid hormone requirements in patients with primary hypothyroidism.¹³ However, the effect of estrogen in patients with central hypothyroidism is less apparent. Women may not require the same degree of

Table 4 Dose comparisons of different desmopressin formulations¹³

| Formulation | Spray | Tablet | Melt | Injections |
|------------------|---------|--------|--------|------------|
| Dose equivalence | 2.5 ug | 100 ug | 60 ug | NA |
| | 5.0 ug | 200 ug | 120 ug | <0.5 ug |
| | 10.0 ug | 400 ug | 240 ug | <1.0 ug |

thyroid hormone dose increase because of hCG stimulation of an intact thyroid gland.

Nonetheless, it is prudent to thoroughly monitor thyroid hormone levels during pregnancy and adjust the doses accordingly. Many FT4 assays perform poorly during pregnancy; if pregnancy-specific FT4 reference ranges are unavailable, clinicians can use total T4 reference ranges adjusted upward by 50%.¹³ Oral estrogen, but not transdermal therapy, increases serum cortisol-binding globulin levels. Therefore, to prevent hypoadrenalism, women with hypopituitarism who take glucocorticoids may require higher doses if given oral estrogen.⁶⁸ In addition, the thyroid hormones accelerate endogenous cortisol clearance, which may lead to inadequate cortisol production and precipitate an adrenal crisis. Patients with central hypothyroidism must be evaluated for adrenal insufficiency before the administration of thyroid hormone therapy.¹³ If this is not feasible, clinicians must give empiric steroid therapy until a definitive evaluation for adrenal insufficiency occurs. Lastly, adrenal deficiency induces impaired free renal water clearance, obscuring polyuria and possibly partial DI.¹³ It is crucial to monitor the development of DI after the initiation of steroid treatment. In contrast, patients without adrenal insufficiency whose DI has improved should be evaluated for adrenal insufficiency.¹³

Conclusions

Hypopituitarism is a rare chronic condition associated with significant morbidity and reduced longevity. Long-term hormonal replacement therapy requires special monitoring and adjustment at various patient life stages. After optimizing hormone replacement therapy, patients should undergo an annual cardiovascular risk assessment. Particular attention should be paid to blood pressure and lipid levels, and treatment should be initiated if necessary. To optimize the long-term prognosis, the patient should remain under the care of a physician with expertise in the field.

Authors' Contribution

Single authorship.

Compliance with Ethical Principles

No ethical approval is required for the review article type of study.

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Conflict of Interest

None declared.

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