Hypopituitarism

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Hypopituitarism is a complex medical condition with variable clinical manifestations associated with significant morbidity and mortality. The term describes the deficiency of one or more of the hormones of the anterior or posterior pituitary gland. The majority of patients with hypopituitarism have 3–5 hormones deficits.

Hypopituitarism affects approximately 4 out of every 100,000 individuals each year [1] with a prevalence of approximately 45 cases per 100,000 individuals. The causes, clinical features, diagnosis, management of hypopituitarism (including endocrine replacement therapy), interaction of hormone replacement, and long-term management are considered in this chapter.

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Causes

There are numerous causes of hypopituitarism (Tables 8.1 and 8.2). The etiologic factors are determinants in the clinical presentation of this condition. For instance, pituitary apoplexy constitutes a medical emergency with the possibility of acute adrenal crisis and sudden loss of vision. On the other hand, functioning pituitary adenomas lead to a clinical picture that predominates the stigmata of the corresponding hormonal hypersecretion. Signs and symptoms related to local mass effect, including associated secondary hypothyroidism and hypocortisolism, may occur as a nonspecific presentation and remain unrecognizable for a long period of time.

Diagnosis

Clinical Presentation

The clinical presentation of hypopituitarism is often vague and nonspecific, leading to a further delay in diagnosis. Nonspecific symptoms include a feeling of general poor health, increased lethargy, feeling cool, chronic tiredness, reduced appetite, weight loss, and abdominal pain [2, 3]. Hypopituitarism can sometimes develops acutely, leading to a rapid onset of symptoms (excruciating

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Table 8.1 Causes of Hypopituitarism

Neoplasia	*Vascular*
Pituitary adenoma	Pituitary tumor apoplexy
Pituitary carcinoma	Sheehan's syndrome
Craniopharyngioma	Intrasellar carotid artery aneurysm
Pituicytoma	
Fibroma	Subarachnoid hemorrhage
Glioma	
Meningioma	Ischemic stroke
Paraganglioma	*Genetic*
Teratoma	Combined pituitary hormone deficiencies
Chordoma	
Angioma	Isolated pituitary hormone deficiencies
Sarcoma	
Ependymoma	*Infectious*
Germinoma	Viral
Cysts	Fungal
Rathke's cleft and dermoid	Tuberculosis
Ganglioneuroma	Syphilis
Astrocytoma	Bacterial (Others)
Pituitary mestastasis	*Primary empty sella functional*
Brain damage	
Surgery	Drugs
Radiotherapy	Glucocorticoid excess
Radiosurgery	Megestrol acetate
Traumatic brain injury (TBI)	Suppressive thyroxine treatment
Infiltrative/inflammatory disease	
Lymphocytic hypophysitis	Dopamine
Granulomatous hypophysitis	Anabolic sex steroids
Xanthomatous hypophysitis	GnRH agonists
Sarcoidosis	Nutritional
Langerhans cell histiocytosis	Obesity
Giant cell granuloma	Malnutrition
Wegener's granulomatosis	Caloric restriction
Hemochromatosis	Chronic/Acute critical Illness
	Idiopathic

headache, meningism, and cardiovascular collapse) necessitating admission and intensive care management, as is often seen in patients with tumor apoplexy.

The signs and symptoms of underlying diseases can sometimes follow hypopituitarism [3]. Symptoms attributed to the local effects of tumoral masses in the sellar region with suprasellar extension, such as headaches, rhinorrhea, and visual disturbances (typically bilateral hemianopsia, but can also occur as unilateral) frequently remain unrecognized by patients, mostly men, for a long period of time.

Deficits of anterior pituitary hormones may be secondary to hormone excess caused by functioning pituitary tumors, which produces a complex picture combining hormone excess and deficiencies, such as suppression of gonadotropins in hyperprolactinemia, growth hormone deficiency (GHD) caused by cortisol excess in Cushing's syndrome [4] or growth hormone (GH) secreting macroadenoma that causes acromegaly and hypogonadism [5]. The presence of central Diabetes Insipidus (DI) usually indicates a non-pituitary lesion affecting the hypothalamus or pituitary stalk. Preoperatively, pituitary adenomas rarely cause DI.

Somatotropin Deficiency

Children

GHD in childhood promotes short stature and delayed bone age with slow growth velocity. Idiopathic GHD is the most common etiology. GH does not appear to have a relevant role in fetal growth. Therefore, in general, children are born with normal length, weight, and general appearance. However, microphallus and cryptorchidism may be present, especially with gonadotropin associated deficiency. Prolonged jaundice, hypoglycemia-associated seizures (when GHD occurs in conjunction with Adrenocorticotropic Hormone (ACTH) deficiency), and midline abnormalities suggest a congenital etiology.

Recognition of GHD is more common from the first 12–18 months after birth, with slow growth as an early sign and a consequent downward shift in the normal growth curve. Children tend to present with adiposity around the trunk. They have immature body and facial traits, a high-pitched voice, prominent forehead, depressed mid-face development, delayed dentition, and small hands and feet.

Table 8.2 Genetic forms of multiple pituitary hormone deficiencies

	HESX1	OTX2	LHX3	LHX4	SOX3	SOX2	PROP1	POU1F1
GH	+	+	+	+	+	+/–	+	+
LH/FSH	+/–	+/–	+	+/–	+/–	+	+	–
PRL	+/–	–	+	–	+/–	–	+	+
TSH	+/–	+/–	+	+/–	+/–	–	+	+/–
ACTH	+/–	+/–	+/–	+/–	+/–	–	+/–	–
ADH	+/–	–	–	–	+/–	–	–	–
Inheritance	AR/AD	AD	AR	AD	XL	AD	AR	AR/AD
Pituitary involvement	Normal/ Hypoplastic AP; normal/ectopic PP	Normal/hypoplastic AP; altered stalk; Ectopic PP	Hypoplastic, normal or enlarged AP	Normal/hypoplastic AP; normal or ectopic PP	Hypoplastic AP; Ectopic PP	Normal/ hypoplastic AP; Hypothalamic hamartoma	Hypoplastic, normal or enlarged AP and normal PP	Normal/ hypoplastic AP
Extra-pituitary phenotype	SOD; normal optic nerves	Anophthalmia or no ocular pathology; Chiari malformation	limited neck rotation or no; SD	Cerebellar anomalies; Chiari malformation	Variable learning difficulties; HCC	Anophthalmia; Microphthalmia; DD; SD; HCC; Aesophageal atresia	No involvement	No involvement

AD autosomal dominant, *AP* anterior pituitary, *AR* autosomal recessive, *DD* developmental delay, *PP* posterior pituitary, *HCC* hypoplasia of corpus callosum, *SD* sensorineural deafness, *SOD* septo-optic dysplasia, *XL* X-linked, + deficiency, – no deficiency

Adults

The severity of the clinical manifestations of GHD in adults depends on the timing of onset. In general, patients present nonspecific symptoms, such as fatigue, decreased energy, low mood, and altered body composition with increased fat and decreased lean body mass and muscle strength, as well as reduced bone mineral density, compromised metabolism of glucose and lipids, and poor quality of life [6]. Childhood-onset GHD patients have a lower lean body mass, bone mineral content, and better quality of life compared to adult-onset GHD patients.

Gonadotropin Deficiency

The clinical presentation of male hypogonadism depends on the time of onset of androgen deficiency. In men with recent onset hypogonadism, the physical examination is usually normal, while diminished facial and body hair, gynecomastia, and small soft testes are features of longstanding hypogonadism [2]. The principal signs and symptoms of androgen deficiency in men are loss of libido, decreased sexual potency, loss of body hair (axillary and pubic), infertility, and low bone mineral density. The threshold testosterone level below which symptoms of androgen deficiency and adverse health outcomes occur and testosterone administration improves outcomes in the general population is currently not known [7].

Female adolescents have primary amenorrhea and lack of breast development, whereas in adult women, gonadotropin deficiency leads to reduced secretion of estradiol, resulting in infertility and oligo/amenorrhea. Low estrogen is also responsible for genital atrophy and decreased breast volume in chronic hypogonadism. There is a reduction of pubic and axillary hair, especially when concomitant dysfunction of the corticotroph axis is present.

At the prepubertal age, no obvious clinical signs or symptoms are present until the normal age of puberty onset (9–14 years in boys and 8–13 years in girls), when a lack of signs of normal pubertal development are then observed. It should be emphasized that micropenis with or without associated cryptorchidism is an important clinical clue that suggests congenital hypogonadotropic hypogonadism (where there is lack of the normal fetal secretion and postnatal surge of gonadotropins) rather than acquired hypogonadotropic hypogonadism [8].

Thyrotropin Deficiency

The clinical picture of central hypothyroidism is very similar to primary hypothyroidism, but is often milder. Symptoms include cold intolerance, dry skin, decreased appetite with mild weight gain, and fatigue [9]. The presence of goiter usually indicates primary thyroid disease. In children, decreased growth velocity with impairment of neurological development is an important sign.

Corticotropin Deficiency

ACTH deficiency leads to decreased glucocorticoid levels. Mineralocorticoid secretion is preserved, since it is primarily modulated by the renin–angiotensin system. Hyperpigmentation is typical of primary adrenal disease and is absent in central disease. Symptoms of ACTH deficiency are largely nonspecific, including weakness, fatigue, anorexia, weight loss, arthralgia, postural hypotension, and tachycardia [10]. Hyponatremia, hypoglycemia, and eosinophilia may also occur. Ultimately, if left untreated, ACTH deficiency may lead to death due to vascular collapse, since cortisol is needed to maintain vascular tone. Mild ACTH deficiency may remain clinically unnoticed when cortisol production is sufficient for preventing symptoms in the absence of clinical stressors (e.g., infections). Hence, laboratorial evaluation is recommended in all patients at risk of ACTH deficiency.

Antidiuretic Hormone (ADH) Deficiency

ADH deficiency results in polyuria (urine volume >3 L/day in adults) and polydipsia. If the thirst mechanism is not present, as is the case in some

patients with hypothalamic lesions, then lack of polydipsia leads to a high risk of life-threatening dehydration and hypernatremia [11].

Diagnostic Testing

The diagnosis of hypopituitarism can often be made through simultaneous measurements of basal anterior pituitary and target gland hormone levels. Each axis should be assessed in patients suspected of having partial or complete loss of pituitary function, because the impairment in these patients is often partial rather than complete.

Low or inappropriately normal serum levels of pituitary hormones in conjunction with low peripheral hormones indicate hypopituitarism. FSH, LH, estradiol (women), testosterone (men), prolactin, TSH, free thyroxine (FT4), 9 am cortisol, and insulin-like growth factor-I (IGF-I) tests form the baseline parameters to assess. In addition, dynamic studies are necessary in most cases for documenting hypopituitarism, particularly for assessing GH secretory reserve and the ACTH-adrenal axis (Table 8.3) [5].

Somatotropin Deficiency

Children

GHD in children is based on auxological data, which is considered the gold standard in such diagnosis [12]. An appropriate differential diagnosis must be performed ruling out other causes of growth failure, such as hypothyroidism, Turner syndrome, and systemic diseases.

Evaluation should be considered when patients present with one of the following conditions: (1) short stature of more than 2.5 standard deviations (SD) below the mean; (2) growth failure, which is defined as height velocity less than 2 SD below the mean for age; (3) a combination of less severe short stature (2–2.5 SD below the mean for age) and growth failure (growth velocity less than 1 SD); (4) clinical picture suggesting hypothalamic-pituitary dysfunction, such as hypoglycemia, microphallus, intracranial tumor, or history of cranial irradiation with decelerating growth; and (5) evidence of deficiency in other hypothalamic–pituitary hormones [13].

The pulsatile nature and short half-life of GH preclude the random measurement of serum GH levels as a useful tool for diagnosing GHD. Thus, IGF-I and IGF-binding Protein 3 (IGFBP-3) are appropriate initial tests for GHD in children providing that conditions such as poor nutrition, hypothyroidism, and chronic systemic diseases are excluded. These hormones reflect an integrated assessment of GH secretion because of negligible diurnal variation [14].

IGF-I and IGFBP-3 measurements should be interpreted in relation to reference ranges that are standardized for sex and age. An important drawback to using serum IGF-I for GHD diagnosis is that its values are low in very young children and overlap in GHD patients and normal children. In this context, IGFBP-3 levels, which are less related to age, are more discriminatory than IGF-I levels at the lower end of the normal range [15].

These tests present less than adequate sensitivity, although specificity is high. Thus, in patients with severe GHD, IGF-I and IGFBP-3 levels are invariably reduced; On the other hand, patients with milder abnormalities of GH secretion demonstrate normal levels of IGF-I and its binding protein in a significant percentage of cases [16].

Despite these limitations, measurement of IGF-I and IGFBP-3 levels associated with provocative testing in an appropriate clinical context is now commonly performed when investigating GHD in childhood.

GH Stimulation Testing in Children

Provocative GH testing has several caveats. They are not physiological, since the secretagogues used do not reflect normal GH secretion; the cut-off level of normal is arbitrary and the tests are age dependent. Furthermore, the tests rely upon GH assays of variable accuracy and are all uncomfortable, cumbersome, and risky for the patient [12, 17]. Therefore, there is currently no gold standard provocative GH test for GHD in children. As a result, subnormal responses to two secretagogues are necessary for diagnosis, with

Table 8.3 Hormone testing for pituitary function

	Criteria for hormone deficiency
Somatotropic axis	
Baseline	
IGF-I	Low/low-normal
GH	No usefulness
Provocative tests	
Clonidine test (only for children)	<7–10 μg/L
Insulin tolerance test	Children: <7–10 μg/L
	Adults: <5.1 μg/L
	Transition period: <6.1 μg/L
GHRH-Arg test (only for adults)	Adults:
	Lean <11.5 μg/L
	Overweight <8.0 μg/L
	Obese <4.2 μg/L
	Transition period: <19.0 μg/L
Glucagon test	Children: <7–10 μg/L
	Adults: <2.5–3 μg/L
Gonadotropic axis	
Baseline	
Male	
Testosterone	Low
FSH/LH	Low or inappropriately normal
Female	
Estradiol	Low
FSH/LH	In younger women: low or inappropriately normal
	In postmenopausal women: inappropriately low
Provocative test	
GnRH	Not useful in adults
Thyrotropic axis	
Baseline	
Free T4	Low, low-normal
TSH	Low, normal or slightly increased
Provocative test	
TRH	Not useful
Corticotropic axis	
Baseline	
Cortisol (morning)	<3 μg/dL (<80 nmol/L)
	>18 μg/dL (>500 nmol/L): hypocortisolism excluded
ACTH (morning)	Low or normal
Provocative tests	
Insulin tolerance test	Peak Cortisol <18 μg/dL (<500 nmol/L)
250 μg ACTH test	Peak Cortisol <18 μg/dL (<500 nmol/L)
Overnight metyrapone test	11-deoxicortisol <7 μg/dL (<200 nmol/L), low cortisol
CRH (human or ovine)	ACTH: Peak <2–4× baseline
	Cortisol: Peak <20 μg/dL (555 nmol/L)
Antidiuretic hormone	
Dynamic test	
Water deprivation	Maximal Urinary Osmolality (MUO) < 300 mOsm/kg/H_2O plus >50 % increase in MUO after desmopressin (Complete DI)

Table 8.4 Protocols of dynamic tests for investigation of anterior pituitary (GH and ACTH) and posterior pituitary (ADH) deficiencies

Provocative tests	Dosage	Time of hormone collection	Side effects/drawbacks
GH			
Clonidine (only for children)	5 μg/kg, up to 250 μg, PO	GH: 0, 30, 60, 90 min	Drowsiness; false negative results
Insulin tolerance test	Regular insulin 0.05–0.15 IU/kg, IV	GH: 0, 15, 30, 60, 90, 120 min	Severe hypoglycemia and medical surveillance required
Glucagon	0.03 mg/kg (up to 1 mg) IM/SC; if >90 kg, 1.5 mg	GH: 0, 60, 90, 120, 150, 180, 210, 240 min	Late hypoglycemia; very prolonged test; not well validated in adults
GHRH-ARG (only for adults)	GHRH (1 μg/kg, IV bolus) + Arginine (0.5 g/kg, up to 30 g, IV, over 30 min)	GH: 0, 30, 60, 90, 120 min	Very influenced by adiposity
ACTH			
$ACTH_{1-24}$	250 μg IV/IM	Cortisol: 0, 30 and 60 min	Adrenal atrophy is required
Insulin tolerance test	Regular insulin 0.05–0.15 IU/Kg, IV	Cortisol: 0, 15, 30, 60, 90, 120 min	See above
Overnight metyrapone	30 mg/kg, PO, at midnight (maximum 3 g)	11-deoxycortisol and cortisol: 8 am	Limited availability; adrenal crisis
CRH (human or ovine)	1 μg/kg, up to 100 μg, IV	Cortisol and ACTH: 0, 15, 30, 60, 90, 120 min	Flushing; expensive
Dynamic test	*Procedure*		*Side effects/Drawbacks*
ADH			
Water deprivation	Nothing allowed by mouth; patient voids; weight is recorded; Serum Na^+ and urine Osm are measured at baseline. Weight is checked after each liter of urine is passed. In each voided urine, measure urine Osm and when two consecutive measurements differ <10 % and subject has lost 2 % of BW, plasma sample for Na^+, Osm and VP should be drawn. DDAVP 2 μg IV/IM is administered and urine Osm and volume are measured every 30 min in the next 2 h. Dehydration is stopped if patient has lost >3 % of BW or if serum Na^+ becomes elevated.		Difficulties in differentiate partial hypothalamic DI from primary polydipsia

PO per oral, *Osm* osmolality, *BW* body weight, *VP* vasopressin

the exception of patients presenting with a central nervous system disorder, multiple pituitary hormone defects, or a known genetic defect. In these cases, one test is sufficient to establish the diagnosis [18].

These stimulation tests are performed after an overnight fasting. After the pharmacologic stimulus, serum samples are collected at intervals designed to capture the peak GH level. A "normal" response is defined by a serum GH concentration of greater than 7–10 mcg/L, although the ideal threshold may vary with the assay used. Of note, all patients should be euthyroid and should not be under supraphysiological doses of glucocorticoids before any testing is performed (Tables 8.3 and 8.4).

Clonidine, an α-2 adrenergic receptor agonist, promotes GH release, mainly through GHRH secretion. It is a stronger stimulant for growth hormone release, and therefore false negative results can follow. On the other hand, children presenting with a GH subnormal response to such stimulus rarely secrete normal GH in response to any other stimuli [19]. The test commonly causes hypotension and drowsiness that may last for hours and promote late hypoglycemia.

Insulin-induced hypoglycemia is a potent stimulant of GH release and, therefore, the Insulin Tolerance Test (ITT) is among the most specific tests for GHD. However, safety concerns have prevented the widespread use of this test. The proposed mechanism by which hypoglycemia promotes GH secretion is through the

suppression of somatostatin tone and stimulation of α-adrenergic receptors [20]. This test requires constant supervision by a clinician and is contraindicated in children less than 2 years of age.

Administration of glucagon promotes GH secretion through a poorly understood mechanism, with the activation of central noradrenergic pathways as a plausible hypothesis [21]. Glucagon presents mild and transient side effects, such as nausea, vomiting, and sweating, and therefore is a very good choice for infants and young children who are more susceptible to the risks of insulin-induced hypoglycemia.

Adults

In adults, the clinical picture of GHD is subtle and nonspecific, and therefore the diagnosis relies on biochemical testing. Patients with structural hypothalamic and/or pituitary disease, surgery, or irradiation in these areas as well as TBI, SAH, or evidence of other pituitary hormone deficiencies should be evaluated for acquired GHD. Otherwise, the presence of three or more pituitary hormone deficiencies associated with a low IGF-I is highly predictive of GHD, in which case provocative testing is not necessary [22]. In addition, patients should receive adequate replacement of other deficient hormones before GH stimulation testing is performed.

GH Stimulation Testing in Adults

ITT is considered the most validated test currently available and is the diagnostic test of choice for GHD in adults. However, it is contraindicated in patients with seizure disorders or ischemic heart disease and requires monitoring, even in healthy adults. Adequate hypoglycemia (<2.2 mmol/L) is not always achieved, and therefore, larger doses of insulin up to 0.3 U/kg may be necessary in obese patients and those with fasting blood glucose above 5.5 mmol/L [23]. An assay cutoff of 5.1 μg/L is recommended for diagnosis [22].

A GHRH and arginine test (GHRH-Arg test) is a very potent and reproducible test. Arginine potentiates the response to GHRH presumably through the inhibition of hypothalamic somatostatin secretion [24]. This combined test is not affected by gender or age and shows few side effects with no hypoglycemia. On the other hand, the assay cutoff for GHD diagnosis depends on the body mass index (BMI) [25]. In addition, GHRH directly stimulates the pituitary, and patients with GHD of hypothalamic origin, mainly after radiotherapy, could present a falsely normal GH response [26].

Administration of glucagon allows for the assessment of GH and ACTH-cortisol reserves, and has few side effects with minimal contraindications. It is a good choice when other tests are unavailable or contraindicated. In adults, an assay cutoff between 2.5 and 3.0 μg/L is recommended for GHD diagnosis [22].

Transitional Period

In the transition period (i.e., after the cessation of linear growth and completion of puberty), the majority of GHD patients must be retested. Those patients with conditions causing multiple pituitary hormone deficiencies (MPHD) (i.e., three or more pituitary hormone deficits), can continue on GH therapy, but require determination of an adequate dose. Other patients without MPHD but who present with known mutations or irreversible structural hypothalamic-pituitary lesions/damage should be screened for serum IGF-I levels after terminating therapy for at least 1 month. IGF-I levels below −2 SD are sufficient for GH therapy reinstitution. If the IGF-I level is within the normal range, then one provocative testing is mandatory for GH therapy in case of a subnormal response.

In the remaining patients, mostly with idiopathic causes, a serum IGF-I test and one provocative test must be performed, and in case of discordant results, a second provocative test is necessary for the diagnosis of persistent GHD [22, 27].

It is unclear whether different assay cutoffs should be adopted during this transitional period, as opposed to GHD assay cutoffs in adults. Some studies suggest that the assay cutoffs in these cases should be higher than for older adults, with levels of 6.1 μg/L and 19.0 μg/L for the ITT and GHRH-arg, respectively [28, 29].

Gonadotropin Deficiency

In men, low or inappropriately normal levels of gonadotropins combined with low levels of serum testosterone are indicative of secondary hypogonadism. Semen analysis is indicated when considering fertility and may demonstrate a reduced sperm count or possibly azoospermia.

In younger women, oligo/amenorrhoea with low serum estradiol levels and low or inappropriately normal FSH and LH concentrations is consistent with secondary hypogonadism. In postmenopausal women, the absence of the normal rise of FSH and LH levels is sufficient for establishing a diagnosis.

In secondary hypogonadism, serum prolactin should always be measured to exclude hyperprolactinemia, which might occur for several reasons, such as prolactinomas, sellar and parasellar masses causing pituitary stalk compression, and use of drugs with antidopaminergic activity.

In adults, there is no usefulness in performing the gonadotropin-releasing hormone (GnRH) provocative test because it does not provide any additional information [5].

Thyrotropin Deficiency

Evaluation of the thyrotrophic axis is based on the measurement of basal serum TSH and thyroid hormone levels. Central hypothyroidism is diagnosed when serum TSH levels are low or inappropriately normal coupled with low levels of serum free T4. Occasionally, TSH levels may be slightly elevated but usually remain lower than 10 mIU/mL. In these patients, the elevation of serum TSH is associated with decreased bioactivity due to increased sialylation [30]. In patients with concomitant GH and TSH deficiencies, serum-free T4 may be normal (usually at the lower tertile), decreasing only after GH replacement [31, 32]. More recently, it has been proposed that echocardiography can be useful in the evaluation of patients with hypothalamic-pituitary disease and free T4 levels within reference range, as some of these patients present signs of tissue hypothyroidism, a condition that could be named "subclinical central hypothyroidism" [33].

The TRH stimulation test has been performed in the past to diagnose central hypothyroidism [34]. However, this test is not currently recommended due to a lack of accuracy [35].

Corticotropin Deficiency

Cortisol secretion follows a circadian cycle, being highest in the early morning and lowest at midnight. Hence, a basal serum cortisol measurement may not reflect disturbances of the hypothalamus-pituitary-adrenal (HPA) axis. In addition, alterations in the levels of cortisol-binding globulin (CBG), which is frequently seen in clinical practice (e.g., higher levels of CBG, and consequently serum total cortisol, during oral estrogen treatment as a contraceptive) may also mask the diagnosis of central hypoadrenalism. Therefore, early morning serum cortisol (between 07:00 and 09:00) may be measured as a first step in the evaluation [10]. Stimulation tests are frequently required for corticotropic assessment. The most commonly used stimuli in clinical practice are insulin-induced hypoglycemia, Metyrapone, synthetic ACTH ($ACTH_{1\text{-}24}$), and CRH (Tables 8.3 and 8.4).

Hypoglycemia is a potent activator of the HPA axis, and the ITT is usually regarded as the "gold standard" for diagnosis (see more details in "GH stimulation testing").

$ACTH_{1\text{-}24}$ administration is currently the most commonly used test in clinical practice for assessing HPA axis. Adrenal atrophy is required for the test to be positive in cases of ACTH deficiency. Hence, this test should not be performed within 2 weeks of an insult to the hypothalamus or pituitary (e.g., pituitary surgery) [36]. A low-dose (1 μg) $ACTH_{1\text{-}24}$ test has been reported to induce improved sensitivity by some studies [37] but not others [38].

Metyrapone decreases serum cortisol by inhibiting the enzyme 11-beta-hydroxylase and this test is usually not performed due to limited availability of the drug.

CRH has been used to differentiate hypothalamic from pituitary disease in secondary adrenal insufficiency. However, CRH stimulation is not particularly useful in diagnosing secondary adrenal insufficiency because individual responses to exogenous CRH are extremely variable.

ADH Deficiency

DI may be diagnosed with a proper clinical presentation, for example, in a patient with known pituitary/hypothalamic disease if other causes of polyuria (e.g., diabetes mellitus, use of diuretics) are excluded. Serum sodium is usually above the middle of the reference range, but hypernatremia is not seen in patients with an intact thirst mechanism. In situations where diagnosis is not clear-cut, a water deprivation test is warranted. Maximum urine osmolality is less than 300 mOsm/Kg H_2O in patients with complete DI. In patients with subnormally elevated osmolality after water deprivation (300 mOsm/Kg < osmolarity < 800 mOsm/Kg H_2O), further steps are needed, including magnetic resonance imaging (MRI) of the hypothalamic-pituitary region and/or a therapeutic trial with Desmopressin [11].

Imaging

MRI is currently the single best imaging procedure in the investigation for most sellar masses. After hypopituitarism has been confirmed, MRI should be performed to exclude tumors and other lesions of the sellar and parasellar region. When this is not possible, computerized tomography (CT) provides a suitable alternative. Micro- and macroadenomas of the pituitary as well as other sellar masses, such as craniopharyngiomas and meningiomas, usually take up contrast to a lesser degree than the normal pituitary. Craniopharyngiomas and even pituitary adenomas may have a partially cystic content and, therefore, have low-intensity signals. Hemorrhage has a high-intensity signal on both T1- and T2-weighted images. On the other hand, asymptomatic pituitary adenomas are found upon autopsy in approximately 11 % of individuals. Such adenomas may also be commonly seen as incidental findings (incidentalomas) on head CT or MRI scans performed for other reasons [39].

Recent MRI studies of the pituitary in patients who had suffered a TBI demonstrated pathological changes consistent with vascular injury. In the acute phase, the pituitary glands of these patients are significantly enlarged and may also present other abnormalities, such as hemorrhage, infarction, and partial stalk transection [40]. In the chronic phase, patients often demonstrate pituitary volume loss or empty sella, perfusion deficits, or lack of a posterior pituitary signal. Such abnormalities were reported to occur in 80 % of patients with hypopituitarism compared to 29 % of those without hypopituitarism [41].

Neuro-Ophthalmic Exam

Patients with a known pituitary tumor must be carefully followed for evidence of growth with early chiasmal-optic nerve compression. The frequency of visual evaluation must be individualized based on the size of the tumor and its relation to critical structures. Goldmann perimetry is useful in plotting the visual field defects and also assists in follow-up.

Management

Understanding the underlying pathophysiology in each patient and recognizing the probability for recovery of function are among the most important issues to be emphasized in the management of patients with hypopituitarism. Treatment is based on the underlying disease that leads to pituitary insufficiency.

Pituitary tumors may be treated with medical therapy, surgery, radiotherapy, or a combination of these modalities depending on the tumor subtype and clinical presentation [5]. Whereas prolactinomas are almost exclusively treated with dopamine agonists, neurosurgical removal is indicated for most other pituitary sellar and parasellar masses. Infections

(e.g., meningoencephalitis, tuberculosis, or syphilis) are treated with antibiotics or antivirals and granulomatous infiltrations (e.g., sarcoidosis) are treated with immunosuppressants.

The goal of hormone replacement therapy is to achieve normal levels of the circulating hormones in order to restore normal physiology as close as possible and to avoid the symptoms of deficiency with minimal side effects. Target peripheral hormones, rather than deficient pituitary hormones, should be replaced, except for GH deficiency, ADH deficiency, and gonadotropins, when fertility is desired [5]. Hormone replacement therapy should be started as soon as the diagnosis of hypopituitarism is made (Box 8.1). It is very important to carefully evaluate whether hypopituitarism is likely to be reversible or whether it is permanent, thereby requiring life-long hormone replacement therapy.

Hormone Replacement Therapy

Hyposomatotropism

Children

Childhood GHD should be treated as soon as possible in order to improve linear growth. The individual response to GH therapy is widely variable and unpredictable. Dosing is mainly based on weight and can range from 0.021 to 0.050 mg/kg/day (0.033 mg/kg/day is the most suitable initial dose) up to 0.1 mg/kg/day in adolescents. It should be given once a day by subcutaneous injection, and should be adjusted based on growth response and IGF-I levels [42, 43].

Therapy should be started as early as possible in order to achieve the best results in growth where patients can achieve height within the mid-parental target height [44].

GH therapy in children is safe and adverse events are uncommon. Idiopathic intracranial hypertension (pseudotumor cerebri) is a rare occurrence that tends to occur early in therapy, and if it occurs then drug discontinuation and subsequent cautious reintroduction is necessary. Some patients may present increased insulin resistance, which appears not to translate into marked glucose abnormalities [45].

The goals of therapy are to achieve therapeutic levels of IGF-I that are slightly above the mid-normal range (approximately 1 SD above the mean) adjusted for age, pubertal stage, and growth velocity above the 75th percentile curve [46, 47]. An evaluation is performed 4 weeks after beginning treatment, and in case of an adequate IGF-I response, the length/height should be rechecked every 3–6 months and IGF-I levels should be rechecked every 6–12 months.

Caution is necessary with unmasking hypothyroidism after GH therapy as previously discussed. Thus, free T4 should be assessed every 3 and 6 months after initiation of this therapy and yearly thereafter.

Adults

In adults, GH dosing regimens are not weight-based as in children, but rather are initialized with a lower dose and then titrated according to clinical parameters and IGF-I levels. The recommended GH starting dose is 0.2–0.3 mg/day for most patients and 0.1–0.2 mg/day for the elderly patients that are more susceptible to adverse events linked to therapy [22]. A target for IGF-I levels is the upper half of normal range.

The most common side effects, which occur in 5–18 % of patients, are joint stiffness, peripheral edema, arthralgias, and myalgias. Carpal tunnel syndrome and increased blood pressure are infrequent, but when present, are related to supraphysiological doses in most cases. When this occurs, a reduction in the dose is appropriate [48].

Although there are no conclusive data of a GH role in the development or recurrence of malignant diseases, GH is contraindicated in adult patients with an active malignancy. A slight increase in the risk for DM has been observed with GH therapy, and therefore diabetic patients may require changes in the doses of current medications [22].

Adjustments should be performed every 1–2 months during dose titration. A clinical response, IGF-I levels, and side effects should guide the choice of dose. After titration, evaluation should be performed at 6 months intervals.

Box 8.1 Hormone Replacement Regimens

GH deficiency

Adults: GH therapy 0.1–0.2 mg in elderly; 0.2–0.3 mg in adults; 0.4–0.5 mg, SC, in younger people; adjustment based on clinical response, adverse effects, and IGF-I levels that should be maintained in the middle/upper half of the normal range.

Children: GH therapy 0.033 mg/kg/day and up to 0.1 mg/kg/day, SC, during puberty; adjustments based on growth response and IGF-I levels that should be maintained 1 standard deviation (SD) above the mean.

FSH/LH deficiency

Adult male:75–100 mg of testosterone enanthate or cypionate IM weekly or 150 mg every 2 weeks; one or two 5 mg nongenital testosterone patches applied nightly over the skin; 5–10 g of a 1 % testosterone gel applied daily over skin; 30 mg of bioadhesive buccal testosterone every 12 h. Other options: 2 % of testosterone topical solution, 2 % testosterone gel, oral testosterone undecanoate, injectable testosterone undecanoate, testosterone-in-adhesive matrix patch, and testosterone pellets.

Infants/*Pubertal development* (*boys*): Infants and children with micropenis, three courses of testosterone enanthate 25 mg IM monthly, and another three courses can be repeated if necessary. At 13 years of age, testosterone enanthate or cypionate 25–50 mg IM dosed monthly; increase dose every 6–12 months until the adult replacement level is achieved (3–5 years).

Adult female: Oral contraceptive (20–35 μg ethinyl estradiol), conjugated estrogen 0.625–1.25 mg, estradiol valerate 1–2 mg, or transdermal application of estradiol 50–100 μg/day. Add progestagen in case of an intact uterus.

Pubertal development (*girls*): At 11 years of age, conjugated estrogen (0.15 mg daily or 0.30 mg on alternate days), ethinyl estradiol 2.5–5 μg, or 17β-estradiol 5 μg/kg daily, or estrogen release patches 25 μg 17β-estradiol (0.08–0.12 μg/kg/day) can be subdivided into 6–8 fragments. After 6 months or in case of spotting or menstrual bleeding, cyclic progestagens should be added.

TSH deficiency

Adults: Levothyroxine: initial dose: 75–125 μg/day in most cases (in elderly, start with 25 μg/day). Adjust the dose based on clinical response and serum free T_4 levels. Serum free T4 levels should be in the upper half of the reference range (see text).

Children: <6 months: 8–10 μg/kg/day; 6–12 months: 6–8 μg/kg/day; 1–5 years: 5–6 μg/kg/day; 6–12 years: 4–5 μg/kg/day

ACTH deficiency

Adults: Hydrocortisone three times a day: more commonly 10 mg early morning, 5 mg mid-day, and 5 mg early evening; prednisolone 2.5–5.0 mg early morning; prednisone, 2.5–5.0 mg/day. Adjustment based on clinical assessment. Double or triple the oral dose in case of exercise, or mild febrile disease. Use parenteral (IV/IM) dose if vomiting or diarrhea occur or if surgery is performed (hydrocortisone, 200–300 mg/day in 3–4 divided doses). DHEA 25–50 mg/daily as a trial in symptomatic women.

Children: oral hydrocortisone 10–24 mg/m^2/day or cortisone acetate 13.5–32 mg/m^2/day or prednisolone 3–5 mg/m^2/day; dexamethasone usually avoided.

ADH deficiency

Adults: Desmopressin: start with 5–10 mcg as a single dose at night before the patient goes to sleep. Increase until there is no nocturia (increments of 5–10 mcg). Add a morning dose if bothersome polyuria present during the day. Eventually, another dose can be given during the afternoon. Equivalence of nasal solution to pills: 2.5–5.0 mcg (nasal) = 0.1 mg (pill). Dose titration is needed if preparation is changed.

Children (*below 12 years of age*): Same initial doses of Desmopressin, but maximum daily doses are 30 mcg (nasal) and 0.8 mg (oral).

Transitional Period

In the transition phase, the recommended dose is 0.4–0.5 mg/day with the goal of achieving IGF-1 levels between 0 and +2 SD with adjustments made at 1–2 month intervals. Reassessment should be made every 6 months thereafter until the patient is in their mid-twenties [22, 27].

Hypogonadism (in the Adult Female)

Estrogen deficiency requires replacement for the relief of symptoms, such as loss of libido and dyspareunia as well as for the prevention of osteoporosis and premature cardiovascular disease. Epidemiological studies in women with anterior pituitary deficiency have demonstrated excessive cardiovascular mortality in untreated versus treated hypogonadism [49]. Thus, it is strongly recommended to replace sex steroids in younger women until the average age of menopause is reached (approximately 52 years of age in healthy subjects). On the other hand, findings of large studies of sex hormone replacement therapy in non-pituitary postmenopausal patients have shown an increased risk of cardiovascular and neoplastic diseases. Therefore, termination of sex hormone substitution in hypogonadal women after the average menopause age is recommended [50, 51].

The biological potency of 20 μg ethinyl estradiol, 1.25 mg conjugated estrogen, and 100 μg transdermal 17β-estradiol is comparable [52]. In premenopausal women, an oral contraceptive containing 20–35 μg ethinyl estradiol is an effective form of replacement therapy. Alternatively, oral estrogen preparations (conjugated estrogen 0.625–1.25 mg daily or estradiol valerate 1–2 mg) given cyclically or continuously with a progestagen can be administered. Transdermal application of estradiol (50–100 μg/day) is preferred over oral preparations because it avoids hepatic first-pass metabolism. In addition, the transdermal preparation minimizes the synthesis of procoagulatory factors and acute phase proteins, which are potential vascular risk factors [53], and eliminates the growth-hormone resistant effects of estrogen on IGF-I production in the liver [54]. All women who have an intact uterus should receive concomitant progesterone therapy. Breast cancer is clearly an absolute contraindication for sex steroid replacement therapy.

Pubertal Development

The goal for therapy in this case is to approximate normal development, and the appropriate age for intervention is around the chronological age of 11 years. Conjugated estrogens (initial dose 0.15 mg daily or 0.3 mg on alternate days), ethinyl estradiol (2.5–5 μg daily), or 17β-estradiol (initial dose 5 μg/kg daily) may be administered, and the dose should be gradually increased every 6–12 months over the following 2–3 years until the adult replacement dose is reached. After 6 months of therapy or in case of spotting or menstrual bleeding, cyclic progestagens (usually medroxyprogesterone 5–10 mg daily or norethisterone 0.7–1.0 mg daily) should be added for 12–14 days every month [55].

Estrogen-release patches offer an alternative treatment option. The smallest commercially available patch releases 25 μg 17β-estradiol daily. The patch can be divided into six to eight fragments, and each fragment allows a release of 0.08–0.12 μg/kg daily. Application of the patch may be limited to nighttime in order to mimic the pattern of estrogen secretion that is predominantly nocturnal during the initiation of puberty [56]. The dosage should be increased every 6–12 months until the adult replacement dosage is achieved.

Fertility Treatment

Pulsatile GnRH is mostly used for ovulation induction in patients with hypothalamic hypogonadotropic hypogonadism and normal gonadotropin levels. However, such therapy should only be performed at centers with extensive experience in ovarian stimulation techniques.

Gonadotropin therapy is indicated in patients with gonadotropin deficiency or GnRH resistance, but can also be used in patients with GnRH defects [57]. Ovulation induction is initiated with 75 IU daily of a preparation containing only FSH or a mixture of FSH and LH (human menopausal gonadotropins). Careful ultrasound monitoring is recommended to ensure that only one or two follicles develop in order to prevent ovarian superstimulation and prevent multiple pregnancies. Once a follicle has become mature, a single dose of 5,000 IU of human chorionic gonadotropin (hCG) is administered to stimulate ovulation, which occurs within 36–48 h of administration.

Conception occurs in 5–15 % of cycles and cumulative conception rates average between 30 and 60 % [57].

Hypogonadism (in the Adult Male)

The aim of androgen substitution is to restore the serum testosterone concentration to the normal range (in the mid-normal range) in order to maintain secondary sexual characteristics, prevent loss and optimize bone mass, and improve sexual function [7].

The route of delivery depends on availability, patient preference, consideration of pharmacokinetics, treatment burden, and cost. Testosterone therapy is contraindicated in patients with prostate cancer, untreated severe obstructive sleep apnea, and uncontrolled or poorly controlled heart failure [7].

Oral Testosterone

Oral testosterone undecanoate is commercially available in many countries under various brand names in 40 mg capsules, but is not available in the United States. It is absorbed through the lymphatic system and bypasses the portal vein due to esterification at the 17β position. The daily dose is 80–240 mg given throughout the day with meals. However, this drug has low bioavailability and substantial interindividual and intraindividual variability in absorption [58]. Therefore, it is more suitable for patients who cannot tolerate transdermal or intramuscular administration.

Intramuscular Depot

Testosterone enanthate and testosterone cypionate are 17β esters of testosterone that have been the standard preparations for testosterone treatment for decades and have been proven to be safe with few unwanted side effects. Both esters are more lipophilic than native testosterone and have a long half-life and duration of action.

After intramuscular administration of testosterone enanthate, serum testosterone peaks to maximal supraphysiological levels in approximately 10 h, followed by a gradual decline to low normal or even subnormal levels [59]. Intramuscular doses of testosterone enanthate or cypionate from 100 mg/week or 150–200 mg every 2 weeks are biologically effective. Serum testosterone should be monitored between midway injections aiming at a serum level between 350 ng/dL (12–3 nmol/L) and 750 ng/dL (24–5 nmol/L). Some clinicians prefer to monitor serum testosterone levels immediately prior to the next injection with a goal of achieving a level in the low normal range. Dose adjustment is performed by varying injection intervals or injection dosage.

Testosterone undecanoate (Nebido®) is another ester of testosterone that has a markedly longer half-life (34 days) and duration of effect than testosterone enanthate and cypionate. Intramuscular injection of testosterone undecanoate 1,000 mg every 3 months leads to constant physiological serum testosterone levels without the undesired initial peak in drug concentration observed with the other depot formulations. A reduction in the injection interval between the first and second administration is recommended [60] and with this loading dose, sufficient steady state testosterone levels may be achieved more rapidly. Serum testosterone should be monitored at the end of the injection interval with the goal of achieving a serum level of testosterone in the mid-normal range. Dose adjustment is performed by varying the injection intervals.

Transdermal Systems

Transdermal systems are a popular treatment modality for hypogonadal men. Transdermal gel and patches provide a useful delivery system for normalizing serum testosterone in these patients [61]. The transdermal gel has the best pharmacokinetic properties of all the available formulations and can achieve stable serum testosterone concentrations within the normal range using a noninvasive

topical application that is applied once a day on non-pressure areas of the body. Potential limitations of transdermal systems include a high rate of skin irritation observed with patches and the possibility that the testosterone gel may be transferred to other individuals through skin contact [62]. Four testosterone gels are currently available in United States, including AndroGel®, Testim®, Axiron®, and Fortesta®. A multicenter study conducted by Swerdloff et al. [63] (Testosterone Gel Study Group) showed that a daily transdermal application of a hydroalcoholic gel containing 1 % testosterone (AndroGel®) at 5.0 and 10.0 g of gel (equivalent to 50 and 100 mg) increased serum testosterone levels in hypogonadal men to within the normal range. Treatment should be started with 5.0 g and adjusted as necessary up to a maximum of 10.0 g. Testim® is another brand of hydroalcoholic gel with the same concentration.

The 2 % formulation of testosterone topical solution (Axiron®) is a non-occlusive topical formulation administered to the axilla, instead of the hands. A multicenter study conducted by Wang et al. [64] in hypogonadal men treated with 30–90 mg of this preparation showed that application of the gel restored physiological testosterone levels in 84.8 % of treated patients. This finding is similar to results previously reported with testosterone gel and mucoadhesive buccal therapies. The suggested dose of Axiron® is 60 mg (30 mg applied to each axilla once a day), with adjustment of the dose ranging from 30 to 120 mg, as determined by the serum testosterone concentration.

A novel 2 % testosterone gel for the treatment of hypogonadal male (Fortesta®) is also supplied in a metered dose pump, which is applied to the front and inner thighs. A multicenter study [65] in hypogonadal men followed for 90 days demonstrated that a single daily dose of this preparation restored normal levels of testosterone in more than 75 % of hypogonadal patients, with a low risk of supraphysiological testosterone levels. The recommended starting dose is 40 mg once a day (2 g/2 mL of gel) with adjustment of the dose ranging from 10 to 70 mg, as determined by the serum testosterone concentration.

The transdermal system patch (Androderm®) delivers approximately 5 mg of testosterone every 24 h and results in normal serum testosterone concentrations in most hypogonadal men [66]. The application of one or two testosterone patches is recommended to be applied nightly over the skin of the back, thigh, or upper arm, away from pressure areas. Testosterone serum levels can be assessed 3–12 h after the application of the patch. The dose should be adjusted to achieve testosterone levels in the mid-normal range. The scrotal patch is no longer available in the United States.

Testosterone in an adhesive matrix patch is now available in many countries. The recommended regimen consists of 2×60 cm^2 patches that delivers approximately 4.8 mg of testosterone per day and lasts for approximately 2 days. However, some patients experience skin irritation with this preparation [7].

Buccal Tablet

A controlled release testosterone buccal system (Striant SR®) contains 30 mg of testosterone and mucoadhesive excipients, which rapidly adhere to the buccal mucosa and slowly form a gel. Transbuccal delivery of testosterone substantially circumvents hepatic first-pass metabolism. A study by Wang et al. [67] demonstrated that the administration of this preparation maintained serum testosterone concentrations within the normal range in most hypogonadal men. The recommended dose is 30 mg applied to the buccal region twice a day. Testosterone serum levels can be assessed immediately before or after application of the fresh system. Gum-related adverse events occurred in 16 % of treated subjects.

Pellets

Subcutaneous pellets (Testospel®) provide stable physiological testosterone levels, but a minor surgical procedure is required for administration [68]. The pellets are implanted into the subdermal fat of the lower abdominal wall, buttock, or thigh.

The dose and regimen vary with formulation. The manufacturer recommends implantation of three to six 75 mg pellets every 3–6 months [7]. Extrusion of the pellets and infection are the main risks of this treatment.

Monitoring During Androgen Therapy

Men younger than 40 years of age may not need prostate monitoring as they are at low risk for the development of prostate cancer. In men 40 years of age or older with a baseline prostatic specific antigen (PSA) level greater than 0.6 ng/mL, rectal digital examination should be performed before initiating treatment, and PSA levels should be checked 3–6 months after the start of treatment and annually thereafter. A urological consultation is necessary if there is an increase in serum PSA concentration to a level greater than 1.4 ng/mL within any 12 month period of testosterone treatment. Hematocrit should be checked at baseline, at 3–6 months after the start of therapy, and annually thereafter. If the hematocrit is greater than 54 %, then the treatment should be stopped until it decreases to a safe level [7].

Infants/Pubertal Development

Infants and children with micropenis (penile length less than 2.5 cm at birth and in infancy) related to congenital hypopituitarism may be treated with three courses of testosterone enanthate 25 mg given IM each month with the goal of increasing penis size. If the desirable increase in penile length (>0.9 cm) has not occurred, then another three course trial can be repeated [8].

There is no general consensus regarding the best time to induce pubertal development. An acceptable proposal may be to induce pubertal development at 13 years and obtain a slow and progressive increase. A monthly dose of testosterone enanthate or cypionate 25–50 mg IM may be used. The dose should be kept as low as possible in order to preserve maximal growth potential. The dose should be increased every 6–12 months until reaching the adult replacement therapy within 3–5 years [57].

Fertility Treatment

In secondary hypogonadism, spermatogenesis and fertility can be induced. Men with prepubertal onset hypogonadism are more likely to require replacement of FSH as well as LH, whereas men with postpubertal onset are more likely to require replacement of LH only.

The classical gonadotropin regimen combines hCG and human menopausal gonadotropin (hMG) given as IM or subcutaneous (SC) injections, depending on the available preparation [69]. After stopping testosterone treatment, hCG can be used initially at a dose of 2,000 IU twice a week to stimulate spermatogenesis. The dose is titrated against testicular volume and serum testosterone, which should be measured every 1–2 months, with the goal of achieving levels between 400 and 900 ng/dL within 3–4 months after initiating treatment. Some patients require as little as 500 IU per dose, while other patients need as much as 10,000 IU per dose. Sperm count is measured every 2–4 weeks, but the value is not used to adjust the hCG dose. Most patients who eventually reach a normal sperm count (over 20 million/mL) do so within 6 months, but some require 12–24 months. The addition of hMG should be considered if the sperm count does not reach one-half of the normal level within 12–24 months. The pharmaceutical preparation of hMG contains FSH and is used to replace FSH for stimulating spermatogenesis in men who are infertile due to secondary hypogonadism. Recombinant human FSH is also available, but has not been as well studied in men and is more expensive. FSH appears to be necessary for the initiation of spermatogenesis, but not for its maintenance or reinitiation. Therefore, for patients with prepubertal onset of secondary hypogonadism, the treatment should be started with both hCG 2,000 IU and hMG three times a week while titrating hCG doses based on serum testosterone levels.

Thyrotropin Deficiency

Levothyroxine is the replacement of choice for central hypothyroidism [70]. Most patients use 75–125 mcg/day of L-T_4 (for pediatric dosages, see Box 8.1). Laboratory monitoring of serum-free T4 levels should be performed. The FT_4 levels should remain in the upper half of the reference range for patients with concomitant untreated GH deficiency in order to ensure adequate replacement [31]. In eusomatotropic patients, the FT_4 levels should be in the mid-normal reference range [31, 71] (see "Hormone Replacement Therapy Interactions" below).

ACTH Deficiency

Glucocorticoid replacement is a priority because its deficiency is potentially life-threatening. Replacement therapy should be initiated before the beginning of thyroxine and/or GH replacement, since these latter treatments may precipitate adrenal crisis. There is no consensus on the best glucocorticoid replacement regimen [10]. Many centers use hydrocortisone (15–20 mg/day) in divided doses in an attempt to mimic circadian variation (e.g., 10–15 mg in the morning and 5 mg in the early afternoon; see Box 8.1). Equivalent doses of prednisone, dexamethasone, or cortisone acetate have also been used. Approximate equivalent doses to 20 mg of hydrocortisone include cortisone acetate, 25 mg, prednisone, 5 mg, and dexamethasone, 0.75 mg. Mineralocorticoid is not required in ACTH deficient patients, since its secretion is under the control of the renin–angiotensin system. For children, hydrocortisone is usually the glucocorticoid of choice (10–24 mg/m^2/day in divided doses). Prednisolone (3–5 mg/m^2/day) is also used, albeit less frequently. Due to its higher potency and possible negative effects on growth, dexamethasone is avoided during childhood.

As a general rule, during acute illness, the usual glucocorticoid replacement dose is increased two to three times over a course of at least 3 days or more, if needed. If patients cannot take oral glucocorticoids or experience severe illness, then in IV/IM hydrocortisone is given as 200–300 mg/day in 3–4 doses (e.g., 50 mg every 6 h) [10, 72].

Adult women with hypopituitarism show decreased levels of androgens, including dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S), androstenedione, and testosterone. Some studies on DHEA replacement therapy to these patients have shown beneficial results on quality of life as well as improved mood and sexual function [73–76], whereas other studies have not shown such benefits [77, 78]. A meta-analysis that included randomized studies on the effect of DHEA replacement therapy on the quality of life of primary or secondary adrenal insufficient patients showed a small improvement in quality of life and depression, but no effect on anxiety and sexual well-being [79]. In the same meta-analysis, the most commonly reported side effects were greasy skin, hirsutism, acne, scalp itching, and increased apocrine sweat secretion and odor [79]. However, to date there is insufficient evidence to recommend routine DHEA replacement to these patients [72]. Moreover, in many countries, DHEA is only available as a dietary supplement, and therefore there are often variable and unreliable amounts of the drug in each pill. When DHEA is replaced, the usual dosage ranges from 25 to 50 mg in a single morning dose [80]. Clinical effects are observed only after several weeks of treatment. Monitoring should include measurement of DHEA-S (24 h after the previous dose) as well as free testosterone or total testosterone with sex hormone-binding globulin (SHBG) and estimation of free testosterone. If side effects are observed, then the dosage may be decreased by 50 %.

ADH Deficiency

Since polyuria and nocturia impair the quality of life, Desmopressin, a vasopressin analogue, should be given to most patients with DI [81]. Desmopressin is usually started as a single dose at night before the patient goes to sleep (e.g., 1 puff), which is increased until nocturia is controlled. A second dose (in the morning) and less commonly a third dose (in the afternoon) may be

added as needed. Desmopressin is usually available as nasal spray, with one puff delivering 10 mcg. It is also available as a pill at a concentration of 0.1 mg per dose. In the inpatient setting, Desmopressin may also be given intravenously or subcutaneously at a dosage of 2–4 mcg/day in two divided doses.

Hormone Replacement Therapy Interactions

A critical aspect in the management of patients with hypopituitarism is the interplay between different replacement therapies. Remarkably, GH status impacts thyroid and adrenal replacement, and estrogen influences growth hormone dosages.

GH increases the conversion of T_4 to T_3 [31]. Hence, patients with combined and untreated GH and TSH deficiencies may show normal serum T_4 levels, usually at the lower tertile, which masks the diagnosis of central hypothyroidism. Serum T_4 levels fall below the normal range only after GH replacement in these cases [32]. On the other hand, a decrease in serum T_4 levels after GH replacement should be evaluated carefully, since T_3 levels usually concomitantly rise. If serum T_4 levels fall to the mid-normal range, an increase in the dosage of levothyroxine is usually not necessary. Additionally, during concomitant GH and levothyroxine replacement therapy, serum T_3 measurements may help to detect thyroxine over replacement [71].

In contrast to the action of GH on thyroid axis, GH enhances the conversion of cortisol to the biologically inactive cortisone through 11β-hydroxysteroid dehydrogenase type 1 [82]. Therefore, GH replacement may induce glucocorticoid insufficiency. This effect has been observed in patients with multiple pituitary deficiencies [83], but not in patients with isolated GH deficiency [84].

Oral estrogen replacement decreases the effect of GH on hepatic tissue, which consequently decreases IGF-I levels. Thus, patients on oral estrogen should have their dosage of GH increased [52, 85]. Since this effect is not observed in patients on transdermal estrogen due to lower concentrations of estrogen in the liver, this mode of administration is usually preferred in GH-deficient patients.

Long-Term Management

While radiotherapy is associated with progressive hypopituitarism, in the case of a pituitary tumor, even if hypofunction is present before surgical treatment, pituitary function should be reassessed postoperatively, as nearly as 50 % of pituitary deficiencies will resolve. Lifelong substitution therapy may thus not be necessary.

There is no evidence that GH replacement therapy is associated with the development of cancer, although the association of IGF-I levels and cancer in epidemiological studies has been explored. In addition, the evidence linking GH replacement therapy in GHD patients with the reversal of the highest rates of mortality observed in hypopituitarism is inconclusive.

More studies are needed in order to determine whether testosterone replacement in hypogonadal men increases the risk of developing or converting histological prostate cancer to the clinical form.

Potential Future Therapy

The presence of stem cells in the pituitary gland, which can give rise to all pituitary hormone cells, implies that these cells can be replaced after being lost or damaged. These stem cells could be of great usefulness in the treatment of hypopituitarism and may also have utility in the long-term management of pituitary deficiencies [86].

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