CHAPTER

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Panhypopituitarism

Minal Mohit

INTRODUCTION

Panhypopituitarism is a condition of inadequate or absent production of the anterior pituitary hormones. It is frequently the result of other problems that affect the pituitary gland and either reduce or destroy its function or interfere with hypothalamic secretion of the varying pituitary-releasing hormones. Hypopituitarism refers to the deficiency of one or more pituitary hormones. It is associated with increased morbidity and mortality. Clinical manifestations are influenced by the cause, severity, and rate of onset of pituitary hormone deficiency. Adult patients with hypopituitarism receive substitutive hormone treatment for growth hormone, secondary glucocorticoid, sex steroid, and thyroid hormone deficiency.

EPIDEMIOLOGY

Limited information is available on the epidemiology of hypopituitarism. A Swedish survey estimates the prevalence of hypopituitarism to be 175 cases per million. A Spanish study has reported a prevalence of hypopituitarism of 290 and 450 cases per million from two cross-sectional surveys in 1992 and 1999, respectively, and a corresponding incidence of 60 per million per year.

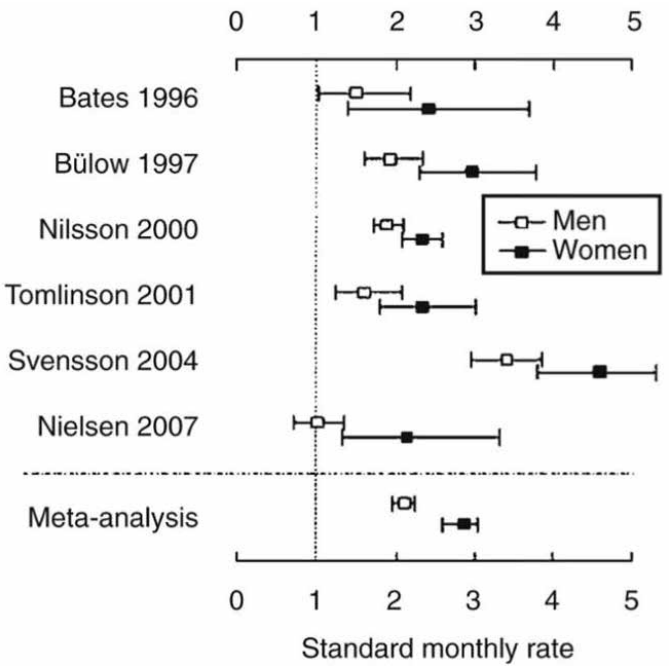

Fig. 1: Standard mortality rates (SMR) and 95% confidence intervals (CI) in individual studies on patients with nonmalignant pituitary diseases not associated with excess adrenocorticotropic hormone (ACTH) or growth hormone (GH) secretion, and in the weighted meta-analysis (bottom line). Results are shown for men (open boxes) and women (black boxes) separately. (From Nielsen EH, Lindholm J, Laurberg P. Excess mortality in women with pituitary disease: a meta-analysis. Clin Endocrinol 67:693–697, 2007.)

MORTALITY

Mortality is increased in hypopituitarism. Data from six epidemiologic studies, comprising patients aged between 46 and 52 years who were followed for 10 to 13 years, report increased mortality with standardized mortality rates (SMRs) from 1.2 to 2.2. The higher mortality arises from cardiovascular and cerebrovascular disease and appears to be greater in women (Figure 1). Craniopharyngiomas carry a worse prognosis than pituitary adenomas, and radiotherapy has been identified as a factor that increases mortality. GH deficiency has been implicated as a major contributor to excess mortality in hypopituitarism because it is the only defect not replaced in the studies of hypopituitarism. However, the contribution to overall mortality of other risk factors, such as radiotherapy and suboptimal replacement therapies for other hormone deficits, is the subject of ongoing investigation.

CAUSES

Major causes of hypopituitarism are shown in (Table 1). The most common cause is a pituitary adenoma or treatment with pituitary surgery or radiotherapy.

PITUITARY AND HYPOTHALAMIC MASS LESIONS

Pituitary microadenomas, though found commonly (1.5% - 27%) at autopsy, are very rarely associated with hypopituitarism and tend to run a benign course. Macroadenomas are less common but are more frequently associated with pituitary hormone deficiencies; some 30% of patients with pituitary macroadenomas have one or more anterior pituitary hormone deficiencies. The causative mechanism of hypopituitarism is compression of the portal vessels in the pituitary stalk, secondary to the expanding tumor mass directly or to increased intrasellar pressure, which explains the potential reversibility of pituitary dysfunction after surgery in some patients.

Derangement of central endocrine regulation also occurs with parapituitary space-occupying lesions such as craniopharyngiomas, Rathke's cleft cysts, arachnoid cysts, chondromas, chordomas, suprasellar meningiomas, astrocytomas of the optic nerve, and primary tumors of the third ventricle.

PITUITARY SURGERY

The incidence and degree of hypopituitarism after surgery depend on the size of the original tumor, the degree of infiltration, and the experience of the surgeon. There is a possible deterioration of postoperative

Table 1: Causes of Hypopituitarism

Neoplastic: Tumors involving the hypothalamic-pituitary (HP) axis
Pituitary adenoma
Craniopharyngioma
Glioma (hypothalamus, third ventricle, optic nerve)
Surgery: for HP axis tumors
Radiotherapy
HP axis tumors
Brain tumors
Head and neck cancer
Acute lymphoblastic leukemia
Autoimmune
Lymphocytic hypophysitis
Vascular
Sheehan's syndrome
Pituitary apoplexy
Intrasellar carotid artery aneurysm
Subarachnoid hemorrhage
Granulomatous disease
Sarcoidosis
Tuberculosis
Histiocytosis X
Wegener's granulomatosis
Genetic (table 2)
Combined pituitary hormone deficiencies
Isolated pituitary hormone deficiencies
Developmental
Midline cerebral and cranial malformations
Traumatic
Head injury
Perinatal trauma
Infection
Encephalitis
Pituitary abscess
Iron-overload states
Hemochromatosis
Hemosiderosis (thalassemia)
Idiopathic

pituitary function, and assessment of pituitary function should be performed promptly after surgery. But on the other hand, surgery for pituitary adenomas may also be associated with significant recovery of pituitary function. Postoperative improvement is more likely if no tumor is found on postoperative imaging, or if the tumor is not invasive. The pituitary hormone most likely to recover is thyroid-stimulating hormone (TSH), followed in order

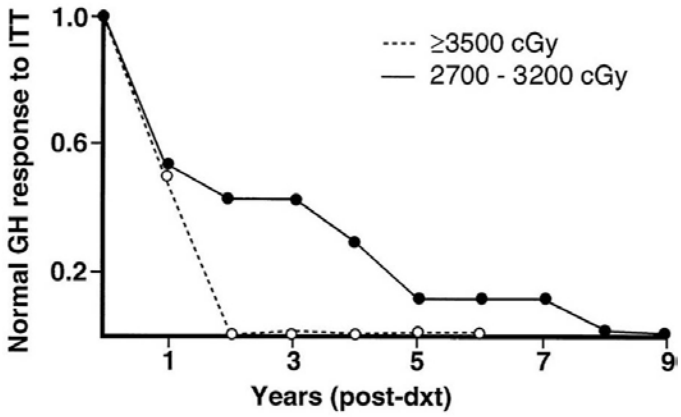

Fig. 2: The incidence of growth hormone (GH) deficiency in children receiving 27 to 32 Gy or ≥35 Gy of cranial irradiation for a brain tumor in relation to time from irradiation (dxt). This illustrates that the speed at which individual pituitary hormone deficits develop is dose dependent; the higher the radiation dose, the earlier GH deficiency occurs. (Courtesy the Department of Medical Illustrations, Withington Hospital, Manchester, England.)

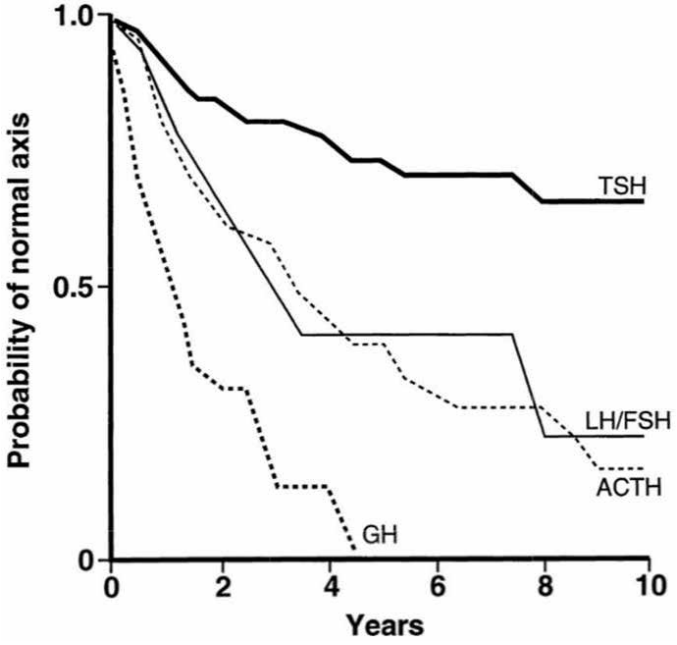

Fig. 3: Life-table analysis indicating probabilities of initially normal hypothalamic-pituitary-target gland axes remaining normal after radiotherapy (3750 to 4250 cGy). Growth hormone (GH) secretion is the most sensitive of the anterior pituitary hormones to the effects of external radiotherapy, and thyroid-stimulating hormone (TSH) secretion is the most resistant. In two thirds of patients, gonadotropin deficiency develops before adrenocorticotropic hormone (ACTH) deficiency. FSH, Follicle-stimulating hormone; LH, luteinizing hormone. (From Littley MD, Shalet SM, Beardwell CG, et al: Hypopituitarism following external radiotherapy for pituitary tumors in adults. Q J Med 70:145–160, 1989.)

by adrenocorticotropic hormone (ACTH), gonadotropins, and GH. Recovery of pituitary function occurs early, within 8 weeks after surgery.

Table 2: Genetic Causes of Hypopituitarism

	Gene Defect	Hormone Deficiencies
Combined	Pit-1 (POU1F1, GHF1)	GH, TSH, PRL
	PROP-1	GH, LH/FSH, TSH, ACTH, PRL
	HESX1 (Rpx)	GH, LH/FSH, TSH, ACTH, ADH
	LHX3/LHX4	GH, LH/FSH, TSH, PRL
	PITX2	GH, PRL
Isolated	hGH	GH
	GHRH receptor gene	GH
	KAL	FSH/LH
	GnRH receptor gene	FSH/LH
	DAX1/AHC	FSH/LH
	TBX19 (Tpit)	ACTH
	TSH-β gene	TSH
	TRH receptor gene	TSH

RADIOTHERAPY

Deficiency of one or more anterior pituitary hormones is almost invariable when the hypothalamic-pituitary axis lies within the fields of radiation. Hypopituitarism also develops in patients who received radiation therapy for nasopharyngeal carcinomas, parasellar tumors, and primary brain tumors, as well as in children who underwent prophylactic cranial irradiation for acute lymphoblastic leukemia or total body irradiation (TBI) for a variety of tumors and other diseases.

The radiobiological impact of an irradiation schedule is dependent on the total dose, the number of fractions, and the duration and length of follow-up (Figure 2). Somatotrophs are the most sensitive to radiation damage (Figure 3). Endocrine testing should be performed on a yearly basis for at least 10 years and again at 15 years.

GENETIC CAUSES

Mutations in genes encoding for the KAL, HESX-1, Prop-1, and Pit-1transcription factors result in deficiency of one or more anterior pituitary hormones. Mutations in early appearing transcription factors tend to cause more extensive hormone deficiencies (Table 2).

TRAUMATIC BRAIN INJURY

Traumatic brain injury (TBI) is an under-appreciated cause of hypopituitarism. It was first reported in 1918. Meta-analysis of 19 studies, which included more than 1000 patients, demonstrated a pooled prevalence of hypopituitarism following TBI of 27.5%. Prevalence of diabetes insipidus is 26% in the acute phase and is decreased to 6.9% among long-term survivors. Risk factors of traumatic hypopituitarism include basal skull fracture, diffuse axonal injury, raised intracranial pressure, and prolonged stay in the intensive care unit. All patients should undergo screening for hypopituitarism between 3 and 6 months after injury.

LYMPHOCYTIC HYPOPHYSITIS

Lymphocytic hypophysitis, an immune-mediated diffuse infiltration of the anterior pituitary with lymphocytes and plasma cells, occurs predominantly in women and often is first evident in pregnancy or after delivery. The classic presentation is peripartum hypopituitarism, often with a pituitary mass and visual failure, whereas in later stages, the gland may atrophy, leaving an empty sella.

PITUITARY APOPLEXY

Pituitary apoplexy is the abrupt destruction of pituitary tissue that results from infarction or hemorrhage into the pituitary, usually into an underlying pituitary tumor. Severe headache accompanies a variable degree of visual loss or cranial nerve palsy. Consequent pituitary hormone deficiencies may develop rapidly. In Sheehan's syndrome, pituitary infarction occurs secondary to severe postpartum hemorrhage and ensuing circulatory failure.

GRANULOMATOUS DISEASES

Granulomatous diseases, including sarcoidosis, tuberculosis, and Langerhans cell histiocytosis, can affect the hypothalamic-pituitary axis and cause hypopituitarism, including diabetes insipidus.

CLINICAL FEATURES

Presentation of hypopituitarism can be nonspecific. It is affected by degree, type, and rate of onset of the pituitary hormone deficiency. Local pressure effects or hormonal hypersecretion may complicate the clinical picture. Hypopituitarism arising from an expanding mass lesion or from irradiation produces a characteristic evolution of pituitary failure caused by an initial loss of GH secretion, followed by LH and FSH, and finally by failure of ACTH and TSH secretion. The onset of symptoms is insidious, typically occurring with mild headaches, lethargy, fatigue, disinterest, weight gain, low mood, and declining libido—symptoms mimicking depression. Rarely, anorexia and weight loss may arise from ACTH deficiency and may be mistaken for and lead to extensive investigations for occult malignancy. Progressive mass expansion causes increasingly severe headaches or visual symptoms from chiasmal compression. The symptoms and signs of individual hormone deficiency are listed in Table 3. The features of isolated deficiencies of each axis are described below.

GH DEFICIENCY

Adults with GH deficiency, whether dating from childhood or acquired in later adult life, have a range of metabolic, body compositional, and functional abnormalities Table 4.

GONADOTROPIN DEFICIENCY

In male patients, the clinical features of gonadotropin deficiency differ according to whether the deficiency was acquired before or after pubertal age. If acquired before pubertal age, clinical examination reveals a small penis, small testes, and eunuchoid proportions (span exceeds a height of 5 cm). Hypogonadism acquired postpubertally

Table 3: Symptoms and Signs of Hormone Deficiencies

Hormone Deficiency	Symptoms and Signs
Growth hormone	Please refer to Table 13-6 in the section Growth Hormone Deficiency.
Gonadotropins	In men: poor libido/ impotence, infertility, small soft testes, reduced facial/body hair
	In women: amenorrhea/ oligomenorrhea dyspareunia, infertility, breast atrophy
Thyroid-stimulating hormone	Growth retardation in children; decrease in energy; constipation; sensitivity to cold, dry skin, weight gain
Adrenocorticotropic hormone	Weakness, tiredness, dizziness on standing, pallor, hypoglycemia
Prolactin	Failure of lactation
Antidiuretic hormone	Polyuria, polydipsia, nocturia, hypotension

is associated with a reduction in testicular size, loss of facial and body hair, and thinning of the skin, leading to the characteristic finely wrinkled facial skin of the "aging youth." Other effects include a decrease in skeletal muscle mass, bone mineral density, sexual function, libido, and general well-being. Azoospermia is an almost inevitable consequence of hypogonadotropic hypogonadism. Partial LH deficiency may result in low circulating testosterone levels and gynecomastia with preserved testicular size and fertility, as intratesticular testosterone levels remain high enough to maintain spermatogenesis.

In a teenage girl, hypogonadotropic hypogonadism is associated with primary amenorrhea and absent breast development. In the adult woman, amenorrhea or oligomenorrhea, infertility, breast atrophy, vaginal dryness, and dyspareunia occur; pubic and axillary hair remains unless ACTH deficiency also is present.

ADRENOCORTICOTROPIC HORMONE DEFICIENCY

ACTH deficiency is the most life-threatening component of hypopituitarism. If the onset is abrupt, as in pituitary apoplexy, the clinical picture may be dominated by profound shock in the most serious form. Patients with chronic ACTH deficiency usually present with chronic progressive symptoms of chronic fatigue, anorexia, and weight loss, sometimes mimicking anorexia nervosa or an occult malignancy. Patients on long-term glucocorticoid therapy can develop adrenal atrophy secondary to ACTH suppression. Examination may reveal pallor of the skin, in contrast to the hyperpigmentation of Addison's disease, and in female patients particularly, loss of secondary sexual hair occurs. In severe ACTH deficiency, particularly in childhood, hypoglycemia can occur: Cortisol deficiency results in increased insulin sensitivity and a decrease

Table 4: Syndrome of Adult Growth Hormone Deficiency

Symptoms
• Increased body fat • Reduced muscle bulk • Reduced strength and physical fitness • Reduced sweating • Impaired psychological well-being - Depressed mood - Anxiety - Reduced physical stamina - Reduced vitality and energy - Increased social isolation
Signs
• Overweight • Increased adiposity, especially abdominal • Poor muscular development • Reduced exercise performance • Thin, dry skin • Depressed affect
Investigations
• Peak GH response to hypoglycemia <3 μg/L (all patients) • Low IGF-1 (60% of patients) • Hyperlipidemia: high LDL cholesterol, low HDL cholesterol • Elevated fasting insulin • Reduced bone mineral density

GH, Growth hormone; IGF, insulin-like growth factor; LDL, low-density lipoprotein; HDL,high-density lipoprotein.

in hepatic glycogen reserves. Hyponatremia, although less commonly seen than in Addison's disease because of preservation of aldosterone secretion, may be the presenting feature of ACTH deficiency, particularly in the elderly.

THYROID-STIMULATING HORMONE DEFICIENCY

Thyroid-stimulating hormone (TSH) deficiency occurs late in most pituitary disorders. Symptoms include fatigue, weakness, inability to lose weight, constipation, and cold intolerance, in keeping with the symptoms of primary hypothyroidism. However, symptoms generally are milder than in primary hypothyroidism, because some residual TSH secretion often is preserved.

ANTIDIURETIC HORMONE DEFICIENCY

Polydipsia and polyuria with nocturia are the classic features of diabetes insipidus resulting from antidiuretic hormone (ADH) deficiency. If the patient is unable to keep up with the fluid loss, hypotension and hypovolemia ensue. The features of diabetes insipidus may be masked by the presence of ACTH deficiency, because of the

consequent hypovolemia and reduced glomerular filtration rate. Only when cortisol replacement therapy is commenced may the polyuria and polydipsia of diabetes insipidus be revealed.

DIAGNOSIS AND ENDOCRINE EVALUATION

Imaging

MRI is the scanning technique of choice, as it offers higher resolution than CT scanning and is able to demonstrate microadenomas as small as 3 mm in diameter. MRI also has provided insights into the morphologic abnormalities that arise from developmental defects of the pituitary gland. CT is used in situations where MRI is contraindicated, such as when arterial clips or a pacemaker is present. CT has a valuable role in defining bone anatomy in preparation for surgery.

Endocrine Evaluation

The endocrine assessment of a patient with suspected hypopituitarism usually involves measurement of both baseline and stimulated hormone levels. Evaluation of baseline function involves prolactin, TSH, thyroxine (T_4), cortisol, LH, FSH, and testosterone in men, and estradiol in women. Baseline blood testing reliably identifies hypothyroidism, hypogonadism, and severe hypoadrenalism due to pituitary insufficiency.

DYNAMIC TESTING

Growth Hormone Deficiency

Three widely accepted approaches for assessing GH secretory status include measuring

1. peak GH response to a provocative test, which include the insulin tolerance test (ITT); arginine, glucagon, clonidine, and growth hormone-releasing hormone (GHRH) alone or in combination with arginine or pyridostigmine
2. spontaneous GH secretion, and
3. serum concentrations of GH-regulated proteins such as insulin-like growth factor 1 (IGF-1) and IGF-binding protein-3 (IGFBP-3).

Adult Gonadotropin Deficiency

In women of postmenopausal age, gonadotropin levels are clearly low or undetectable, whereas in premenopausal women, amenorrhea (or less commonly, oligomenorrhea), in addition to low estradiol levels and low or normal gonadotropin levels, provides sufficient evidence of the diagnosis. In adult men, a similar picture of low testosterone levels and low or inappropriately normal gonadotropin levels is seen.

Adrenocorticotropic Hormone Deficiency

In normal people, the highest plasma cortisol levels are found between 6:00 AM and 8:00AM, and the lowest before midnight. Plasma cortisol and ACTH concentrations are elevated during physical and emotional stress, including acute illness, trauma, surgery, infection, and starvation. If a 9:00 AM cortisol level is less than 100 nmol/L, particularly in an unwell patient, cortisol deficiency is highly likely, whereas a baseline level greater than 500 nmol/L indicates normality; dynamic assessment of the hypothalamic-pituitary-adrenal (HPA) axis is not necessary under these circumstances. A paired plasma ACTH level will help distinguish between primary and secondary glucocorticoid deficiency: In primary cortisol deficiency (Addison's disease), the ACTH level will be high, whereas in secondary glucocorticoid deficiency, the ACTH level will be low or inappropriately normal.

The insulin tolerance test (ITT) evaluates the response of the HPA axis to the potent stressor of hypoglycemia, and it is generally the "gold standard" in the confirmation of secondary adrenal failure. It is also the test of growth hormone reserve in patients with pituitary disease. Following injection of a standard dose of intravenous insulin (0.1 unit/kg),[57] cortisol concentrations are measured serially. Upon achievement of adequate hypoglycemia (<2.2 mmol/L), a peak cortisol response of between 500 and 600 nmol/L generally is accepted as adequate.

The short Synacthen (tetracosactrin) test sometimes is used as a surrogate test of ACTH deficiency on the basis that the adrenal gland will respond to an exogenous bolus of synthetic ACTH when there is a normal endogenous ACTH reserve and the gland is not atrophic. Although it is a good test of adrenal reserve, it does not directly test pituitary ACTH reserve. In a patient with organic pituitary disease, a normal response to Synacthen does not exclude mild or recent ACTH deficiency.

Thyroid-Stimulating Hormone Deficiency

Secondary hypothyroidism is associated with reduced concentration of free or total T_4 in association with a serum TSH concentration below the normal range, analogous to the biochemical findings in secondary hypogonadism.

Antidiuretic Hormone Deficiency

The diagnosis of ADH deficiency first requires confirmation of polyuria, which is defined as the excretion of more than 3 L of urine per 24 hours (40 mL/kg/24 hours). The usual first-line investigation is an 8-hour fluid deprivation test. The test should be performed under strict observation because severe fluid and electrolyte depletion can occur. Plasma osmolality, urine volume, and osmolarity are measured hourly for 8 hours, after which a synthetic analogue of ADH (desmopressin) is given intramuscularly (IM). The urine osmolality then is remeasured. In a normal subject, ADH is secreted throughout the test, water is absorbed normally, and a subsequent elevation of urine osmolality occurs. In diabetes insipidus, the urine fails to concentrate (normal subjects achieve a urine osmolality at least twice the plasma osmolality) because of a lack of ADH; hence, plasma osmolality increases. Urine concentrates adequately only after administration of desmopressin. In cases in which the results of a water deprivation test are inconclusive, ADH measurement is helpful. A definitive diagnosis of ADH deficiency can be established by infusing hypertonic saline for 2 hours to increase plasma osmolality to more than 300 mOsm/kg, with regular 20 to 30 minute blood sampling to estimate plasma osmolality and ADH. In nephrogenic diabetes insipidus, ADH values are above the normal reference range, whereas in cranial diabetes insipidus, values are at the lower end of or below the normal reference range.

MANAGEMENT

Treatment for hypopituitarism can be separated into

Table 5: Endocrine Replacement Therapy for Hormone Deficiencies

Hormone Deficiency	Replacement Hormones and Typical Daily Dose Range (Oral, if Not Stated Otherwise)
Growth hormone	Please refer to Table 13-7 in the section Growth Hormone Deficiency.
Gonadotropins (female)	Estrogen:
	Estradiol valerate: 1-2 mg, transdermal: 25-100 µg
	or conjugated equineestrogens: 0.625-1.25 mg
	PLUS Progesterone (examples):
	Norethisterone, 0.7-1 mg, transdermal: 170-250 µg
	or Levonorgestrel, 250 µg, transdermal: 7 µg
	or Medroxyprogesterone acetate, 5 mg
Gonadotropins (male)	Testosterone:
	Intramuscular (as testosterone esters): 250 mg every 2-3 wk
	or Transdermal: 5-7.5 mg
	or Implant: 600-800 mg every 4-6 mo
Thyroid-stimulating hormone	Thyroxine, 75-200 µg/day
Adrenocorticotropic hormone	Glucocorticoid (preferred schedule): Hydrocortisone, 10 mg morning, 5 mg noon, 5 mg evening, to 10 mg t.i.d.
Prolactin	Nil
Antidiuretic hormone	Desmopressin (DDAVP), 300-600 µg (in divided doses); intranasal, 10-40 µg (in divided doses)

those therapies directed at the underlying disease process and endocrine replacement therapy Table 5.

HORMONE REPLACEMENT IN HYPOPITUITARISM

Endocrine replacement therapy should aim to mimic the normal hormonal milieu as far as possible, thus improving symptoms while avoiding overtreatment.

GROWTH HORMONE DEFICIENCY

GH secretion is greater in younger individuals than in older ones, and in women than in men. Therefore the starting dose of GH in young men and women is 0.2 and 0.3 mg/day, respectively, and in older individuals 0.1 mg/day (Table 6). Dose determination based on body weight is not recommended because of large interindividual variation in absorption and in sensitivity to GH, as well as the lack of evidence that a larger replacement is required for heavier individuals in adults. GH is administered in the evening to mimic the greater secretion of GH at night. Dose escalation should be gradual, individualized, and guided by clinical and biochemical response. Long-acting preparations of human GH are under evaluation for long-term safety and efficacy.

Table 6: Treatment Guidelines for Growth Hormone (GH) Replacement in Adult GH Deficiency

Pretherapy	Adequate replacement of other hormone deficiencies
	Pituitary imaging
	Body composition
	IGF-1, BSL, lipids
Starting dose	0.2 mg/day for men and 0.3 mg/day for women
Adjustments	Small monthly increment, 0.01-0.15 mg/day
Monitor	IGF-1 (dose titration)
	BSL, lipids
	Weight, body composition, quality-of-life measures
Side effects	Edema, arthralgia, myalgia, paresthesia
Dosage considerations	Avoid weight-based regimens.
	Women require more GH than men.
	Elderly require less GH than the young.
	Requirements are greater with oral than with transdermal estrogen therapy in women.
Contraindications	Malignancy, intracranial hypertension, proliferative retinopathy

BSL, Blood sugar level; *IGF-1,* insulin-like growth factor-1.

Serum IGF-1 is the most useful biochemical marker of GH response, the level of which should be maintained within an age-adjusted normal range. Clinical monitoring should include physical examination, including anthropometric measurements such as waist circumference and skin folds, and careful history, with particular attention to quality-of-life questions, assessment of body composition with dual x-ray absorptiometry and lipid measurements.

GONADOTROPIN DEFICIENCY

In both sexes, sex steroid replacement therapy is important for the maintenance of normal body composition, skeletal health, and sexual function, and it is the most appropriate

form of replacement therapy in patients not desirous of fertility.

Estrogen Replacement

In women, this can be provided by many standard hormone replacement therapy preparations. Progesterone must be given (cyclically or continuously) in all women with an intact uterus to prevent the possible effect of unopposed estrogen on the endometrium, that is, dysfunctional bleeding or endometrial cancer. The dose of estrogen should not be supraphysiologic (as in the oral contraceptive pill) unless a clear indication, such as strong patient preference, exists, or a patient with partial gonadotropin deficiency still has occasional menstrual cycles, along with a desire for contraception. Although estrogen can be delivered as a tablet, patch, gel, or implant, a nonoral route is recommended because of reduction of insulin-like growth factor (IGF)-1 and fat oxidation by oral estrogen. However, an international surveillance study on 315 hypopituitary women taking estrogen replacement demonstrated significant predominance of oral versus transdermal estrogen use (86% vs. 14%). Women on oral estrogen had a significantly greater waist/hip ratio after GH treatment, with lower IGF-1 levels at the end of the study period on twice the GH dose received by women on transdermal estrogen. Therefore a nonoral route is highly recommended.

Androgen Replacement

The choice of preparation of androgen replacement depends on local availability and patient preference. IM injection of testosterone can be associated with disturbing fluctuations in sexual function, energy level, and mood, mirroring the changes in testosterone concentrations. Transdermal testosterone systems, which are an alternative, are available as patch systems (nonscrotal or scrotal) or as the recently introduced testosterone gel. Both formulations are able to maintain physiologic testosterone profiles in most patients, but skin irritation, the need for scrotal shaving, and drying time after gel application are some of the potential drawbacks of both transdermal systems. Testosterone undecanoate has become available as an intramuscular injection, which achieves stable serum testosterone levels over a 10- to 14-week period. This new preparation has essentially replaced testosterone implants as replacement therapy.

Androgen replacement therapy should always be monitored to ensure physiologic mean testosterone levels. Suboptimal replacement doses result in low trough levels, whereas supraphysiologic doses can promote secondary polycythemia and progression of prostate cancer; therefore, regular monitoring of hemoglobin and prostate-specific antigen is recommended.

Gonadotropin and Gonadotropin-Releasing Hormone Therapy

In the hypogonadotropic hypogonadal patient, fertility can be achieved with gonadotropin therapy in both men and women. The choice of therapy lies between gonadotropin replacement and GnRH. The former is the traditional therapeutic approach; initially, LH "activity" is provided by human chorionic gonadotropin (hCG) administered subcutaneously (SC) or IM at a dose of between 1000 and 2000 IU, two to three times weekly. Spermatogenesis is unlikely within the first 3 months of therapy. Treatment with hCG alone is continued for 6 months, with regular sperm counts to monitor progress. If adequate spermatogenesis is not achieved, then FSH in the form of human menopausal gonadotropin (hMG) or a recombinant FSH is added. The dose of FSH is increased if adequate spermatogenesis is not achieved after 6 months of combination therapy. The alternative regimen in patients with idiopathic hypogonadotropic hypogonadism and Kallmann's syndrome is pulsatile GnRH therapy. GnRH is administered SC via a catheter attached to a minipump. This regimen appears to offer few advantages over gonadotropin therapy in men but may cause less gynecomastia. Both regimens may take up to 2 years to achieve adequate spermatogenesis.

In women with hypogonadotropic hypogonadism, pregnancy rates up to 80% are reported after therapy with pulsatile GnRH or gonadotropins. Again, the choice of therapy lies between gonadotropin therapy and pulsatile GnRH, but obvious advantages accrue to GnRH therapy if the patient has enough residual gonadotroph function. Pulsatile GnRH therapy is more likely than hMG to result in development and ovulation of a single follicle, thereby reducing the risks for ovarian hyperstimulation and multiple gestation. However, in practice, GnRH therapy may not be practicable, and in more than 50% of women with organic pituitary disease, residual gonadotroph function is not sufficient to support this method.

ADRENOCORTICOTROPIC HORMONE REPLACEMENT

The modern approach to glucocorticoid replacement is to mimic physiologic levels, ensuring sufficiency during times of acute illness, and to prevent over-replacement, which is associated with adverse metabolic outcomes. Patients must be educated to increase the replacement dose twofold to threefold in case of an intercurrent illness or when undergoing surgery. Patients should wear an appropriate Medic-alert bracelet or necklace and should be issued an IM hydrocortisone pack and taught how to self-administer in the event of protracted vomiting. Hydrocortisone directly replaces the missing hormone. Cortisone acetate is metabolized to cortisol and has a slower onset of action with longer biological activity. Both prednisolone and dexamethasone have longer half-lives, thus allowing daily administration. Generally, the lowest replacement dose tolerated by the patient is preferred (10 to 20 mg/day). Indeed higher serum concentrations of total cholesterol, low-density lipoprotein, triglycerides, and waist circumference were observed with increasing doses of glucocorticoid levels in a study comparing the metabolic phenotypes of patients with growth hormone deficiency treated with different formulations and doses of glucocorticoids. Doses should be divided to suit individual needs.

THYROID-HORMONE STIMULATING HORMONE DEFICIENCY

Secondary hypothyroidism is treated with thyroxine (T_4) replacement therapy, as is primary hypothyroidism. The normal starting dose in a young patient without evidence of cardiac disease is 1.5 mcg/kg/day. Lower starting doses are used in the elderly and in patients with evidence of ischemic heart disease. In patients with suspected hypopituitarism, thyroxine therapy should

be delayed until ACTH deficiency has been excluded or treated, because the risk for worsening the features of cortisol deficiency is present. Goal of replacement is to be to restore the serum-free T_4 concentration to the normal range. Measurement of TSH is unhelpful in the monitoring of T_4 replacement therapy in secondary hypothyroidism.

ANTIDIURETIC HORMONE DEFICIENCY

Desmopressin is the drug of choice for the treatment of ADH deficiency. It is available in a number of preparations, including oral, intranasal, parenteral, and the recently available oral form. Dosages vary as much as 10-fold between individuals, with no apparent relation to age, sex, weight, or degree of polyuria. The drug should be started at low dose and increased gradually until urine output is controlled. Overdosage carries a risk for hyponatremia, and sodium levels should be checked after therapy is commenced or changed.

CONCLUSIONS

Hypopituitarism increases morbidity and mortality in affected patients. The extent to which GH deficiency contributes to such excess morbidity and mortality awaits confirmation from longer-term studies. Adequate and appropriate hormone replacement is mandatory in the treatment of hypopituitary patients. Based on global evidence of efficacy and safety, adults with GH deficiency should also have replacement with GH, a principle consistent with the tenet of hormone replacement for hormone deficiency in the practice of endocrinology.

The modern management of hypopituitarism and GH deficiency should also focus on their prevention. By restriction of surgery to experienced centers and replacement of conventional radiotherapy with stereotactic surgery, the incidence of long-term hypopituitarism will be significantly reduced. Furthermore, greater use of medical therapy for acromegaly with somatostatin analogues and a GH-receptor antagonist should mean fewer hypopituitary patients in the future.

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