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**Hypopituitarism**

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# **ABSTRACT**

# Hypopituitarism refers to complete or partial failure of secretion of anterior and/or posterior pituitary hormones. It may arise as a result of congenital defects in the development of individual anterior pituitary cell types or hypothalamic function, acquired disease of the pituitary or hypothalamus, or from infundibular lesions which interfere with the hypothalamic control of the pituitary. The multiple aspects of normal pituitary function serve to predict the wide range of clinical manifestations of hypopituitarism which are determined by the severity, extent and duration of the condition. This chapter provides an overview on essential endocrine diagnostic investigations, treatment effect, safety and monitoring of specific hormone replacement. For complete coverage of this and related areas of Endocrinology, please visit our free online textbook, WWW.ENDOTEXT.ORG.

# **INTRODUCTION**

Hypopituitarism refers to complete or partial failure of secretion of anterior and/or posterior pituitary hormones. It may arise as a result of congenital defects in the development of individual anterior pituitary cell types or hypothalamic function, acquired disease of the pituitary or hypothalamus or from infundibular lesions which interfere with the hypothalamic control of the pituitary. The multiple aspects of normal pituitary function serve to predict the wide range of clinical manifestations of hypopituitarism which are determined by the severity, extent and duration of the condition. Onset may be in childhood or adult life and is generally permanent, requiring one or more specific hormone replacements.

# **ETIOLOGY OF HYPOPITUITARISM**

The major causes of hypopituitarism are shown in Table 1.

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| **Table 1: Causes of Hypopituitarism**  |  |
| Congenital  | Isolated pituitary hormone deficiency  | KAL, DAX-1, GH-1, GnRH, GHRH and TRH receptor mutations, Prader-Willi and Bardet-Beidl syndromes  |
| Multiple pituitary hormone deficiency  | PIT-1, PROP-1, HESX-1, SOX 2 mutations  |
| Neoplastic  | Pituitary adenoma  | Functioning and Non-functioning  |
| Peri-pituitary tumors  | Craniopharyngioma, Rathke's cleft cyst, meningioma, glioma, germ cell tumor, metastases (esp. breast, renal, lung), Langerhans cell histiocytosis  |
| Vascular  | Infarction  | Sheehan's syndrome, pituitary apoplexy, Aneurysms  |
| Inflammatory/Infiltrative /Immunological |  | Sarcoidosis, Wegener's granulomatosis, giant cell granuloma, lymphocytic hypophysitis, haemochromatosis, CTLA-4 inhibitors  |
| Infection  |  | Tuberculosis, syphilis, mycoses  |
| Post-irradiation  |  | Pituitary, nasopharyngeal, cranial  |
| Miscellaneous  |  | Empty sella, Traumatic brain injury |

# **Congenital**

Formation of the normal pituitary during embryonic development depends on the juxtaposition of cells of neurectodermal origin, which form the posterior pituitary, and endodermal cells derived from the primitive stomadeum, which form the anterior pituitary. Congenital forms of hypopituitarism are best considered as being derived either from hypothalamic or pituitary origin. Defects of RPX/HESX-1, PROP-1, and PIT-1 are associated with varying degrees of inherited hypopituitarism in humans (1). Autosomal dominant mutations of the arginine vasopressin-neurophysin II gene give rise to familial antidiuretic hormone (ADH) deficiency (cranial diabetes insipidus -CDI). Congenital multiple pituitary hormone deficiency (MPHD) may be associated with hypoplasia of the anterior pituitary and ectopic location of the posterior pituitary in a superior position; the underlying mechanism for this condition, once thought to be a consequence of birth trauma, remains undetermined but a congenital molecular defect is likely.

Hypogonadotropic hypogonadism is a recognized feature of both Prader-Willi and Bardet Biedl syndromes. The salient features of the currently described transcription factor defects are indicated below.

# HESX-1 MUTATIONS

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HESX-1 is a member of the homeobox gene family. It is expressed as a prelude to the development of Rathke's pouch. Mutations of the HESX-1 gene in humans are associated with septo-optic dysplasia and evolving hypopituitarism. Septo-optic dysplasia is characterized by the classical triad of optic nerve hypoplasia, midline neuroradiological abnormalities such as agenesis of the corpus callosum, and pituitary hypoplasia with consequent panhypopituitarism (2). Expression of the HESX-1 gene precedes expression of PROP-1 and PIT-1, and its consequences are more extensive.

# PIT-1 DEFECT

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PIT-1 is a pituitary specific transcription factor found in somatotrophs, lactotrophs, and thyrotrophs in the anterior pituitary gland from early fetal development and throughout life. Autosomal recessive defects of PIT-1 are associated with combined deficiencies of growth hormone (GH), prolactin and thyroid stimulating hormone (TSH)(3;4). Humans with PIT-1 mutations generally do not release detectable amounts of GH after GHRH stimulation.

# PROP-1 DEFECT

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The PROP-1 gene encodes a transcription factor with a single paired-like DNA-binding domain. Individuals with a single inactivating mutation in PROP-1 have deficiencies of luteinizing hormone (LH), follicle stimulating hormone (FSH), GH, Prolactin and TSH (5). Their pituitary glands may be small, normally sized, or large with extrasellar extension. Pituitary degeneration may produce acquired deficiency of adrenocorticotropic hormone (ACTH). Growth restriction and GH responses to GHRH stimulation are more variable in children with PROP-1 mutations. This variability does not seem to be dependent on the type of PROP-1 mutation because variability exists within sibships. PROP-1 mutations appear to be much more common than PIT-1 mutations as a cause of multiple pituitary hormone deficiency (MPHD) (6;7). Clinical suspicion of these mutations should be high in any individual with early onset MPHD, even in those with an intrasellar or suprasellar mass lesion.

# KAL

Isolated gonadotropin deficiency with hyposmia (Kallmann's syndrome) may be inherited as an X-linked disorder, autosomally or occur sporadically. The X-linked disorder occurs in approximately 1/10,000 to 60,000 live births (8) and a mutation in the KAL-1 gene is the basis for the disease. Gonadotropin-releasing hormone (GnRH) neurons develop in the medial olfactory placode and, during embryonic development, migrate to the hypothalamus; the KAL protein is essential for the initiation and maintenance of this process. Patients with the disorder usually present in late adolescence with delayed pubertal initiation or progression and characteristically exhibit hyposmia. They may develop eunuchoid proportions and usually demonstrate hypotrophic testes and a short penis; other features which are specific to X-linked Kallmann's syndrome include unilateral renal agenesis and synkinesis (mirror movements) whereas midline facial defects, choanal atresia, short metacarpals, malrotation of the gut and ocular coloboma are more common in autosomal and sporadic forms of the condition.

# DAX-1

Mutations in DAX-1, another X chromosome gene, cause hypogonadotropic hypogonadism in association with congenital adrenal hypoplasia in males. DAX-1 encodes an orphan nuclear hormone receptor within a novel DNA-binding domain, that has a critical role in the development of the hypothalamus, pituitary, adrenal and gonads (9). DAX-1 appears to influence the maintenance of testicular epithelial integrity and spermatogenesis.

# GH1 GENE MUTATIONS

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Mutations in the major GH gene, GH1, result in severe isolated GH deficiency and may be familial with either a dominant or recessive pattern of inheritance. Other single gene mutations affecting individual anterior pituitary hormones or pituitary receptors for hypothalamic peptides are indicated in Table 1.

# SOX 2

SOX2 belongs to the SOX family of transcription factors which are expressed in various stages of embryonic development and cell differentiation and play critical roles from the earliest stages of development, in particular expression of anterior neuroectoderm. De novo truncating mutations of SOX2 are found in individuals with bilateral anophthalmia and anterior pituitary hypoplasia and often hypopituitarism (10;11)

# **Tumors**

Pituitary adenomas are the most common cause of adult-onset hypopituitarism (12;13). Craniopharyngiomas are numerically the next most prevalent and may present as sella and/or suprasellar masses.

## PITUITARY ADENONA

Pituitary tumors can be non-functioning or secrete one or more anterior pituitary hormones. They are classified according to size and the presence of extrasellar extension; magnetic resonance imaging (MRI) permits accurate measurement of maximum diameter and tumors are conventionally classified as microadenomas (less than 10mm), macroadenomas (between 10 and 40 mm in diameter), and giant adenomas (> 4 cm) (14). The reported prevalence of pituitary tumors is approximately 10 per million with an average annual incidence of approximately 30 per million depending on tumor type, age and gender with the highest incidence occurring in pre-menopausal women. Pituitary adenomas may cause typical clinical syndromes resulting from hypersecretion of one or more anterior pituitary hormones. Approximately 25-30% will not present with these symptoms, so they will only be detected when tumor expansion and local compression of the surrounding structures emerges. Postmortem studies reveal a prevalence of incidental intrasellar adenomas of 10-20%.

Clinically non-functioning pituitary adenomas (NFPA) are non-or low grade-secreting tumors which frequently synthesize and secrete free alpha or beta glycoprotein subunits but do not cause clinically recognized symptomatology. In contrast to secreting pituitary tumors, no accepted medical therapy exists; therefore, the treatment of choice is surgical debulking, often followed by external radiation therapy. Pituitary tumors which hypersecrete will result in clinical syndromes of acromegaly, hyperprolactinemia, Cushing's disease, and secondary hyperthyroidism.

## CRANIOPHARYNGIOMAS

Craniopharyngiomas are benign neoplastic lesions which are presumed to originate from the embryological remnants of Rathke's pouch. They may be located in the suprasellar region, within the sella or both and because of infiltration of surrounding structures they may have extensive adverse consequences. They account for 1% of all intracranial tumors in adults and 6-13% of intracranial tumors in children (15). Peak incidence is in the first decade with a subsequent increase in incidence between 50-60 years of age. Adamantinomatous craniopharyngiomas occur in children and typically contain both cystic and solid components; the cystic fluid contains a lipid rich secretion. By contrast, squamous papillary craniopharyngiomas develop in adults and are rare in younger patients. They are predominantly solid tumors with small well-defined cavities containing less lipid rich fluid. Craniopharyngiomas in adults have a generally better prognosis in respect to endocrine, visual and other neurological deficits than those in children (16).

## RATHKE’S CYSTS

Rathke's cysts are epithelial cysts that are thought to originate from the remnants of Rathke's pouch. Their location can be intrasellar, with or without suprasellar extension and, in rare cases, purely suprasellar. They present more commonly in adults, in contrast to craniopharyngiomas (17). Symptomatic Rathke's cleft cysts may result in amenorrhea/galactorrhea by causing disinhibition hyperprolactinemia, hypogonadism in the male, visual disturbance and headache. The diagnosis of an intrasellar Rathke's cyst cannot be made with absolute certainty on radiological grounds and differentiation between craniopharyngiomas and Rathke's cysts can be difficult, due to their clinical and radiologic similarities. Definitive diagnosis is often only made histologically.

## PERIPITUITARY TUMORS

Perisellar meningiomas are well circumscribed masses originating from the sphenoid ridge and are associated with a variable amount of hyperostosis. Most meningiomas are single, but may occasionally be multiple, the latter almost exclusively in females.

Primary intracranial germ cell tumors are neoplasms which arise from aberrantly migrated primordial germ cells. Histologically, the tumor types are similar to those occurring in the gonads and are classified as germinomas (similar to seminomas and dysgerminomas) and non-germinomatous germ cell tumors which may consist of teratomas, yolk sac tumor, embryonal carcinomas and choriocarcinomas. Their incidence varies geographically, accounting for 2-3% of all childhood primary CNS tumors in Western countries, but 4-15% in Japan (18-20). The clinical presentation is most commonly in the first two decades of life with diabetes insipidus, visual failure and hypopituitarism. A recent report has highlighted the favorable response to a combined chemotherapy-radiotherapy protocol (20).

Metastasis to the pituitary gland may present as an intrasellar mass resulting in hypopituitarism, diabetes insipidus or pressure effects. In a published series of 500 consecutive autopsy examinations of cancer patients in whom the pituitary fossa and gland were examined, pituitary metastases were found in 3.6% (21). Pituitary metastases have been described in patients with primary malignant tumors of breast, lung, kidney, thyroid, bladder, uterus, pancreas, and colon.

## **Vascular**

The term pituitary apoplexy denotes the clinical consequences of hemorrhage or infarction in a pre-existing adenoma. The expansion of the mass to neighboring cranial nerves, cavernous sinus, optic pathways, or diencephalon results in localizing signs or altered conscious state. It commonly presents with sudden onset of severe headache, visual disturbance or opthalmoplegia due to cranial nerve (CN III, IV or VI) palsies (22). The clinical syndrome of pituitary apoplexy usually evolves fully within hours to two days. The incidence is reported to be in the order of 0.6-9.1% of surgically treated pituitary adenomas (23) and the age range of occurrence is broad, from the first to ninth decade. Apoplexy is usually spontaneous, but an important predisposing factor is hypertension; systolic and/or diastolic hypertension was seen in 26% of patient in a retrospective analysis (24). Other reported predisposing factors include diabetes mellitus, radiation therapy, anticoagulant therapy, bleeding disorders, head trauma, sudden changes in arterial or intracranial pressure (for example, during carotid angiography), bromocriptine, and postpartum hemorrhage (Sheehan's syndrome). Sheehan's syndrome denotes pituitary necrosis after postpartum hemorrhage and hypovolemia; it may cause hypopituitarism either immediately or after a delay of several years, depending on the amount of tissue destruction and is rare with modern obstetric care (25).

Suprasellar or intrasellar aneurysms of the carotid arteries or suprasellar aneurysms of the anterior or posterior communicating arteries may present as an expanding mass within the fossa. Intrasellar aneurysms may lead to hypopituitarism. Histologically, typical degenerative sclerotic changes of the arterial wall are found with chronic inflammatory changes. Occasionally an aneurysm may result in the development of an arteriovenous fistula in the cavernous sinus.

# **Immunological/Inflammatory Disease**

Inflammatory lesions of the pituitary gland will clinically and radiologically mimic pituitary tumors with mass effects causing headaches, visual field impairment, and variable degrees of hypopituitarism.

Lymphocytic hypophysitis classically presents as a pituitary mass lesion with partial hypopituitarism, particularly in relation to pregnancy (26). It has been speculated that many cases of pituitary failure occurring postpartum, which had been attributed to Sheehan's syndrome, may in fact have been caused by lymphocytic hypophysitis (27;28). In this condition, the interstitial tissue of the adenohypophysis is more or less densely infiltrated by lymphocytes and plasma cells. As a result, necrosis of hormone-producing cells in the anterior pituitary and subsequent fibrosis is seen. The primary etiology is thought to be autoimmune, because the histological findings are similar to other organ-specific autoimmune diseases. (29;30) Partial hypopituitarism, commonly isolated ACTH deficiency, or with TSH deficiency, is seen in approximately 80% of patients, with LH and FSH tending to be preserved.

Sarcoidosis is a multisystem disorder, characterized by the presence of non-caseating granulomas; it most often affects the lungs and the reticuloendothelial system although virtually any organ can be involved. Central nervous system sarcoidosis occurs with a 5-15% incidence (31;32) and symptoms of a hypothalamic-pituitary disease are present in less than 1% of all patients (33). Neurosarcoidosis affects primarily the leptomeninges of the brain base and posterior fossa; subsequently a local granulomatous infiltration of the hypothalamus and/or pituitary occurs. Coexisting optic nerve infiltration occurs in many patients causing central and peripheral visual defects. In terms of anterior pituitary function, LH, FSH and GH deficiency are frequent but TSH and ACTH are relatively preserved.

Langerhans cell histocytosis is a rare disease characterized by aberrant proliferation of a specific dendritic (Langerhans) cell belonging to the monocyte-macrophage system (34). Deposits occur at multiple sites within the body, and frequently involve the hypothalamo-pituitary axis (35). Diabetes insipidus is a well recognized and common feature of this condition but anterior pituitary dysfunction also occurs frequently.

Ipilimumab, a cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitor, is an IgG1 monoclonical antibody against CTLA-4 that is used for metastatic melanoma and other tumors. As a consequence of immune activation, secondary hypophysitis has been reported in 10-15% of ipilimumab treated patients (36). In severe hypophysitis, immune reactions induced extensive necrosis of the adenohypophyseal architecture. Pituitary autoantibodies against thyrotrophs, corticotrophs, and gonadotrophs were identified in patients with ipilimumab induced hypophysitis (37). Patient usually present with headache and fatigue, the diagnosis of hypopituitarism with multiple deficiencies is made 2-3 months or later after initiation of ipilimumab. Central hypothyroidism is most frequent, followed by central hypocorticism and hypogonadism.

# **Infections**

Bacterial pituitary sepsis is a rare phenomenon which may arise as a consequence of hematogenous spread or by extension from sinus or meningeal sepsis with subsequent pituitary abscess formation. Small pituitary abscesses have been described at post mortem in patients dying from septicemia. Chronic infection predisposes to necrosis of pituitary tissue with subsequent hypopituitarism. Pituitary tuberculomas may present as space occupying lesions (38) but this appears to be a very rare phenomenon; isolated manifestation of the disease is rare and it is more likely to occur in the context of generalized tuberculous infection with meningitis. Gumma formation, as a manifestation of tertiary syphilis, may occur in the sella region but is extremely rare.

Fungal pituitary infection may occur as a complication AIDS (39) and pituitary necrosis with hypopituitarism has been described in toxoplasmosis (40).

# **Radiation Therapy**

Hypopituitarism is a common complication of irradiation administered for pituitary adenomas, head and neck tumors, intracranial malignancy or as adjunctive cranial irradiation for acute lymphoblastic leukemia. Although fractionated radiotherapy with daily doses of <200 cGy is well tolerated and safe in terms of neurological sequelae, the majority of patients who have undergone external irradiation will manifest some degree of pituitary failure during long term follow up. In general, this is a relatively late complication and is rarely evident in less than 3 years in patients with completely normal baseline pituitary function. Growth hormone reserve is particularly susceptible and is progressively more likely with time so that periodic assessment of residual pituitary function is mandatory; a five year follow up study after external pituitary irradiation therapy reported, 100% GH deficiency, 91% LH-FSH deficiency, 77% ACTH deficiency and 42% TSH deficiency (41).

# **Traumatic Brain Injury**

Traumatic brain injury (TBI) is common, the prevalence of endocrine dysfunction in these patients ranges from 15-68% (42), with estimated annual incidence 30 patients per 100,000 population per year. Abnormal axes during the acute phase of injury may recover over time, but other pituitary hormone deficits may evolve later even at 6 months after the initial insult. A prospective longitudinal study looking at patients with severe TBI, found that 6% of their patients had proven severe GHD when evaluated after 12 months (43) . Multiple pituitary deficiencies or isolated pituitary deficiencies (TSH or ACTH) were very rare.

# **Empty Sella Syndrome**

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An enlarged empty sella may be primary (due to a congenital diaphragmatic defect) or secondary to surgery, radiation, or pituitary infarction. The majority of patients with congenitally empty sella have normal pituitary function. Hypopituitarism (and/or hyperprolactinemia) may be found in instances due to previous pituitary disease. Occasionally, a cystic pituitary mass may simulate an empty sella on CT or MRI, necessitating a cisternogram for precise delineation.

# **CLINICAL MANIFESTATION OF HYPOPITUITARISM**

The clinical impact of pituitary insufficiency is dependent on the extent and severity of hormone deficiencies (Table 2), the duration of the disease, and the age of onset; childhood onset hypopituitarism has consequences for all aspects of somatic development in addition to the pathophysiological effects of specific hormonal deficiencies. In addition, there may be clinical features relating to the mass effect of causative lesion or specific consequences attributable to hypersecretion of prolactin, GH, ACTH, or TSH from individual tumor types. Hypopituitarism classically develops in sequential order with the secretion of growth hormone, then gonadotrophins being affected first, subsequently followed by TSH and ACTH. Prolactin deficiency is rarely seen, except in Sheehan's syndrome which is associated with failure of lactation. ADH deficiency is almost never seen as a primary feature of pituitary adenomas but is a usual presenting manifestation of germ cell tumors, pituitary metastases, and granulomatous disorders.

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| **Table 2: Summary of Clinical Features of Hypopituitarism** |
| **Hormone deficiency** | **Presentation** | **Symptoms and signs** |
| Adrenocorticotrophic hormone | Acute | Fatigue, weakness, dizziness, nausea, vomiting, circulatory failure. As in Addison's disease, except lack of hyperpigmentation, absence of hyperkalemia  |
| Chronic | Tiredness, pallor, anorexia, nausea, weight loss, myalgia, hypoglycemia  |
| Gonadotrophins  | Children | Delayed puberty  |
| Men | Impaired fertility, impotence, reduced libido, decreased muscle mass and strength, decreased bone mass, decreased erythropoiesis and hair growth, fine wrinkles, testicular hypotrophy  |
| Women | Amenorrhea, oligomenorrhoea, infertility, loss of libido, dyspareunia, fine wrinkles, breast atrophy, osteoporosis, premature, atherosclerosis |
| Thyroid-stimulating hormone | Children | Growth retardation  |
| Adult | Fatigue, cold intolerance, constipation, weight gain, dry skin, slow relaxing reflexes  |
| Growth hormone | Children | Growth retardation, short stature, increased adiposity  |
| Adult | Reduced exercise capacity, impaired psychological wellbeing, increased cardiovascular risk, increased central obesity, reduced lean body mass  |
| Prolactin |   | Failure of lactation  |
| Antidiuretic Hormone |   | Polyuria, polydipsia including nocturnal  |

## **Growth Hormone Deficiency**

GH deficiency (GHD) in adults is characterized by decreased exercise tolerance, decreased mood and general well-being, decreased quality of life, central adiposity, hyperlipidemia, increased predisposition to atherogensis, and reduced bone remodelling activity. Fine facial wrinkles may result from a deficiency of growth hormone in addition to hypogonadism. The patient will usually have dry thin skin which contrasts with the thickened skin and increased sweating found in acromegaly. Adults with long-standing GHD are often overweight, have reduced lean body mass, increased fat mass, especially visceral fat, relative insulin resistance, and reduced total bone mass. There is a reduction in cardiac and physical performance. GHD is associated with increments in total cholesterol, LDL-cholesterol, and apolipoprotein B (44-46). Studies in Sweden and the UK, in patients with hypopituitarism receiving controlled thyroid and steroid hormone replacement but without growth hormone replacement, have demonstrated an approximately two-fold increase in cardiovascular mortality compared to the general population. (45) and the increase in standardized mortality ratio is more striking in females (47).

The accumulating evidence suggests that the cardiovascular morbidity cannot be explained solely by suboptimal glucocorticoid' gonadal steroid or thyroid hormone replacement and unsubstituted growth hormone deficiency is probably an important contributing factor. The decreased bone mineral density found in GHD is associated with increased fracture risk (48).

The clinical features of anterior pituitary hypofunction described in this chapter will concentrate on adult onset hypopituitarism. Many of the symptoms and signs of a specific pituitary hormone deficiency are similar to those that occur in patients with a primary deficiency of the target gland, but there are exceptions.

## **Adrenocorticotrophic Hormone Deficiency**

Cortisol and adrenal androgen secretion are ACTH dependent and are variably decreased in hypopituitarism. Patients with combined ACTH and LH deficiency are completely androgen deficient, a phenomenon which may be particularly important when considering optimum regimens for gonadal steroid replacement in females. Because aldosterone secretion is largely determined by activation of the renin-angiotensin system, it is relatively preserved in the hypopituitary patient. Major symptoms of ACTH deficiency are non-specific and include fatigue, weakness, headache, anorexia, weight loss, nausea, vomiting, abdominal pain, myalgia, and decreased concentration. Hypoglycemia may be present at diagnosis. Hyponatremia is common and is attributable to reduced renal free water clearance consequent upon cortisol deficiency with an additional contribution from TSH deficiency if present. Hyperkalemia, which is a frequent finding in primary adrenal failure, does not occur in hypopituitarism because of the relative preservation of aldosterone secretion. Over and above the effects of secondary hypogonadism, reduced adrenal androgen production further exacerbates loss of body hair, particularly in women.

## **Gonadotrophin Deficiency**

The gonadotrophins are responsible for gonadal sex-steroid production, secondary sexual development, maintenance of secondary sexual characteristics and fertility.

Gonadotrophin deficiency in males results in secondary hypogonadism with consequent testosterone deficiency; clinical features include loss of libido, erectile dysfunction, oligospermia, reduced erythropoiesis, and decreased lean body mass. Testosterone, via estradiol derived by aromatization, has an important role in the regulation of bone mineralization and, therefore, hypogonadism results in decreased bone mineral density.

Clinical features of secondary hypogonadism in females include oligo/amenorrhea, breast atrophy, decreased secondary sexual hair (especially if combined with ACTH deficiency), and predisposition to osteoporosis.

## **Thyroid Stimulating Hormone Deficiency**

The clinical features of secondary thyroid failure are similar to those of primary thyroid failure with the exception that weight gain is less likely to be a feature if ACTH deficiency is also present. Classical features include cold intolerance, fatigue and myalgia. Physical examination may demonstrate periorbital edema and delayed reflex relaxation. Hyponatremia and normochromic normocytic anemia are also seen, the former being exacerbated by cortisol deficiency and the latter by secondary hypogonadism and GH deficiency.

## **Prolactin**

Mild hyperprolactinemia, due to lactotroph disinhibition by mass lesions, commonly co-exists with hypopituitarism. Measurement of serum prolactin is an essential investigation in all patients with pituitary disease, but the differential diagnosis of hyperprolactinemia requires careful consideration.

## **Antidiuretic Hormone Deficiency**

Cranial diabetes insipidus (CDI) is characterized by polyuria and polydipsia, due to decreased secretion of ADH by the neurosecretory cells terminating in the posterior pituitary. If the excessive water excretion exceeds intake, the patient will become progressively water deplete with eventual reduction in circulating volume. It is more common with tumors of the hypothalamus, pituitary metastases, lymphocytic hypophysitis, sarcoidosis, Langerhan's cell histiocytosis, craniopharyngiomas, and Rathke's cleft cysts. (49). It is also commonly seen post-neurosurgery and after head injury. Because cortisol is an essential pre-requisite for normal glomerular filtration and free water clearance, CDI is masked by co-existing ACTH deficiency only to become evident clinically after commencement of glucocorticoid replacement. CDI as a primary manifestation of pituitary adenoma is extremely unusual.

# **INVESTIGATION OF SUSPECTED HYPOPITUITARISM**

In hypopituitarism, basal serum hormone measurements may be all that is required to confirm the insufficiency; however, dynamic testing is mandatory for the diagnosis of partial deficiencies. Pituitary function testing is required for all patients presenting with pituitary disease and in patients in whom an evolving endocrine deficiency is anticipated, e.g. those who have received pituitary or cranial radiotherapy.

# **Baseline Investigations**

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Basal concentrations of the anterior pituitary hormones and hormones produced by their respective target glands should be measured. Serum samples should be taken unstressed, with no physiological or pharmacological manipulation, between 7 and 9am when serum cortisol and testosterone levels are highest. This is important given that the decision to proceed to dynamic testing is based on these levels. The pituitary hormones may remain within the normal range despite low levels of target hormones indicating that target gland failure is consequent upon understimulation by the pituitary. Baseline investigations (Table 3) are sufficient for the diagnosis of secondary hypothyroidism and hypogonadism and will also confirm virtually complete ACTH deficiency (50).

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| **Table 3: Baseline Investigation of Pituitary Function**  |
| 1. Adrenocortical axis: serum cortisol (0900)2. Thyroid axis: free T4, TSH3. Gonadal axis: men -testosterone (9am and fasting), SHBG, albumin, LH, FSH; women-estradiol, LH, FSH, progesterone (Day 21 if menstruating) 4. Prolactin 5. Insulin-like growth factor-1, growth hormone6. Paired plasma and urine osmolality  |

# **Dynamic Testing**

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Stimulation tests are used when hypofunction is suspected and are designed to assess the reserve capacity to form and secrete hormone. In contrast, suppression tests are used when endocrine hyperfunction is suspected and are designed to determine whether negative-feedback control is intact, as in the administration of glucocorticoids to inhibit corticotrophin secretion in suspected Cushing's syndrome or in the administration of glucose in suspected acromegaly. Dynamic pituitary function tests may assess the hypothalamic-pituitary unit (e.g. insulin tolerance test, glucagon and arginine tests) or directly stimulate the anterior pituitary with pharmacological doses of synthetic hypothalamic peptides and the pituitary hormone response measured (e.g. TRH, GnRH, GHRH tests).

## HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

Baseline and dynamic tests are valuable in diagnosis of ACTH deficiency. With virtually complete ACTH deficiency, the 0900 serum cortisol is less than 100 nmol/L, whereas if the serum cortisol is 400-500 nmol/L or more, ACTH deficiency is unlikely. (51-53). Therefore, dynamic testing of ACTH reserve is required if the basal serum cortisol measured lies between 100 and 400-500 nmol/L. The insulin tolerance test (ITT) or glucagon test may be used to assess the adequacy of the hypothalamic-pituitary-adrenal axis. If the patient is taking hydrocortisone this should be discontinued for 24 hours; prednisolone cross reacts in the cortisol assay and therefore should not be administered within 24hrs of investigation of adrenocortical reserve. The rationale of the ITT is to produce physiological stress in a controlled environment by inducing hypoglycemia with intravenous insulin. Hypoglycemia is a powerful stimulus which, in the presence of an intact hypothalamic-pituitary axis, stimulates GH and ACTH release and a rise in serum cortisol levels. Although the safety of ITT has been questioned, the only absolute contraindications are ischemic heart disease, epilepsy, or unexplained loss of consciousness, untreated hypothyroidism or hypoadrenalism, and glycogen storage disease (53). A decrement in plasma glucose to less than 2.2mmol/L is required for the test to be valid. With normal ACTH reserve the serum cortisol should rise to at least 550 nmol/L. Patients who show a normal cortisol response, can withstand major surgery without corticosteroid replacement; patients with subnormal responses but satisfactory basal values (>250 nmol/L) may not require regular replacement therapy but should be fully informed and carry a steroid card. All other patients with subnormal cortisol responses will require hydrocortisone replacement. The ITT should only be performed by fully trained staff in designated units. Hypoglycemia may occasionally require reversal with intravenous glucose (50% in adults but limited to 10% in children to avoid the risk of cerebral edema).

The glucagon stimulation test (GST) may be used for the assessment of ACTH/cortisol and GH reserve when the ITT is contraindicated (54). The subcutaneous injection of glucagon causes a transient rise in plasma glucose. During the subsequent fall in plasma glucose, ACTH and GH are released and measured. Serum cortisol cut off values are similar to those described for the ITT. Glucagon is less reliable than the ITT as a test of ACTH/ cortisol reserve; it is a less powerful stress stimulus and hence false positive results are a recognized problem.

The short Synacthen (Cortrosyn in the USA) test (SST) was originally introduced as a test for primary adrenal failure. It involves the intramuscular or intravenous injection of a pharmacological dose (250mcg) of synthetic ACTH, with measurement of the serum cortisol response at 30 and 60 minutes. The test does not distinguish primary from secondary adrenal insufficiency, and it cannot test pituitary ACTH reserve directly. The 30-minute serum cortisol response is advocated as a surrogate test of ACTH reserve and has been widely used because of its simplicity However, there is no study showing that a normal SST indicates that the hypothalamic-pituitary-adrenal axis is capable of responding normally to major illness or stress. Demonstrations of good correlations between peak serum cortisol responses on ITT and 30-minute responses on SST have been published and are intuitively predictable. However, false negatives with the SST are well recognized although this may be partially obviated by the use of lower synacthen doses (1mcg). Nonetheless, the concern about false negative results and the fact that assessment of GH reserve is also frequently required serve to limit the use of the SST in the investigation of pituitary function.

A recent study comparing the ITT, low dose ACTH, and GST in the evaluation of the HPA axis and GH-IGF-1 axis in patients with pituitary disorders concluded that all three tests were well correlated in terms of peak cortisol and GH response (55) . However, low dose ACTH stimulation gave a higher peak cortisol response. Therefore, the cut-off level for the diagnosis of insufficiency of the HPA axis needs to be individualized for each test.

## GROWTH HORMONE

Normal GH secretion is pulsatile, with four or six pulses per 24hr, mostly at night in association with REM sleep. A single measurement of serum growth hormone is rarely useful although the fortuitous coincidence of blood sampling at the time of a GH secretory peak may exclude growth hormone deficiency (GHD). A stimulatory test is therefore usually required to assess somatotroph reserve. Most, actions of growth hormone are mediated through hepatically or locally-derived insulin-like growth factor-1 (IGF-I). Measurement of a baseline serum IGF-I is a specific but insensitive test of growth hormone deficiency in patients with pituitary disease. Importantly, IGF-I declines with normal aging. In adult onset GHD, 30% of patients may have a serum IGF-I in the lower half of the age-related reference range the percentage increasing with age (56). Therefore, a low serum IGF-I, in an adequately nourished patient without liver dysfunction, strongly supports a diagnosis of GHD but a normal serum IGF-I cannot exclude it.

A rigid and precise biochemical diagnosis of GHD is required in the context of justification of growth hormone replacement (GHR). The ITT is one of the most reliable provocative tests of GH secretion and currently remains the test of choice for this purpose; it has the advantage of assessing ACTH reserve simultaneously. Severe GHD is defined as a peak GH response to insulin induced hypoglycemia of less than 3 ng/mL (9mU/L) (57). Obesity may blunt the GH response to dynamic testing so that the diagnosis of GHD should only be made in the context of structural pituitary disease or previous cranial irradiation and/or additional pituitary hormone deficits.

If the ITT is contraindicated an alternative test for assessment of GH reserve is required and glucagon, arginine and a combination of arginine and GHRH or growth hormone-releasing peptides may all be used for this purpose. The combination of GHRH plus arginine is the most powerful provocative test of GH secretion but appropriate normative data are required (58-60).

## PITUITARY-THYROID AXIS

In the appropriate clinical context, secondary hypothyroidism can be diagnosed on the basis of a low serum thyroxine (T4, total or free) in the presence of low or low normal TSH (TSH is rarely undetectable in hypopituitarism). However, it should be borne in mind that any systemic illness may produce a reversible reduction in serum T4 (sick euthyroid state).

Dynamic testing using thyrotrophin releasing hormone (TRH) has no diagnostic value for secondary hypothyroidism or predicting a risk of developing TSH deficiency. Although patients with hypothalamic disease may show a delayed response to TRH, this test is seldom used in pituitary reserve assessment. Furthermore, intravenous TRH may precipitate hemorrhagic infarction of pituitary adenomas.

## PITUITARY-GONADAL AXIS

Symptoms of sex steroid deficiency, menstrual disturbance, a low serum estradiol or low serum testosterone in the presence of normal or low concentrations of FSH/LH are the mainstay of diagnosis of hypogonadotropic hypogonadism. The gonadotrophin releasing hormone (GnRH) test has virtually no diagnostic value but is used to confirm gonadotroph reserve in the setting of pulsatile GnRH therapy for infertility.

## POSTERIOR PITUITARY FUNCTION

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Basal investigations include plasma and urine osmolalities obtained simultaneously. In overt CDI the plasma osmolality is usually raised in the presence of inappropriately dilute urine. The diagnosis of partial CDI is confirmed by means of a water deprivation test followed by demonstration of response to desmopressin (see Chapter on Posterior Pituitary).

# **Imaging the Pituitary**

Magnetic resonance imaging (MRI) is the optimum method of imaging, with computerized tomography (CT) as an acceptable alternative. The only disadvantage to MRI is its insensitivity in defining pathological calcification and lack of signal from corticated bone. Gadolinium contrast should not be used when performing an MRI in a pregnant woman (60A). CT may be required to demonstrate calcification in craniopharyngiomas and hyperostosis; it is also used by many surgeons to define skeletal anatomy prior to surgery.

# **MANAGEMENT OF HYPOPITUITARISM**

Hypopituitarism, once established, is usually permanent. However, resection of pituitary tumors may, on occasion, result in resumption of normal pituitary function.

Although a seemingly straightforward clinical exercise, hormone replacement therapy cannot simulate normal physiology precisely. With the exception of GHR and treatment of infertility, replacement therapy is achieved by administering target hormones. The aim of hormone replacement is to safely eliminate or minimize the symptoms and clinical signs of specific hormone deficiencies.

## **Hypoadrenalism**

Hydrocortisone, (cortisol) is now the most widely used form of glucocorticoid replacement in patients with primary and secondary adrenal insufficiency. There is no universal agreement regarding the appropriate dose, timing and monitoring of hydrocortisone replacement. Normal individuals demonstrate undetectable serum cortisol and ACTH when asleep at midnight, with a rise during the early hours of the morning to reach a peak at 0800-0900hr, followed by a steady decline throughout the rest of the waking day. There are variable peaks of cortisol secretion due to other factors such as stress, meals and exercise. Cortisone acetate requires conversion to hydrocortisone, under the influence of 11ß-hydroxysteroid dehydrogenase type 1 (11β-HSD1); the requirement for reductase conversion and the fact that the enzyme activity is altered in patients with GHD renders cortisone intuitively less satisfactory than hydrocortisone for replacement purposes. Prednisolone has been advocated by some on account of its longer duration of action than hydrocortisone. However, because it cannot be measured routinely, it is impossible to fine tune the replacement dose. The alternative synthetic glucocorticoid replacement, dexamethasone, is even less satisfactory because of wide interindividual variations in metabolic clearance rates.

Traditional hydrocortisone replacement utilized twice daily dosing but many patients report fatigue or headache in the afternoon on this regimen. There is evidence that many patients 'feel better' on thrice daily regimes (61). Recent cross-sectional studies did not demonstrate any superiority between thrice a day versus twice daily replacement in terms of quality of life (62) . The average daily requirement is approximately 20mg of hydrocortisone. This should be given as 10 mg on waking, 5 mg at lunchtime and 5 mg in the early evening. Enzyme-inducing drugs (especially, phenytoin, carbamazepine, and rifampicin) will increase metabolism of corticosteroids and should prompt an increment in replacement doses. Doses are therefore fine-tuned according to patients well-being and multiple serum cortisol levels (day curve, HCDC) taken during the day in many centers. (50;63). Some centers have attempted to utilize urine free cortisol measurements to adjust the hydrocortisone dose; however, this is unreliable because saturation of cortisol binding globulin (CBG) following oral hydrocortisone results in supraphysiological urine free cortisol excretion (64). The HCDC should demonstrate adequate levels of cortisol throughout the day, without excess peak (cortisol eg >1000nmol/l) or trough (eg <100nmol/l) levels before or after doses. Data on salivary cortisol day profiles needs further studies. Studies suggest that measuring salivary cortisol levels several times throughout the day may assist in titrating oral glucocorticoid replacement therapy (64A, 64B).

In clinical practice, there is no reliable measure to be certain if patients are receiving optimal glucocorticoid replacement therapy. As a result, patient may be over- or under- treated with resultant morbidity (65). There is a significant increase in 11β-HSD1 activity resulting in abnormalities in corticosteroid metabolism in patients with ACTH deficiency treated with conventional doses of hydrocortisone (66). In ACTH-deficient patients daily hydrocortisone dose of >20mg/day is associated with increase waist to hip ratio. The induction of 11β-HSD1 is associated with central adiposity and has an important role in the development of the metabolically adverse hypopituitary phenotype.

Conventional hydrocortisone cannot mimic the circadian rhythms of cortisol release; in particular the early morning rise in cortisol which declines slowly throughout the day. This has led to the development of a modified release formulation of hydrocortisone (MR-HC, Chronocort®) which can be taken late at night thus allowing a delayed and sustained release (67). A study in healthy men demonstrated that MR-HC 20mg and 10mg, given at 2300 and 0700 hours respectively, could achieve a near normal cortisol circadian rhythm (68). A subsequent phase II study demonstrated that the MR-HC mimics the normal circadian pattern closer to physiological baseline(69); however, the studied preparation is no longer available. An alternative modified formulation (Plenadren®) incorporates an immediate release and delayed release components, which displays diurnal plasma cortisol levels similar to physiological profile. Once daily Plenadren® has been shown to reduce weight, blood pressure and improve glucose metabolism when compared with thrice daily dosing(70).

The effects of continuous subcutaneous hydrocortisone infusion (CSHI) has been compared with conventional oral hydrocortisone (71) in patients with Addison’s disease. CSHI produced a more physiological circadian rhythm, normalization of morning ACTH and restoration of nocturnal serum cortisol levels. It also resulted in improvement in quality of life when compared with conventional oral dosing.

Patients with ACTH deficiency on hydrocortisone therapy will not respond to surgery, trauma, infections, and severe illnesses with increased cortisol concentrations. They therefore require supplemental hydrocortisone therapy with increased oral doses during minor disease, or administration of intramuscular hydrocortisone 100 mg every 6-8 hours with more severe disease or if oral intake is compromised. When intramuscular injections are contraindicated, a continuous intravenous infusion of hydrocortisone at a rate of 1-3 mg per hour will provide satisfactory replacement for the severely ill patient. Maintenance mineralocorticoid is not required since aldosterone secretion is usually preserved.

Patients should carry a 'steroid card' and wear a 'medic-alert' bracelet to indicate their requirement for supplemental hydrocortisone in the event of severe illness or trauma. They and their families should understand the importance of life long compliance, be taught to double the hydrocortisone dose in the event of minor illness and understand the need for parenteral glucocorticoid replacement if vomiting or diarrhea occurs. An 'emergency' ampoule of hydrocortisone should be provided for domiciliary emergency intramuscular injection and the patient instructed on its use.

Dehydroepiandrosterone (DHEA) is an androgen produced by the adrenal cortex and is also under the regulation of corticotrophin and is thus deficient in hypopituitarism. In hypopituitarism, DHEA supplementation (25-50mg per day) has shown benefit with respect to well-being and sexual function (72,73). Furthermore, in patients who are replaced with GH, DHEA can augment the IGF-I response hence leading to a reduction of GH dose in females (74). Currently, there is no licensed preparation of DHEA available, and it is considered to be a food supplement rather than a bioactive drug. Not all patients respond. Furthermore, the androgenic side effects such as greasy skin, acne, and increased body hair may be a limiting factor although generally responsive to dose reduction.

## **Secondary Hypothyroidism**

Synthetic levothyroxine sodium (for example, Synthroid) is the preferred form of replacement. It has a long half life, allowing a once daily dose. Liothyronine (T3) displays superior gastrointestinal absorption, but its short half life requires two to three daily doses. Use of T3 is largely restricted to thyroid cancer patients undergoing frequent isotopic imaging or treatment, and occasionally the initiation of thyroid hormone replacement when a gradual increase is desired.

Commencing thyroid hormone replacement in patients with severe, untreated ACTH deficiency may result in hypoadrenal crisis. In the situation of combined deficiency, hydrocortisone should always be commenced before thyroxine. The duration of hypopituitarism and presence of co-morbidities, especially ischemic heart disease, should be considered. Young patients with a short history of hypopituitarism and TSH deficiency may commence an initial thyroxine dose of 100mcg daily. On the other hand, in patients with a long history of hypopituitarism or elderly patients, a low dose of 25 -50mcg daily should be commenced, in order to minimize the risk of precipitation of cardiac events. Alternatively, replacement may be initiated with T3 followed by a cross over to T4 once safety is established.

Alteration of the hypothalamic-pituitary-thyroid axis following growth hormone replacement is well documented (75-77). Growth hormone deficiency will mask central hypothyroidism in a significant proportion of hypopituitary patients both in children and adults. It has been observed that apparently euthyroid hypopituitary patients will require commencement or an increase in thyroxine replacement following initiation of growth hormone replacement. A higher target serum free T4 in the upper half of the reference range is appropriate in the growth hormone deficient patient who is not on growth hormone replacement.

Unlike primary hypothyroidism, in which serum TSH is a sensitive marker of under-or over-replacement, there is no biochemical marker to indicate the optimum level of replacement in TSH deficiency. The serum free T4 is the best method for assessing replacement adequacy in hypopituitarism. By analogy with serum T4 levels in adequately replaced primary hypothyroidism, a conventional recommendation is to maintain serum free T4 in the upper part of the reference range for normal individuals (78). Serum total T4 levels are elevated artefactually by conditions which increase serum thyronine binding globulin, especially estrogen administration.

## **Gonadotrophin Deficiency**

Choice of replacement ranges from oral, transdermal, intramuscular or subcutaneous administration of gonadal steroids to gonadotrophin or gonadotrophin-releasing hormone therapy if and when fertility is desired.

## WOMEN

Estrogen replacement should be offered to all women with secondary hypogonadism under the age of 50 years in order to avoid immediate symptoms of estrogen deficiency and prevent premature reduction in bone mineral density. The addition of progesterone is mandatory if the uterus is intact in order to avoid unopposed estrogen stimulation of the endometrium with the attendant risk of hyperplasia and neoplasia. The standard regimen for replacement involves the daily administration of estrogen with progesterone co-administrated for 12-14 consecutive days during a 4-week cycle; menses occur cyclically after progesterone withdrawal. Alternatively, a continuous regimen may be employed in which estrogen and progesterone are combined. The latter may be preferred by older patients and there are no adverse effects described apart from unpredictable menstrual bleeding during the initial few months of therapy in a minority of patients.

Estrogen replacement can be administrated via the oral, transdermal and subcutaneous routes. Oral estrogens undergo extensive hepatic first-pass metabolism necessitating average doses of 1-2 mg estradiol, or equivalent, per day.

Transdermal preparations are usually applied twice weekly and provide 50-100mcg of estradiol per 24 hours in a cyclical combination with a progestagen. Skin irritation may occur but transdermal therapy is the first choice in patients with complex pituitary disease, since it avoids the effects of oral estrogen on other hormone binding proteins. Furthermore, in women on concomitant GH replacement, IGF-I generation is greater when transdermal rather than oral estrogen is used, therefore decreasing the dose of GH required.

Subcutaneous implants are inserted six monthly, but tachyphylaxis is a frequent problem and limits the value of this regimen.

There is evidence that in women aged 50-75, estrogen monotherapy or combined estrogen/progestin are associated with increased risk of invasive breast cancer and thromboembolism. In older women or women with pre-existing atherosclerosis, the data demonstrates that hormone therapy is not beneficial and is likely harmful (77A). In contrast, in younger women or women without pre-existing atherosclerosis studies suggest that hormone therapy is either modestly beneficial or neutral (77A). The decision on the use of hormonal therapy is complex and one must balance the risks and benefits (77B). The effect of selective estrogen receptor modulators (SERMs) have become available and raloxifene is licensed for this purpose. Raloxifene has very little effect on the vasomotor symptoms of estrogen deficiency. Tibolone, an agent with estrogenic, progestagenic and weak androgenic activity, can provide an alternative treatment for post menopausal symptoms and also exerts favorable effects on bone.

In some patients with combined LH/FSH and ACTH deficiency low libido may be a problem despite conventional estrogen and progesterone replacement. This may be a consequence of complete androgen deficiency and may respond to low dose testosterone replacement (e.g. 50-100 mg subcutaneous implants every 6 months). Oral combinations of estradiol and testosterone are also available. FSH and LH injections are necessary for fertility; recombinant forms of both are now available and this treatment is usually supervised through fertility clinics.

## MEN

Apart from relief of the symptoms of hypogonadism, androgen replacement is also important in maintaining bone integrity, muscle mass, and normal eythropoesis (79).

A common method of androgen replacement is as an intramuscular depot injection of testosterone ester (e.g. testosterone enanthate, 75-100mg intramuscularly weekly, 250mg intramuscularly every three weeks). The ensuing supraphysiological peaks and troughs of serum testosterone may lead to fluctuations in mood, libido and energy levels but treatment is generally very well tolerated. Depot testosterone injection has become available; testosterone undecanoate (Nebido), can be administrated intramuscularly every three months (80), and maintains physiological testosterone levels without major fluctuation.

Oral testosterone undecanoate is administered two or three times a day. It is extensively metabolized to dihydrotestosterone in the intestine and is absorbed via the lymphatic system. It is generally well tolerated and is most useful in patients with partial hypogonadism or in those who are unable to tolerate depot injections.

Testosterone pellets, implanted subcutaneously at a dose between 400-600mg, will provide normal testosterone levels as well as physiological levels of estradiol and dihydrotestosterone for up to six months (81). Peak serum testosterone levels are seen 2-4 weeks post placement with a gradual decline thereafter. The main disadvantage is the need for a skin incision and the occasional complication of local infection and extrusion of the pellets.

Several other systems for testosterone delivery are available and include patches (82) and gels (83) applied to the skin and buccal bioadhesive tablets (84). Transdermal gel (Testogel, Testim) has become very popular; it must be applied daily to maintain desirable serum testosterone levels. Patches can cause skin irritation in approximately 50% of patients. Buccal testosterone (Striant) is placed on the buccal mucosa above the incisor tooth; testosterone is slowly released over 12 hours. However, gum irritation and inconvenience have been reported.

Induction of spermatogenesis requires injections of FSH and LH; our own practice is to administer FSH 300 units three times weekly and LH 1500 units twice weekly; increases in sperm density are not evident for at least 4 months. (For additional information see ref 84A).

Testosterone levels can be measured in blood as a guide to the adequacy of replacement. With intramuscular depot injections, serum testosterone usually peaks at approximately one week after injection with a nadir prior to the next injection. The nadir serum testosterone concentration should approximate the lower end of the normal reference range and this may require adjustment of the frequency of injections. Random serum testosterone is often low or low normal on oral testosterone undecanoate, but the additional measurement of serum dihydrotestosterone is useful.

Published guidelines (85) addressed the concerns of the risk for prostate disease benign or malignant. There is no evidence that the incidence of prostate carcinoma in patients on testosterone replacement is greater than background population risk. Referral to a urologist is recommended if the patient has prostatic symptoms or an abnormal digital rectal examination or elevated serum prostate specific antigen increasing by more than 1.4ng/ml over 12 months. With the increasing use of long-acting testosterone, it is important to monitor the hematocrit to detect polycythemia. The hematocrit should return to normal before testosterone may be reinstituted at a lower dose.

A recent review of the available evidence suggests that testosterone replacement should be offered cautiously in patients with a low risk of recurrence for prostatic neoplasm who have been treated with radical prostatectomy and in whom the PSA has normalized (86). Similarly, a retrospective study has demonstrated that in patients treated with prostatectomy as primary management and a low PSA at baseline, testosterone therapy and concurrent use of 5α reductase did not result in an increase in PSA at 15 months (87). However, patients with no definitive surgery treated with brachytherapy or external beam radiation and a raised PSA at baseline should not be offered testosterone treatment.

## **Diabetes Insipidus**

1-desamino-8-D-arginine-vasopressin (DDAVP) is a synthetic analogue of arginine vasopressin which produces prolonged antidiuresis after intranasal or oral administration in patients with central diabetes insipidus. A therapeutic trial of DDAVP, 10-20mcg intranasally should control polyuria for up to 16 hours. Patients with central diabetes insipidus will have instant improvement in symptoms. In the acute clinical setting, for example where diabetes insipidus follows pituitary surgery, DDAVP is best administrated via the subcutaneous route at a dose of 0.5-1 mcg. Doses of DDAVP that are too high can lead to hyponatremia if patients continue to drink inappropriately despite antidiuresis. Patient education is required to achieve optimum symptom control particularly at night and to maintain a normal serum osmolality and sodium concentration (88). Slight undertreatment, with normal water homeostasis being maintained by thirst mechanisms, is the preferred approach. Many patients will demonstrate adequate control of the condition with a single bedtime dose of intranasal DDAVP but an additional morning dose may be required. Mild degrees of CDI may be treated with oral DDAVP up to 600 µg daily in divided doses. If ADH deficiency is accompanied by a reduced thirst threshold, often resulting in adipsic hypernatremia, it is most important to monitor body weight and urine output on a fixed dose of DDAVP and adjust fluid intake accordingly. Helpful laboratory assessment includes elevation of sodium, urea, creatinine, uric acid, along with ensuing hypokalemia and lack of polyuria.

A recent guideline has been developed for inpatient treatment of diabetes insipidus highlighting that this treatable condition could develop into a life-threatening situation if inappropriately managed (89).

## **Growth Hormone Deficiency**

The rationale and protocol for growth hormone replacement in adults is discussed in the "Adult Growth Hormone Deficiency" chapter (90).

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