Title: Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline

Short Title: Guidelines on Hormonal Replacement in Hypopituitarism

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** Evidence-based reviews for this guideline were prepared under contract with the Endocrine Society.
Abstract

Objective: The objective is to formulate clinical practice guidelines for hormonal replacement in hypopituitarism.

Participants: The participants include an Endocrine Society-appointed Task Force of six experts, a methodologist, and a medical writer. This guideline was co-sponsored by the American Association for Clinical Chemistry, the Pituitary Society and European Society of Endocrinology.

Evidence: This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation system to describe the strength of recommendations and the quality of evidence. The Task Force commissioned two systematic reviews and used the best available evidence from other published systematic reviews and individual studies.

Consensus Process: One group meeting, several conference calls, and e-mail communications enabled consensus. Committees and members of the Endocrine Society, the American Association for Clinical Chemistry, the Pituitary Society and the European Society of Endocrinology reviewed and commented on preliminary drafts of these guidelines.

Conclusions: Using an evidence-based approach, this guideline addresses important clinical issues regarding the evaluation and management of hypopituitarism, including the appropriate biochemical assessments, specific therapeutic decisions to decrease risk of co-morbidities due to hormonal over or underreplacement and management during pregnancy, pituitary surgery and other types of surgeries.
The Clinical Guidelines Subcommittee (CGS) of the Endocrine Society deemed hormonal replacement in panhypopituitarism a priority area in need of practice guidelines and appointed a Task Force to formulate evidence-based recommendations. The Task Force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation group, an international group with expertise in the development and implementation of evidence-based guidelines (Atkins D 2004). A detailed description of the grading scheme has been published elsewhere (Swiglo BA 2008). The Task Force used the best available research evidence to develop the recommendations. The Task Force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of the recommendation, strong recommendations use the phrase “we recommend” and the number 1, and weak recommendations use the phrase “we suggest” and the number 2. Cross-filled circles indicate the quality of the evidence, such that \( \odot \odot \odot \) denotes very low quality evidence; \( \odot \odot \odot \), low quality; \( \odot \odot \odot \odot \), moderate quality; and \( \odot \odot \odot \odot \odot \), high quality. The Task Force has confidence that persons who receive care according to the strong recommendations will derive, on average, more good than harm. Weak recommendations require more careful consideration of the person’s circumstances, values, and preferences to determine the best course of action. Linked to each recommendation is a description of the evidence and the values that panelists considered in making the recommendation; in some instances there are remarks, a section in which panelists offer technical suggestions for testing conditions, dosing, and monitoring. These technical
comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the panelists and their values and preferences; therefore, these remarks should be considered suggestions.

In this guideline, the Task Force made several statements to emphasize the importance of shared decision making, general preventive care measures, and basic principles of hormonal replacement in hypopituitarism. These were labeled as ungraded best practice statements. Direct evidence for these statements was either unavailable or not systematically appraised and considered out of the scope of this guideline. The intention of these statements is to draw attention and remind providers of these principles; these statements should not be considered as graded recommendations (Guyatt GH 2015).

The Endocrine Society maintains a rigorous conflict-of-interest review process for the development of clinical practice guidelines. All Task Force members must declare any potential conflicts of interest. The CGS reviews the conflict-of-interest forms before the Society’s Council approves the members to participate on the Task Force and periodically during the development of the guideline. Participants in the guideline development must include a majority of individuals without conflicts of interest in the matter under study. Participants with conflicts of interest may participate in the development of the guideline, but they must have disclosed all conflicts. The CGS and the Task Force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined as remuneration in any amount from the commercial interest(s) in the form of grants; research support; consulting fees; salary; ownership interest (e.g., stocks, stock options, or ownership interest excluding diversified mutual funds); honoraria or other payments for participation in speakers’ bureaus, advisory boards, or boards of directors; or other financial benefits. Completed forms are available through the Endocrine Society office.
Funding for this guideline was derived solely from the Endocrine Society, and thus the Task Force received no funding or remuneration from commercial or other entities.

Commissioned systematic reviews

The guideline taskforce commissioned 2 systematic reviews to assist with summarizing the evidence base for this guideline. The first review addressed the question of whether adults with panhypopituitarism of any cause have increased all cause mortality. The review identified 12 studies reporting on 26,017 patients. Studies were observational with incomplete adjustment for confounders. Meta-analysis suggested increased mortality in patients with panhypopituitarism (relative risk, RR 1.55; 95% CI, 1.14-2.11). Factors associated with increased mortality were female gender, younger age at diagnosis, underlying diagnosis of craniopharyngioma or aggressive tumor, presence of diabetes insipidus and prior treatment with surgery or radiotherapy. The most common causes of death were malignancies, cardiovascular disease and cerebrovascular disease.

The second review attempted to answer the question of whether GH replacement is associated with risk of pituitary tumor recurrence, secondary malignancy or stroke. The review included 7 studies reporting on 22,654 patients. Meta-analysis did not show an association between GH replacement and pituitary tumor recurrence (RR 0.87; 95% CI, 0.56-1.33) or the risk of secondary malignancies (RR 1.24; 95% CI, 0.65-2.33). There were no data on the outcome of stroke.

Both reviews addressed a question of association and both demonstrated that the evidence overall warrants low certainty in the provided estimates.
Epidemiology, Morbidity and Mortality of Hypopituitarism

Hypopituitarism results from complete or partial deficiency in pituitary hormones and includes adrenal insufficiency, hypothyroidism, hypogonadism, GH deficiency, and (more rarely) diabetes insipidus (DI). Not all disorders that affect the anterior pituitary function may cause DI, and DI can occur without anterior pituitary dysfunction. The disorder is the consequence of diseases that either reduce or destroy secretory function or interfere with the hypothalamic secretion of pituitary-releasing hormones.

The prevalence (probably underestimated) is approximately 45 cases per 100,000 with an incidence of about four cases per 100,000 per year (Regal, M et al., 2001). Considering evidence from the commissioned systematic review and other evidence extracted mostly from contemporary studies with heterogeneous etiologies and management of hypopituitarism, it seems that mortality associated with hypopituitarism is indeed high. Recently published evidence indicate that pituitary hormonal deficits managed with the currently-used substitution protocols might not adversely affect mortality (Ntali G, et al., 2015).

Hypopituitary patients exhibit a lower health status, increased incapacitation and sick days, and higher cost of care. Those with GHD are less often working full time, and more often on sick leave/disability, often live alone, and often with parents. Despite receiving long-term GH replacement, the working capacity of hypopituitary patients remains lower than the general population.

Given the complexity of hypopituitarism, patients are best managed in specialized centers especially when desiring pregnancy, after pituitary apoplexy, when they have enlarging pituitary tumors, when receiving multiple concomitant medications, and/or have a persistent decrease in quality of life (QOL).
Central Adrenal Insufficiency

Central adrenal insufficiency (AI), inadequate cortisol secretion due to adrenocorticotropic hormone (ACTH) deficiency can be secondary (pituitary) and/or tertiary from inadequate hypothalamic corticotropin releasing hormone \(^{11}\).

The prevalence of central AI (excluding exogenous steroids use) is 150-280 per million inhabitants \(^{12}\); almost one-third of patients with pituitary failure may have AI \(^{13-15}\). The reported prevalence after pituitary surgery varies \(^{16-18}\), with up to 90% after craniopharyngioma surgery \(^{19}\). Patients who have undergone cranial radiation for non-pituitary tumors have a high prevalence of hypopituitarism \(^{20, 21}\). The timing of onset of new pituitary deficiencies after radiation varies, but it may take a few years to develop in most cases. (Watson, 2014). A high index of suspicion is required for a diagnosis of AI \(^{22}\), as delaying treatment can result in adrenal crisis (AC) and death. (Arlt, 2003, Bancos et al, 2014, Hahner, 2014, Burman, 2012) Mild ACTH deficiency may manifest as clinically important AI with stress (Wass, 2012).

Central Hypothyroidism

Central hypothyroidism (CH) is caused by the insufficient stimulation of a normal thyroid gland by TSH due to inadequate secretion or action of TRH and/or TSH (Beck-Peccoz P, 2011, Persani L, 2012). Acquired CH is usually associated with other pituitary hormone deficiencies.

Approximately 50% of CH cases are caused by pituitary macroadenomas, while craniopharyngiomas are the most common extrasellar cause, especially in younger patients (Persani L, 2012). The frequency of CH with nonfunctioning pituitary adenomas may reach 43% pre-operatively and 57% post-operatively (Behan L, 2011). CH occurs in up to 65% of patients irradiated for brain tumors, and up to half of those irradiated for nasopharyngeal or paranasal sinus tumors. CH due to traumatic brain injuries or stroke may be increasing in prevalence as more patients survive these events.
Central Hypogonadism

Central hypogonadism in males manifests with low serum testosterone (T) levels and features of testosterone deficiency and/or impaired spermatogenesis; in premenopausal females it manifests with low serum estrogens and impaired ovulation with oligomenorrhea or amenorrhea.

The prevalence can be as high as 95% in patients with sellar tumors and after surgery or radiotherapy; it’s also high for patients who have had cranial irradiation for non-sellar lesions. (Ntali et al, 2015, Trifanescu et al, 2012, Capatina et al, 2013, Fernandez et al, 2009, Karavitaki et al, 2006).

Hyperprolactinemia attributed to tumours or medications is also a common cause of hypogonadism (Karavitaki and Wass, Oxford Textbook of Medicine, 2010).

Untreated gonadotropin deficiency is an independent factor affecting mortality [HR 1.86 (99%CI 1.15-2.45)] (Tomlinson 2001); treatment with sex steroid replacement was associated with a significantly reduced SMR [1.42 (99%CI 0.97-2.07) vs. 2.97 (99%CI 2.13-4.13)] (men and women were not considered separately). Androgen deprivation therapy in prostate cancer is associated with an increased incidence of myocardial infarctions and cardiovascular mortality (Keating et al., 2006; Saigal et al., 2007; Levine et al. 2010) by increasing body weight, decreasing lean body mass, increasing serum LDL and triglycerides, and reducing insulin sensitivity (Smith et al., 2001; Smith et al., 2002; Smith et al., 2006; Levine et al. 2010).

Early menopause is associated with increased risk of cardiovascular and cerebrovascular disease (Atsma et al., 2006; Lokkegaard et al., 2006; Parker et al.; Rocca et al., 2012). Accordingly, bilateral oophorectomy without estrogen replacement before the age of 45 increases cardiovascular mortality (Rivera et al., 2009). Standard mortality ratio (SMR) in females with untreated gonadotropin deficiency is 2.09 (95%CI 0.94-4.65); in those with treated hypogonadism it is 0.94 (95%CI 0.35-2.49).
Central (Neurogenic) Diabetes Insipidus

Central (neurogenic) diabetes insipidus (DI) occurs when the secretion of antidiuretic hormone (ADH) (vasopressin) by the posterior pituitary is insufficient to meet urine concentration requirements. The prevalence of medically treated DI is 7-10 patients per 100,000 inhabitants (Juul KV J Clin Endocrinol Metab. 2014). DI can be congenital or acquired, secondary to a variety of pathological processes including tumors (mostly craniopharyngioma and germinomas), head trauma, inflammatory/autoimmune/granulomatous/infectious diseases involving the hypothalamus and/or posterior pituitary. Sometimes the cause of DI is unknown (“idiopathic DI”), and thought to be autoimmune. In some these cases periodical follow up imaging may unveil the cause, particularly in young patients (Maghnie M, N Engl J Med. 2000).

DI is very rarely encountered in non-operated pituitary adenomas. (Leroy C, Ann Endocrinol (Paris) 2013).

Adult Growth Hormone Deficiency

Adult GH deficiency (AGHD) may be present at childhood, or may occur during adulthood as an acquired condition. About 6,000 cases of GHD are reported each year in the United States (US) with an estimated 50,000 diagnosed adults (Brod JCEM 2014 99:1204). In European reports, AGHD occurs at an annual incidence of 12-19 cases per million (Sassolas EJE 141:595, 1999; Stockholm K 2006 EJE 155:61). The prevalence after traumatic brain injury is estimated at 12% (Tanriverdi Endocrine review, 2015). Whether or not adult GH replacement in patients with proven growth hormone deficiency (GHD) engenders a favorable mortality outcome has not yet been clarified, as long-term controlled trials are lacking. However, GH replacement may improve excess mortality from an SMR of 2.40 (95% CI 1.46-3.34) to 1.99 (95% CI 1.21-2.76), especially in men (Pappachan JCEM 2015). Untreated congenital GHD does not lead to shortened life expectancy (Aguiar-Oliveira MH 2010).
Prolactin deficiency

Prolactin (PRL) deficiency is frequently seen in patients with hypothalamic-pituitary disease at presentation or after surgical and radiation treatment. Acquired PRL deficiency has been suggested as a marker for pituitary damage with a more severe degree of pituitary hypofunction. (Toledano, 2007).

Many cases of hypopituitarism are associated however with hyperprolactinemia, that occurs due to stalk interruption (Tritos, 2015) and absence of dopamine inhibition.
Etiology, Clinical Manifestations

The most frequent causes of hypopituitarism are listed in Table 1.

**Table 1. Causes of acquired adult hypopituitarism**

<table>
<thead>
<tr>
<th>Neoplastic</th>
<th>Infectious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pituitary adenoma</td>
<td>Bacterial</td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>Fungal</td>
</tr>
<tr>
<td>Meningioma</td>
<td>Parasites</td>
</tr>
<tr>
<td>Cysts (Rathke’s cleft,</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>arachnoid, epidermoid,</td>
<td>Syphilis</td>
</tr>
<tr>
<td>dermoid)</td>
<td></td>
</tr>
<tr>
<td>Germinoma</td>
<td></td>
</tr>
<tr>
<td>Glioma</td>
<td>Vascular</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>Pituitary tumor apoplexy</td>
</tr>
<tr>
<td>Ganglioeuroma</td>
<td>Sheehan’s syndrome</td>
</tr>
<tr>
<td>Paraganglioma</td>
<td>Intrasellar carotid artery aneurysm</td>
</tr>
<tr>
<td>Teratoma</td>
<td>Subarachnoid hemorrhage</td>
</tr>
<tr>
<td>Chordoma</td>
<td>Traumatic</td>
</tr>
<tr>
<td>Pituicytoma</td>
<td>Head injury</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>Medications</td>
</tr>
<tr>
<td>Pituitary carcinoma</td>
<td>Opiates (primarily gonadotropin ACTH)</td>
</tr>
<tr>
<td>Metastases</td>
<td>Glucocorticoids (ACTH only)</td>
</tr>
<tr>
<td></td>
<td>Megestrol acetate (ACTH only)</td>
</tr>
<tr>
<td></td>
<td>Somatostatin analogs (GH, ACTH?, TSH?)</td>
</tr>
<tr>
<td></td>
<td>Cytotoxic T-lymphocyte antigen 4 (CTLA-4) blockers (ACTH, TSH, LH/FSH)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment of sellar, parasellar, and hypothalamic diseases</th>
<th>Empty sella</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>Empty sella</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Infiltrative/Inflammatory Disease</th>
<th>Idiopathic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune (lymphocytic hypophysitis, Pituitary and POUF-1 antibodies)</td>
<td></td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td></td>
</tr>
<tr>
<td>Granulomatous (Wegener’s granulomatosis, sarcoidosis Langerhans cell histiocytosis, Giant cell granuloma)</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Xanthomatous hypophysitis</td>
<td></td>
</tr>
</tbody>
</table>
The most common cause of central AI is exogenous glucocorticoids (GCs) that suppress ACTH; however this review focuses on hypopituitarism.

The usual sequential pattern for hormonal deficiencies is the loss of GH initially, followed by gonadotropins, TSH and ACTH, but there are several exceptions (eg. hypophysitis) to this order. It may be challenging to ascribe specific features to a single hormone deficiency; relevant clinical features for each pituitary hormone deficiency are detailed in Table 2.
### Table 2. Clinical Manifestations of Hypopituitarism

<table>
<thead>
<tr>
<th>Symptom/Sign</th>
<th>Pituitary trophic Hormone Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue, weakness</td>
<td>ACTH, TSH, LH/FSH, GH</td>
</tr>
<tr>
<td>Weight gain</td>
<td>TSH</td>
</tr>
<tr>
<td>Weight loss</td>
<td>ACTH</td>
</tr>
<tr>
<td>Decreased exercise capacity</td>
<td>ACTH, TSH, LH/FSH, GH</td>
</tr>
<tr>
<td>Impaired sleep quality</td>
<td>TSH, LH/FSH, GH</td>
</tr>
<tr>
<td>Depression</td>
<td>TSH, GH, LH/FSH</td>
</tr>
<tr>
<td>Cognitive decline</td>
<td>ACTH, TSH, ?GH</td>
</tr>
<tr>
<td>Cold intolerance</td>
<td>TSH</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td></td>
</tr>
<tr>
<td>Pallor</td>
<td>ACTH, LH/FSH</td>
</tr>
<tr>
<td>Dry skin</td>
<td>ACTH, TSH</td>
</tr>
<tr>
<td>Thinning hair, loss of body hair</td>
<td>ACTH, TSH, LH/FSH</td>
</tr>
<tr>
<td><strong>Cardiovascular/metabolic</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>TSH, GH</td>
</tr>
<tr>
<td>Hypotension, particularly orthostatic</td>
<td>ACTH</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>TSH</td>
</tr>
<tr>
<td>Decreased lean body mass, increased fat mass</td>
<td>GH</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>TSH, GH</td>
</tr>
<tr>
<td>Insulin resistance, impaired glucose tolerance</td>
<td>TSH, GH</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>ACTH</td>
</tr>
<tr>
<td>Impaired cardiac function</td>
<td>ACTH, TSH, GH</td>
</tr>
<tr>
<td>Premature atherosclerosis</td>
<td>TSH, GH</td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
<td></td>
</tr>
<tr>
<td>Shortness of breath, dyspnea on exertion</td>
<td>ACTH, TSH</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>ACTH</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>ACTH</td>
</tr>
<tr>
<td>Diarrhea/loose stools</td>
<td>ACTH</td>
</tr>
<tr>
<td>Constipation</td>
<td>TSH</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td></td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>ACTH, TSH, LH/FSH, GH</td>
</tr>
<tr>
<td>Osteoporosis, fractures</td>
<td>ACTH, TSH, LH/FSH, GH</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
</tr>
<tr>
<td>Increased thirst</td>
<td>ADH</td>
</tr>
<tr>
<td>Polyuria, nocturia</td>
<td>ADH</td>
</tr>
<tr>
<td><strong>Reproductive</strong></td>
<td></td>
</tr>
<tr>
<td>Oligo/amenorrhea</td>
<td>ACTH, TSH, LH/FSH</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>LH/FSH</td>
</tr>
<tr>
<td>Low libido</td>
<td>LH/FSH</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>LH/FSH</td>
</tr>
<tr>
<td>Infertility</td>
<td>LH/FSH</td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>LH/FSH</td>
</tr>
</tbody>
</table>

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1. Diagnosis of Hypopituitarism

Establishing the diagnosis and monitoring therapy of hypopituitarism requires understanding hormonal assays characteristics and limitations (Table 4).

In several instances where data was lacking on the central deficiency state, it was extrapolated from studies on primary gland failure. However this evidence may, or may not, be directly comparable to the situation in pituitary disease.

Central Adrenal Insufficiency

Testing for central adrenal insufficiency includes an insulin tolerance test (ITT) and low-dose and standard-dose ACTH stimulation tests (Table 3). Limitations include interpreting test cut-off values and thresholds required for GCs replacement. Although assays have evolved, cortisol levels $<$18.1 mcg/dl (500 nmol/l) post stimulation are accepted as indicative of AI (Table 3). The different tests are also discussed in Endocrine Society clinical practice guidelines (Bornstein S. et al., JCEM, to be published 2016).

1.1 We suggest measuring 8-9 a.m. serum cortisol levels as the first line test for diagnosing secondary AI. (2|ΦOOO)

1.2 We recommend against the use of a random cortisol level to make the diagnosis of AI. (1|ΘΟΟΟ)

1.3 We suggest using a cortisol level $<$3.6 mcg/dl as indicative of AI and a cortisol level $>$15 mcg/dl as to likely exclude the diagnosis of AI. (2|ΦOOO)
1.4 We suggest performing corticotropin stimulation test when AM cortisol values are between 3.6 and 15 mcg/dl to establish the diagnosis of AI. Peak cortisol levels below 18.1 mcg/dl (500 nmol/l) at 30 or 60 minutes indicate AI. (2|©©©)

1.5 We suggest that biochemical testing for the HPA axis be performed at least 18-24 hours after the last hydrocortisone dose or longer for synthetic GCs. (2|©©©)

Evidence

The Endocrine Society has published a guideline on the diagnosis of primary adrenal insufficiency that includes a summary of evidence. (Bornstein S. et al., JCEM, to be published 2016) In the current guideline we emphasize the approach for the patient with central AI. As GCs suppress the HPA axis and there are interferences in cortisol measurements, biochemical testing should be performed at least 18-24 hours after the last hydrocortisone dose or longer for synthetic GCs. (Krasowski, DM, et. al, BMC Clinical Pathology, 2014).

The duration of GC treatment and influence of oral estrogen on total serum cortisol levels (which can increase CBG) should also be considered.

Central Hypothyroidism

1.6 We recommend a single measurement of serum free T4 (fT4) and thyroid-stimulating hormone (TSH). An fT4 level below the laboratory reference range (Table 3) in conjunction with a low, normal, or mildly elevated TSH in the setting of pituitary disease usually confirms the diagnosis of CH. Depending on the clinical context, some patients with pituitary disease and low-normal fT4 levels may also have CH. (1|©©©©)
1.7 We suggest against using dynamic testing of TSH secretion for the diagnosis of CH.

Evidence

TSH levels in CH may be low, normal, or slightly elevated, reflecting decreased 24-hour secretion and altered bioactivity with relatively preserved immunoactivity (Ferretti E, 1999, Persani L, 2000, Alexopoulou O, 2004). In contrast to primary hypothyroidism, TSH and fT4 levels do not correlate (Persani L, 2012). Accordingly, TSH levels alone cannot be used to diagnose or monitor CH.

The combination of a low fT4 and a non-markedly-elevated TSH in a patient with known pituitary disease is diagnostic of CH, unless the patient is severely ill and could have nonthyroidal illness-induced changes in thyroid hormone levels. However, this approach misses a significant number of patients with mild CH, as some pituitary patients with low-normal fT4 levels probably have mild CH. In one study, 18% of adults with CH had fT4 levels in the lowest quartile of the reference range (Alexopoulou O, 2004). Since patients with primary hypothyroidism usually require high-normal or slightly elevated fT4 levels to normalize TSH levels (Jonklaas J, 2014), low-normal fT4 levels in hypopituitary patients may suggest the presence of CH, although it is difficult to confirm this, with the lack of validated measures of thyroid function in these patients. Another study suggested that 10% of high-risk pituitary patients have unrecognized CH with low-normal fT4 levels (Koulouri O 2011). These patients often have a blunted or absent nocturnal surge in TSH levels, but this is impractical for diagnostic use (Persani L, 2012). Suggested approaches for patients with low-normal fT4 levels include starting L-T4 if suggestive symptoms are present, or following fT4 levels over time and starting treatment if the fT4 level decreases by 20% (Alexopoulou O, 2004). However, these recommendations have not been systematically investigated.
T3 or fT3 levels are generally not helpful in CH; most patients with CH have low fT3 levels, but there is considerable overlap between CH and non-CH patients with pituitary disease (Ferretti E, 1999, Alexopoulou O, 2004). Peripheral indices of thyroid hormone action lack sufficient sensitivity and specificity for diagnosing or monitoring (Slawik M, 2007, Martins M, 2007, Persani L, 2012, Doin F, 2012).

Past studies have attempted to categorize CH based on TSH responsiveness to exogenous thyrotropin-releasing hormone (TRH) administration (Hartoff-Nielsen M, 2004), but this has not proven to be useful in clinical practice.

**Growth Hormone Deficiency**

1.8 In patients with suspected GH deficiency, we recommend GH stimulation testing. Single GH measurements are not helpful. (1|⊗⊙⊙⊙)

1.9 We recommend that appropriate body mass index (BMI) cut-offs be employed for assessing adequacy of elicited peak GH values. (1|⊗⊙⊙⊙)

1.10 We suggest against testing biochemically for GHD in patients with clear-cut features of GHD and three other documented pituitary hormone deficits. (2|⊗⊙⊙⊙)
Evidence

Testing for GH deficiency includes insulin tolerance test, glucagon test, and (if available) growth-hormone-releasing hormone (GHRH)-arginine test to elicit GH responses. These tests are detailed in Table 3 and are reviewed in Endocrine Society guidelines (Molitch, 2011).

In adults with a prior diagnosis of childhood onset (congenital or acquired) GHD, the approach to diagnosis is relatively straightforward as patients have short stature. However, as clinical features of acquired adult GHD are often subtle, not necessarily specific to an underlying pituitary disorder, and as many of these signs are in fact commonly encountered in the general population, these patients should all be re-tested as adults. Normal GH secretion is characterized by a heterogeneous, pulsatile pattern; therefore, measuring basal circulating GH levels does not provide useful diagnostic information. While interpreting GH values one should also consider multiple factors including nutritional and hormonal status, exercise, body weight, as well as age, all of which may influence the mass of pituitary GH secretion.

Unlike GH, insulin-like growth factor (IGF)-I levels are relatively reproducible and stable, with a circulating half-life of 24-30 hours. Age-adjusted values measured in an accredited laboratory provide valuable information of net GH bioactivity. Nevertheless, about 20% of adults with GHD may have normal IGF-I levels, particularly males (Hartman, 2007).
Remarks

As most GH reserve tests are associated with high false positive rates, rigorous biochemical evaluation should only be undertaken when the clinical scenario is compatible with a high probability for GHD. One or more of the following prescreening criteria should be fulfilled:

- Young adults previously requiring GH therapy for short stature (isolated GHD with normal pituitary imaging) during childhood should all be retested as adults before continuing adult GH replacement. Many of these patients are found to be GH-sufficient on subsequent retesting.

- Patients should exhibit evidence for pituitary damage including history of pituitary surgery or irradiation for a demonstrated intrasellar lesion, pituitary hypoplasia, hypothalamic mass or infiltration, prior head trauma, contact sports injury, or stroke.
### Table 3. Dynamic tests for the diagnosis of suspected hypopituitarism

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Test</th>
<th>Procedure</th>
<th>Interpretation/ Expected Normal Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH</td>
<td><em>Insulin tolerance</em></td>
<td>Insulin 0.05-0.15 U/kg iv</td>
<td>Glucose should drop &lt;40 mg/dl, 2.2 mmol/L.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood sampling -30, 0, 30, 60, 120 min for GH and glucose</td>
<td>GH should be &gt;3 -5 mcg/L</td>
</tr>
<tr>
<td>GHRH*+Arginine</td>
<td>GHRH 1 mcg/Kg (max 100 mcg) <em>iv</em> followed by arginine infusion 0.5 g/Kg (max 35 g) over 30 minutes</td>
<td>Cut-offs for GH response are BMI-related.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood sampling 0, 30, 45, 60, 75, 90, 105, 120 minutes for GH</td>
<td>Can give false normal GH response if GH deficiency is due to hypothalamic damage (eg., following radiation)</td>
</tr>
<tr>
<td>Glucagon</td>
<td></td>
<td>Glucagon 1 mg (1.5 mg if weight &gt;90 Kg) IM</td>
<td>Cut-offs for GH response should be correlated to BMI (obesity may blunt GH response to stimulation)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood sampling 0, 30, 60, 90, 120, 150, 180, 210, 240 min for GH and glucose</td>
<td></td>
</tr>
<tr>
<td>ACTH</td>
<td><em>Insulin tolerance</em></td>
<td>Insulin 0.05-0.15 U/kg iv</td>
<td>Glucose should drop &lt;40 mg/dl (2.2 mmol/L) Peak cortisol &gt;500-550 nmol/l (&gt;18.1-20 mcg/dL) depending on assay</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood sampling -30, 0, 30, 60, 120 min for cortisol</td>
<td></td>
</tr>
<tr>
<td>Corticotropin standard dose (250 mcg)</td>
<td>ACTH 1-24 (Cosyntropin) 250 mcg IM or IV</td>
<td>Cortisol should be at 30 or 60 min &gt;500-550 nmol/l (&gt;18.1-20 mcg/dL) depending on assay</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood sampling 0, 30 and 60 min for cortisol</td>
<td></td>
</tr>
<tr>
<td>Corticotropin low dose (1 mcg)</td>
<td>ACTH 1-24 (Cosyntropin) 1 mcg <em>iv</em></td>
<td>Cortisol should be at 30 min &gt;500 nmol/l (18.1 mcg/dl) depending on assay</td>
<td></td>
</tr>
<tr>
<td>Hormone</td>
<td>Test</td>
<td>Procedure</td>
<td>Interpretation/ Expected Normal Response</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------</td>
<td>-----------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>ADH</td>
<td>Water Deprivation test</td>
<td>Deprivation of fluids for 8 hours (starting from 8:00 am). Measure weight of patient hourly. Estimate urine volume hourly. Measure plasma and urine osmolality every 2-3 hours. At 04:00 p.m. administer DDAVP 2 mcg IM (if plasma osmolality &gt;305 mOsm/Kg or if 3% loss of body weight with plasma osmolality &gt;305 mOsm/Kg, proceed to DDAVP administration earlier) and allow the patient to drink freely - continue measuring urine osmolality for the next 4 hours hourly and measure hourly urine volumes (if the urine output has not decreased and/or urine osmolality/plasma osmolality &lt;2 but the plasma osmolality has not become concentrated to &gt;295 mOsm/kg, continue water deprivation for a further hour and measure plasma and urine osmolalities – offer DDAVP after this). Stop test if &gt;3% weight loss occurs.</td>
<td>Plasma osmolality &gt;295 mOsm/l with inappropriately hypotonic urine (urine osmolality/plasma osmolality &lt;2) confirms diabetes insipidus (test is stopped). After administration of DDAVP, urine concentrates &gt;800 mOsm/Kg in cases of central diabetes insipidus and &lt;300 mOsm/Kg in nephrogenic diabetes insipidus. In partial diabetes insipidus or primary polydipsia, urine concentrates partially during the water deprivation (300-800 mOsm/Kg) and further investigations are needed (including prolonged water deprivation test or therapeutic trial of DDAVP).</td>
</tr>
</tbody>
</table>

*Presently unavailable in the U.S. [Copyrights pending NK]*
Central Hypogonadism in Males

1.11 In males with suspected hypogonadism, we recommend measuring serum T, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) to establish diagnosis of central hypogonadism. (1|8|8|O)

1.12 We recommend that hormonal testing for central hypogonadism in males be done in the absence of acute/subacute illness and be performed prior to 10 a.m. combined with serum PRL. (1|8|8|O)

Evidence

Central hypogonadism in males manifests with low serum testosterone (T) levels and features of testosterone deficiency and/or impaired spermatogenesis.

Testosterone levels (total, free, and bioavailable) demonstrate a circadian rhythm with maximum serum values between 5:30 a.m. and 8:00 a.m. and trough levels approximately 12 hours later (Plymate et al., 1989; Cooke et al., 1993; Brambilla et al., 2009). Acute/subacute illness alters T levels acting at various levels of the hypothalamo-pituitary-gonadal axis (Spratt et al., 1992; Zitzmann M & Nieschlang E, 2001). Systemic diseases, eating disorders, extensive exercise, and a number of medications or recreational drugs (including glucocorticoids, opiates, ketokonazole, barbiturates, cocaine) (Pugeat et al., 1987; Reddy et al., 2010) affect T levels. Hyperprolactinemia can cause hypogonadotropic hypogonadism and the possibility of a prolactinoma needs to be taken into account as dopamine agonist treatment can reverse the hypogonadism. Two measurements performed with the same assay are preferred for borderline low T values (Brambilla et al., 2007; Bhasin, 2010).
Remarks

Testosterone levels demonstrate an age-related decline (Feldman et al., 2002; Wu et al., 2008);

The Massachusetts Male Aging Study has shown that in healthy men serum T reaches the highest levels at around the age of 30 years with a gradual decline thereafter at a rate of 1-2% annually (Feldman et al., 2002). Values of serum T below which symptoms of hypogonadism occur have not been clearly established.

About 2% of circulating T is free (unbound), 44% is bound to sex hormone-binding globulin (SHBG), and 54% is bound to albumin and other proteins (Dunn et al., 1981). Total T levels at the low end of the reference range are associated with conditions affecting SHBG and albumin (e.g., hypothyroidism, obesity, diabetes mellitus, nephrotic syndrome, liver disease, HIV infection, glucocorticoids, or anticonvulsants). When assessing fertility is required, semen analysis should be performed before starting T replacement. Notably, cases of males with acquired hypogonadotropic hypogonadism treated with testosterone and remaining fertile have been reported (Drincic et al., 2003).

Central Hypogonadism in Females

1.13 In the presence of oligomenorrhea or amenorrhea, we recommend measuring serum estradiol, FSH, and LH. Other causes of menstrual irregularities related to impaired ovulation (hyperprolactinaemia, hyperandrogenism and thyroid disease) should be excluded, particularly if no other pituitary hormone deficits are present. In cases of amenorrhea, pregnancy needs to be excluded.

1.14 We suggest against dynamic testing with gonadotropin-releasing hormone (GnRH), which offers no useful diagnostic information.
1.15 We recommend that in postmenopausal women, the absence of high serum FSH and LH are sufficient for a diagnosis of gonadotrope dysfunction (provided the patient is not on HRT). (1|δ|δ|O)

Central Diabetes Insipidus

1.16 We recommend simultaneously measuring serum and urine osmolarity in patients with polyuria (more than 50 mL/Kg of body weight, 3.5 L in a 70 kg person). In the presence of high serum osmolarity (>295 mosmol/L) urine osmolarity should reach approximately 600 mosmol/L (urine osmolality/plasma osmolality should be ≥2) while urine dipstick is negative for glucose. (1|δ|δ|O)

Evidence

The presence of DI may be obvious with severe forms in the appropriate clinical scenario (e.g., after surgery for hypothalamic or pituitary lesion). In more subtle cases, a water deprivation test is required to document partial inability in concentrating urine. The diagnosis may be particularly challenging when DI is partial and the MRI imaging does not show an obvious pathology. However, in most cases of isolated DI, MRI imaging of the sellar area shows progressive loss of posterior pituitary bright spot (De Bellis A, J Clin Endocrinol Metab 84:3047–3051).

Hormone Assays

Accurate and reliable hormonal measurements are central to diagnosing and monitoring therapeutic interventions. Technical considerations include assay characteristics such as sensitivity and reliability at low levels, interference from replacement hormonal therapy and their analogue (i.e., prednisolone and hydrocortisone in cortisol assays), and samples stability.
We reviewed performance characteristics (sensitivity, specificity, variability (precision), and sample limitations) of widely used assays for GH, IGF-I, prolactin (PRL), FSH, LH, TSH, FT4, T, estradiol (E2), cortisol, and ACTH (Table 4). All assays exhibit adequate sensitivity and intra-assay variability acceptable at <20% (Table 4). However, for some analytes such as E2, T, GH, FT4, and to lower extent gonadotropins, inter-assay variability are large, suggesting that the same assay be used for serial and longitudinal measurements (Table 4) (K. Sikaris, et al, J Clin Endocrinol Metab 2005). In this sense, differences among assays should be considered.

Precautions for sample integrity need to be followed, and the review of questionable results should include sample storage and handling (freeze-thaw) attempts.

Newer liquid chromatography-mass spectrometric techniques (LC-MS)-based assays are increasingly being used with suggested improved sensitivity and reduced interferences. This is particularly true for steroids namely E2 and T. (Rosner W 2013, Kane J 2007). The technology is being applied to thyroid and peptide hormones (Kahric-Janicic N 2007).
### Table 4. Assay characteristics of common automated immunossays

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Assays Detectable Level</th>
<th>Sample Stability</th>
<th>Remarks</th>
<th>Mean Variability (% Imprecision) at stated concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH (mcg/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.002 (2)</td>
<td>Rfg. &lt; 8hrs</td>
<td>Adequate sensitivity far below decision cut-off</td>
<td>6.9%</td>
</tr>
<tr>
<td></td>
<td>0.01 (3)</td>
<td>Frz. &gt; 8 hrs (undetermined duration or about 2 months)</td>
<td>Some assays (4) indicate detection of both 20 and 22 kDa forms</td>
<td>23.1%</td>
</tr>
<tr>
<td></td>
<td>0.030 (4)</td>
<td>Avoid freeze-thawing (activity lost after repeated cycles)</td>
<td>All assays use IRP 98/574 (Lower GH results when compared with earlier standard)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Varied conversion factors applied when converting mUnits/L to ug/L.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Variability between assays at 3.4 ng/mL.</td>
<td></td>
</tr>
<tr>
<td>IGF-I (ng/mL)</td>
<td>20 (3)</td>
<td>Rfg. &lt; 24 hours</td>
<td>Prefer to measure IGF-BP-3 on same sample</td>
<td>13.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Frz. up to 12 months</td>
<td>Variability between assay at 75 ng/mL.</td>
<td></td>
</tr>
<tr>
<td>PRL (ng/mL)</td>
<td>0.6 (1)</td>
<td>Rfg. &lt; 8hrs. If &gt;24hrs remove serum/plasma from gel/cells.</td>
<td>Adequate agreement among assays</td>
<td>7.2%</td>
</tr>
<tr>
<td></td>
<td>0.25 (2)</td>
<td>Frz. &lt;48 hrs (up to 7 days)</td>
<td>Variability at 7.2 ng/mL.</td>
<td>7.1%</td>
</tr>
<tr>
<td></td>
<td>0.3 (3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.047 (4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.4 (5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSH (mIU/mL)</td>
<td>0.05 (1)</td>
<td>Rfg. &lt; 8hrs. If &gt;24hrs remove serum/plasma from gel/cells.</td>
<td>Variability between assays</td>
<td>8.1%</td>
</tr>
<tr>
<td></td>
<td>0.2 (2)</td>
<td></td>
<td></td>
<td>8.9%</td>
</tr>
<tr>
<td></td>
<td>0.3 (3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.1 (4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.66 (5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LH (mIU/mL)</td>
<td>0.5 (1)</td>
<td>Frz. up to 12 months</td>
<td>Variability between assays</td>
<td>7.7%</td>
</tr>
<tr>
<td></td>
<td>0.2 (2)</td>
<td></td>
<td></td>
<td>8.6%</td>
</tr>
<tr>
<td></td>
<td>0.07 (3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.1 (4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.216 (5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH (mcIU/mL)</td>
<td>0.0038 (1)</td>
<td></td>
<td></td>
<td>6.1%</td>
</tr>
<tr>
<td></td>
<td>0.015 (2)</td>
<td></td>
<td></td>
<td>8.3%</td>
</tr>
<tr>
<td></td>
<td>0.004 (3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.005 (4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.015 (5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assay</td>
<td>Lower Nor.</td>
<td>High Nor.</td>
<td>Comment</td>
<td>Variability Between Assays</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
<td>-----------</td>
<td>--------------------------------------------------------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>FT4 (ng/dL)</td>
<td>0.4</td>
<td>12.2%</td>
<td>RT: &lt;8 hrs. If &gt;24hrs remove from gel/cells</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>11.2%</td>
<td>Rfg. &lt;48hrs (up to 7 days)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.1</td>
<td>11.2%</td>
<td>Frz. &gt;48hrs (up to 30 days). Avoid repeated freeze-thawing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.023</td>
<td>11.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.07</td>
<td>11.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone (ng/dL)</td>
<td>4.33</td>
<td>11.4%</td>
<td>RT: &lt;8 hrs. Remove from gel/cells immediately</td>
<td>Overall high between assays</td>
</tr>
<tr>
<td></td>
<td>10.0</td>
<td>15.6%</td>
<td>Rfg. &lt;48 hrs (up to 7 days)</td>
<td>up to 54%</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>15.6%</td>
<td>Frz. Up to 60 days. Avoid more than one freeze-thaw cycle</td>
<td>Variability at 113 ng/dL</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>14.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.9</td>
<td>16.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol (pg/mL)</td>
<td>25</td>
<td>16.9%</td>
<td>RT: &lt; 8 hrs. If &gt;24hrs remove from serum/plasma from gel / cells.</td>
<td>Variable assay sensitivities</td>
</tr>
<tr>
<td></td>
<td>20.0</td>
<td>64.9%</td>
<td>Rfg. &lt;48 hrs (up to 7 days)</td>
<td>Overall high between assays</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>64.9%</td>
<td>Frz. Up to 6 months. Avoid more than one freeze-thaw cycle</td>
<td>Variability at 141 pg/mL</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADH</td>
<td>Limited assays available</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>11-deoxycortisol</td>
<td>Rfg. =&lt;7 days</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frz. =&lt;14 days</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Cortisol (mcg/dL)</td>
<td>1.0</td>
<td>9.5%</td>
<td>RT: &lt; 8 hrs. If &gt;8hrs remove serum/plasma from gel/cells.</td>
<td>Adequate assays sensitivity for diagnosis</td>
</tr>
<tr>
<td></td>
<td>0.4</td>
<td>10.6%</td>
<td>Rfg. &lt;48 hrs (up to 14 days)</td>
<td>Variability at 4.1 mcg/L</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td></td>
<td>Frz. &gt; 48 hrs (up to 30 days)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH (pg/mL)</td>
<td>1.0</td>
<td>25.7%</td>
<td>Collect sample in ice-cooled EDTA-tube. Centrifuge immediately in refrigerated centrifuge. Store frozen in plastic container (Binds to non-siliconized glass). Stable frozen for 14 days.</td>
<td>ACTH 1-24 medication causes negative interference. Variability at 17.4 pg/mL.</td>
</tr>
</tbody>
</table>
Deviation/mean analyte concentration). Only assays with adequate available data are reviewed here. Variability calculated using available data for the lowest analyte concentration. [Raw variability data obtained with permission from published BioRad Unity quality control data (Bio-Rad Laboratories 19500 Jeronimo Road, Irvine, CA 92618). Information on sample stability was summarized from respective manufacturers’ published information.]
2. Treatment

Hormonal Replacement in Panhypopituitarism

As a guiding principle, the taskforce suggests hormonal replacement as close to the physiological pattern as possible.

Glucocorticoid Replacement

2.1 We recommend using hydrocortisone, usually 15-20 mg total daily dose in single or divided doses; if multiple dosing, the highest dose should be given in the morning at awakening, the next either in the afternoon (when using the 2-dose regime) or at lunch, and in the late afternoon (3-dose regime).

(1|⊙⊙⊙)

2.2 We suggest using longer acting GCs in selected cases (e.g., nonavailability, poor compliance or for convenience). (2|⊙OOO)

2.3 We recommend that all patients should be instructed to obtain an emergency card/bracelet regarding adrenal insufficiency. (1|⊙⊙⊙)

2.4 We recommend against using Fludrocortisone in patients with secondary adrenal insufficiency. (1|⊙⊙⊙)
Evidence

**Total daily dose.** Daily physiologic production of cortisol in healthy individuals is about 5-10 mg/m² body surface area corresponding to a replacement dose of approximately 15-20 mg/day. Therefore, it is thought that a dose in this range may avoid under- or over-treatment. As no reliable marker to determine exact GC needs is available, dose requirements are largely estimated initially.

Further dose adjustments depend on clinical status, patient preference, and co-morbidities.

A cortisol day curve has been used in research settings, but has little value for routine clinical use. Prednisolone cross-reacts in many cortisol assays, while dexamethasone exhibits limited cross-reactivity.

Urine free cortisol (UFC) measurements have wide inter and intra variability, thus are rarely useful. For patients with suspected malabsorption or increased steroid metabolic clearance, serial measurements of blood cortisol might be useful.

**Circadian rhythm-multiple daily dosing.** Cortisol secretion exhibits a distinct circadian rhythm; low at the time of sleep onset, and rising early morning, peaking just after the time of waking, then falling during the day. No currently available glucocorticoid treatment regimen is capable of accurately simulating the cortisol normal circadian rhythm. Several regimens, either weight-based or multiple fixed doses 2-3 times per day are commonly employed. Weight-adjusted, 3-times-daily dosing using hydrocortisone (HC) reduces GC overexposure and represents the most refined regime available, although it does not replicate the normal cortisol rhythm. Single daily HC is also frequently used in patients with central AI (Hameed, 2012, Yedinak, 2015).

**Type of glucocorticoid replacement.** Published surveys of current practice for GC replacement therapy include mostly patients with primary AI, however patients with central AI have also been included. Hydrocortisone is the most common GC used for replacement, followed by prednisone, cortisone, and dexamethasone. 11β-hydroxysteroid dehydrogenase-1 converts cortisol acetate to biologically active cortisol, which might reduce circulating cortisol fluctuations. Glucocorticoids of
different potencies can be compared by calculating HC equivalence (HCeq) based on anti-inflammatory
effects (Table 5) \(^{40, 33, 35, 41}\) (Mager et al, 2003). However, this method might sometimes overestimate the
calculation of a replacement dose.
Table 5. Dose equivalence for GC

<table>
<thead>
<tr>
<th>Equivalent Dose</th>
<th>Glucocorticoids</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg</td>
<td>Hydrocortisone</td>
</tr>
<tr>
<td>5 mg</td>
<td>Prednisone</td>
</tr>
<tr>
<td>0.75 mg</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>4 mg</td>
<td>Methylprednisolone</td>
</tr>
<tr>
<td>5 mg</td>
<td>Prednisolone</td>
</tr>
<tr>
<td>25 mg</td>
<td>Cortisone</td>
</tr>
</tbody>
</table>

A high proportion of patients on “conventional” corticosteroid replacement therapy for AI are over-treated or on inappropriate replacement regimens. However, few studies have compared different replacements regimens for central AI. Lower doses of hydrocortisone correlate with improved QOL, health status, and mood. In a randomized, double blind, crossover design, patients received varying multiple doses of HC versus prednisone for 4 weeks at each dose. The HC 10 mg am/5 mg p.m. regimen showed improved physical QOL, but overall QOL did not differ between regimens and remained lower than in healthy controls. In a cross-sectional study, HC doses above 30 mg/day were associated with adverse health status by validated self-assessment questionnaires. Furthermore, 3 times daily intake of HC was not superior to 2 times daily intake. In 2,737 adult hypopituitary patients, those receiving the equivalent of ≤10 mg HC had the best and those receiving ≥25 mg HC had the poorest QOL. These effects could be due to supraphysiological GC exposure, but it is possible that clinicians may have increased GC doses to address unexplained QOL deficits.
New glucocorticoid preparations (not FDA approved). Modified release HC is commercially
approved in Europe as a once-a-day tablet with combined immediate and extended release characteristics
capable of achieving a more physiological plasma cortisol profile. However, the physiological early rise
in morning cortisol is not well mimicked. The new GC preparations have been recently reviewed
(Bornstein et al, 2016).

Androgen Replacement in Women

The risks and benefits have been reviewed in recent Endocrine Society guidelines. The authors
recommended against the routine use of dehydroepiandrosterone due to limited data concerning its
effectiveness and safety in women with AI. The same authors also recommended against the routine
prescription of T in women with hypopituitarism.

Adrenal Crisis

We recommend that patients with suspected adrenal crisis (AC), due to secondary AI, be
treated with an immediate parenteral injection of 50-100 mg HC. (1|0|0|0)

Evidence

Adrenal crisis may be the initial presenting feature of pituitary failure. Despite intact
mineralocorticoid function, patients with secondary AI have a similar if not higher risk of adrenal crisis.
(KIMS Database; Hahner 2010; Burman, 2013). Excess cardiovascular mortality might be
specifically related to AC. Crisis incidence is not influenced by educational status, body mass index,
GC dose, dehydroepiandrosterone (DHEA) treatment, age at diagnosis, hypogonadism, hypothyroidism,
or GHD. Interestingly, the female sex and presence of diabetes insipidus in AC correlated with hospital
admission in one study.

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Immediate GC replacement and fluid resuscitation is similar with primary AI. (Bornstein et al, 2016). Patient education is considered the key in prevention of AC. All patients should receive detailed information on their disease and GC adjustment requirements for stressful situations. Patients should carry an emergency card, bracelet, or necklace and be provided with GCs for emergency administration. These include intramuscular or subcutaneous HC preparations available for self-injection (Bornstein 2016).

**Thyroid Hormone Replacement**

2.6 We recommend treatment with levothyroxine (L-T4) in doses sufficient to achieve serum \( fT4 \) levels in the mid- to upper-half of the reference range. Appropriate L-T4 doses in CH average 1.6 mcg/kg/day, with dose adjustments based on clinical context, age, and \( fT4 \) levels. (1|□□□□)

2.7 We suggest against the use of levotriodothyronine (L-T3), thyroid extracts, or other formulations of thyroid hormones for the treatment of CH. (2|□□□□)

**Evidence**

The standard therapy for CH is L-T4 (1.6 mcg/kg/day). In a randomized, double blind, crossover study, 32 hypopituitary CH patients received L-T4 doses previously adjusted by endocrinologists using best clinical judgment (Slawik M, 2007). Increasing the L-T4 dose from a mean of 1.0 to 1.6 mcg/kg/day led to improvement in hypothyroid symptom scores; mild weight loss; and decreases in BMI, total and LDL cholesterol levels, and serum CK levels. When L-T3 was substituted for some of the L-T4, working memory was slightly better, but at the expense of T3 levels above the reference range. Based on these results, the authors recommended an L-T4 dose of 1.6 mcg/kg/day in CH, with a target \( fT4 \) levels close to the upper limit of the reference range. Nonrandomized and observational studies also report similar findings, with improved fatigue, weight or BMI, waist circumference, and cholesterol levels correlating
with higher L-T4 doses and fT4 levels (Ferretti E, 1999, Shimon I, 2002, Filipsson Nystrom H, 2012, Alexopoulou O, 2004, Klose M, 2013). However, a recent publication described increased risk of vertebral fracture in hypopituitary patients receiving higher daily doses of L-T4, correlated with higher free T4 levels (Mazziotti G, 2014). Therefore, L-T4 doses should be adjusted for age, estrogen status including pregnancy (see below), co-morbidities, and clinical context, including potential risks of overtreatment (Persani L, 2012). Some investigators recommend following fT3 levels or peripheral indicators of thyroid function during L-T4 therapy, since elevated fT3 levels can indicate overtreatment, although these have not been validated (Alexopoulou O, 2004, Persani L, 2012).

The use of L-T3 or other formulations of thyroid hormone has been rarely studied in CH (Slawik M 2007); there are no high-quality studies that document the superiority of these treatments over L-T4 in primary hypothyroidism, and there are potential safety concerns (reviewed in Jonklaas J 2014). Alternate preparations of thyroid hormones or nutraceuticals are not recommended for the treatment of CH.

2.8 We recommend against using serum TSH levels to adjust thyroid replacement dosing in patients with CH. (1|⊕⊕⊕⊕Ο)

Evidence

Many patients with CH have undetectable TSH levels on presentation, and almost all CH patients adequately treated with L-T4 to maintain serum fT4 levels in the mid- to high-normal range will have undetectable TSH levels (Ferretti E, 1999, Shimon I, 2002, Slawik M, 2007, Klose M, 2013). Therefore, undetectable TSH levels should not be interpreted as a sign of overtreatment in CH, even in patients with initial measurable TSH levels.
Remarks

In most clinical situations, patients receiving L-T4 undergo blood sampling at random times of day, or in the morning, prior to taking the day’s L-T4 dose. It is not clear whether the timing of blood sampling in relation to L-T4 dose ingestion affects decisions regarding L-T4 dose adjustment in CH. A randomized controlled study in CH (Slawik M, 2007) measuring fT4 levels 2 hours after dose ingestion reported slightly elevated mean fT4 levels with adequate doses. Therefore, it is recommended to check fT4 before the L-T4 dose.

Testosterone Replacement

2.9 We suggest T replacement for adult males with central hypogonadism and no contraindications, aiming to improve bone mineral density (BMD), libido, sexual function, energy levels and sense of well being, muscle mass and strength, to prevent anemia related to testosterone deficiency, and to reduce fat mass. (2|©©©©)

Evidence

Central hypogonadism in males leads to adverse manifestations and sequelae, which may be reversed by T replacement. Limitations of such studies include that they are not randomized placebo-controlled, they employ various T formulations with different regimes, and they usually are short duration with a small number of patients.

Treatment increases BMD (Katznelson et al., 1996; Behre et al., 1997; Snyder et al., 2000; Wang et al., 2004) and improves trabecular structure (Benito et al., 2005) and bone mechanical properties (Zhnag et al., 2008). Nevertheless, data on the impact on fracture risk are not currently available.
Testosterone replacement results in increased libido, sexual motivation and sexual function (Kwan et al., 1983; Burris et al., 1992; Snyder et al., 2000; McNicholas et al., 2003; Seftel et al., 2004; Wang et al., 2004; Bolona et al., 2007; Zitzmann et al., 2013), mood, sense of well-being, concentration (Burris et al., 1992; Wang et al., 2004; Zitzmann et al., 2013; Blick et al., 2012; Khera et al., 2012; Kovac et al., 2014), self-reported sense of energy (Wang et al., 1996; Snyder et al., 2000), muscle mass and strength (Katznelson et al., 1996; Brodsky et al., 1996; Bhasin et al., 1997), and recovery of anemia related to T deficiency (Snyder et al., 2000). Men with non-replaced hypogonadism due to non-functioning pituitary adenomas scored significantly worse in parameters of health-related QOL questionnaires compared to those with an intact gonadotroph axis or on hormone replacement (Capatina et al., 2013).

Choice of T formulation relies on the risk of specific adverse effects, cost, patient convenience, and preference. For recommendations about T therapy, potential adverse effects, available T formulations, and monitoring of treatment we suggest that clinicians use the Endocrine Society guidelines (Bhasin et al., 2010).

**Estrogen Replacement in Premenopausal Women**

2.10 We recommend gonadal hormone treatment in premenopausal women with central hypogonadism, provided there are no contraindications. (I|⊕⊕⊕O)

**Evidence**

Premenopausal women with central hypogonadism should be offered gonadal hormone replacement (unopposed estrogens for women who have undergone hysterectomy, or combined estrogen-progestogen preparations for those with an intact uterus, to prevent endometrial hyperplasia).
Studies mainly done in women close to or after the natural age of menopause have shown that oral estrogen or combined estrogen/progestogen therapy are very effective in alleviating vasomotor symptoms of hypoestrogenism (hot flushes and night sweats) (MacLennan et al., 2004) and improving vaginal atrophy (Cardozo et al., 1998), urinary frequency, and dysuria (Cardozo et al., 2004). There are no studies on premenopausal women with central hypogonadism, but the published results from women with primary hypogonadism are often extrapolated for this group of female patients.

Treatment with estrogens until age 45 years or longer may reduce the risk of cardiovascular disease and mortality (Lokkegaard et al., 2006; Rivera et al., 2009; Rocca et al., 2012).

Primary ovarian failure is associated with reduced BMD and increased risk of fractures as (Tuppurainen et al., 1995; van Der Voort et al., 2003; Popat et al., 2009). Estrogens protect against fractures (Lindsay et al., 1980; Tuppurainen et al., 1995; van der Klift et al., 2004). BMD and risk of fracture in central hypogonadism are also affected by the presence of other pituitary hormone deficits and/or their treatment (Mo D Lancet 2015; Mazziotti G, 2014, Mazziotti G, 2010 EJE). Studies assessing the clear impact of estrogen treatment on fracture risk are not available. Nonetheless, the literature on primary ovarian failure supports the beneficial effects of estrogen on bone. Furthermore, other general measures optimizing BMD should be offered (including lifestyle measures, weight-bearing exercise, adequate calcium and vitamin D supplementation, and avoiding smoking).

Remarks

Although in younger females the combined estrogen-progestin contraceptive pill may be more acceptable compared with hormonal replacement therapy, studies comparing effects of these two regimes in central hypogonadism are lacking.
Estrogens are available in many forms with different potency (oral, transdermal, topical gels and lotions, intravaginal creams and tablets, and vaginal rings). The choice of the estrogen (and progestin) preparation relies on the risk of adverse effects, cost, patient convenience, and preference.

Follow-up of gonadal hormone replacement includes evaluating symptoms and monitoring for side effects. Measuring serum estradiol levels is not beneficial; moreover some estrogens are not detected by the assays.

Hormonal replacement therapy in women 40-49 years has not been associated with increased risk of breast cancer (Ewertz et al., 2005), and there is no evidence that estrogen replacement in women with premature ovarian failure relates to higher risk of breast cancer (Pitkin et al., 2007).

It is prudent that gonadal hormones be replaced until the mean age of natural menopause (King et al., 2011).

**Growth Hormone Replacement Therapy**

2.11 We recommend offering GH replacement to those patients with proven GHD and no contraindications. We recommend a starting dose of 0.2-0.4 mg/day for patients younger than 60 years and 0.1-0.2 mg/day for patients older than 60 years respectively. (1|⊕⊕⊕O)

2.12 We recommend titration of GH dose and maintaining IGF-I levels below the upper limit of normal, and reducing the dose if side effects manifest. (1|⊕OOO)

2.13 We suggest against administering GH in elderly adults with no history of pituitary disease with age-adjusted low IGF-I levels. (2|⊕OOO)
2.14 We recommend against the use of GH to enhance athletic performance, as this practice is illegal, has poor scientific or ethical justification, and efficacy is not substantiated. (Ungraded Best Practice Statement)

Evidence
GH therapy is approved for replacement in adults with rigorously proven GHD or for treating HIV-related muscle wasting (Clemmons D JCEM 99:409 2014). Younger patients require higher doses, especially if serum IGF-I levels are particularly low.
Table 6. Growth hormone replacement therapy for adult growth hormone deficiency

<table>
<thead>
<tr>
<th>Starting dose</th>
<th>mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 60 yrs</td>
<td>0.2 – 0.4</td>
</tr>
<tr>
<td>Age &gt; 60 yrs</td>
<td>0.1 – 0.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose Titration</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase by 0.1-0.2 mg/day</td>
<td>6 week intervals</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose determinants</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mid-normal age-adjusted IGF-I level</td>
<td></td>
</tr>
</tbody>
</table>

Patient monitoring after initiating adult GH replacement

1. Measure IGF-I 6 weeks after initiating GH replacement, after dose escalations, and every 6 months thereafter
2. Assess body weight, blood pressure, waist circumference and BMI every 6 months
3. Assess thyroid and adrenal function, and replace or adjust replacement doses as indicated
4. Assess metabolic profile including blood sugar and lipids every 6 months
5. Assess bone mineral density by DXA annually
6. Periodically assess residual pituitary mass via a pituitary MRI
7. Assess quality of life

DXA=dual-energy x-ray absorptiometry MRI=magnetic resonance imaging; GH=growth hormone; IGF-I=insulin-like growth factor-1; BMI=body mass index.
Initial low GH replacement doses are preferred as fluid retention is dose-dependent. As women exhibit features of relative GH resistance, they usually require higher starting and maintenance replacement GH doses. (Johansson JCEM 1996 1575-1581) Morbid obesity may also require increased GH dosing.

Remarks

Once the dose has been stabilized, clinicians should monitor for efficacy. Effects of appropriate GH replacement usually manifest within 6 weeks of initiating therapy, but may require a longer time period for maximum benefit.

Overall, GH replacement results in improved lipoprotein metabolism, body composition, and BMD. Visceral adipose tissue mass is decreased by 9% in female patients receiving GH replacement (Beauregard 2008 JCEM 93:2063), while lean body mass improves by up to 7% during the first year of GH replacement (Hoffman JCEM 2004;Gotherstrom JCEM 94:809, 2009). Muscle strength improvement is sustained for at least 10 years (Gotherstrom JCEM 2009). A meta-analyses of 11 randomized trials reported that adult GH replacement resulted in significantly enhanced maximum oxygen uptake and muscle power (Gibney widdowson JCEM 2008). Although GH impact on insulin sensitivity is confounded by the beneficial effects of weight loss, GH itself is an insulin-antagonist. Serum lipoprotein profiles improve with reduced total- and low-density lipoprotein (LDL) cholesterol and increased high-density lipoprotein (HDL) cholesterol, triglycerides, and ApoB 100 levels (Maison P JCEM 89:2192, 2004). Lean body mass cardiac stroke volume and left ventricular mass are increased (Maison 2004 JCEM 89:2192), and cardiovascular risk profile improvement has not been consistently reported (Sesmilo 133:111 Ann Int Med 2000). Effects of GH replacement on BMD are more beneficial in men (Drake Clin Endo 2001) and with patients that have severe bone loss. Increased bone mass occurs after 12 months (Gotherstrom EJE 2007) and fracture development is slowed in patients with no previous osteoporosis (Mo D Lancet 2015).
Side effects of GH replacement at the recommended doses manifest in about 20% of patients, and are usually reversible by lowering the GH dose. Fluid retention, arthralgias, myalgias, paresthesias, carpal tunnel syndrome, sleep apnea, sleep disturbances, and dyspnea have been reported. If replacement doses are too high, insulin resistance with diabetes may occur. Although the development of new cancers and new onset diabetes are of concern, to date the safety profile for GH treatment (using appropriate replacement doses) appears favorable in long-term surveillance studies (Child C EJE 2015). GH administration does not appear to increase the rate of pituitary adenoma recurrence (relative risk 0.887, 95% CI, 0.56-1.33) (van Varsseveld NC 2015, Jasim S & Murad H 2015).

2.15 For administering desmopressin (DDAVP), we suggest individualized therapeutic schedules. While all patients should be offered therapy, some patients with partial DI may not be bothered by polyuria, and may prefer no treatment. To reduce the risk of hyponatremia, we recommend that all patients receiving DDAVP be educated about the risk of overdosing. Patients should experience a periodic phase (at least weekly) of polyuria, during which the effect of the medication has obviously worn off. (Ungraded Best Practice Statement)

2.16 We suggest that in post-pituitary surgery DI, a single attempt to discontinue DDAVP should be made weeks to months after surgery do determine if posterior pituitary function has recovered. (Ungraded Best Practice Statement)

2.17 In cases of adipsic DI, we suggest careful DDAVP and fluid intake titration by frequent weighing and serum sodium level monitoring. (Ungraded Best Practice Statement)

2.18 We suggest that all patients with DI wear an emergency bracelet or necklace that would inform treating medical personnel of their health problem if incapacitated. (Ungraded Best Practice Statement)
Evidence

Non-injectable treatment of central DI with a longer acting analog of vasopressin, desmopressin (1-deamino-8-D-Arginine Vasopressin, DDAVP) acts mostly on the V2 receptor and thus has only minimal vasopressor activity. The treatment of DI in the outpatient setting in patients with an intact thirst mechanism should employ the lowest DDAVP dose that allows adequate rest at night and that causes minimal disruption of individual daytime activities. Indeed, about one quarter of DI patients with an intact thirst mechanism who are treated with DDAVP have mild hyponatremia, caused by the inability to reverse the antidiuretic effect of the drug when fluid intake exceeds requirements (Behal LA, et al., Eur J Endocrinol 2015). Because of differences in work or travel schedules, and because of the high variability of medication response (Juul et al 2011), treatment must be individualized and tailored to patient requirements and practical needs.

DDAVP can be administered subcutaneously, orally, intra-nasally, or sublingually as a melt (the latter form is not available in all countries). In all forms, treatment must be dosed with careful monitoring of clinical response to prevent overdosing, which can result in potentially dangerous hyponatremia (Corona G Plos One). This is particularly important in elderly individuals, who may have increased renal sensitivity to the drug, and/or may have abnormalities in osmoregulation (Juul et al 2013). Oral and sublingual DDAVP absorption rates are <1%, while intranasal is ~6% (Oiso et al 2013). Oral DDAVP is available in 100, 200, and in some countries 400 mcg tablets. Sublingual melts and nasal preparations include a spray (usually 10 mcg per squirt) and a rhinyl tube (dose range 1-10 mcg). The mean dose ratio of sublingual: intranasal DDAVP is 1:24 (Arima et al 2013), and preparation equivalences are shown in Table 7.
Table 7. Dose comparison of available desmopressin formulations

<table>
<thead>
<tr>
<th></th>
<th>Melts</th>
<th>Tablets</th>
<th>Spray</th>
<th>Drops</th>
<th>Injections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>0.25% (CI 0.21-0.31%)</td>
<td>0.16±0.17%</td>
<td>6.0±2.29%</td>
<td>similar to spray?</td>
<td>NA</td>
</tr>
<tr>
<td>Dose Equivalence</td>
<td>60 µg</td>
<td>100 µg</td>
<td>2.5 µg</td>
<td>2.5 µg</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>120 µg</td>
<td>200 µg</td>
<td>5.0 µg</td>
<td>5.0 µg</td>
<td>&lt;0.5 µg</td>
</tr>
<tr>
<td></td>
<td>240 µg</td>
<td>400 µg</td>
<td>10.0 µg</td>
<td>10.0 µg</td>
<td>&lt;1.0 µg</td>
</tr>
</tbody>
</table>

Sometimes hypothalamic pathology or surgery may alter the thirst mechanism due to damaged hypothalamic osmoreceptors. In these cases there is high risk of both hyper and hyponatremia, as patients cannot adjust fluid intake according to thirst (Behan et al 2015). After careful titration (requiring frequent weighing and sodium measurements), a fixed dose of DDAVP and a constant amount of fluid intake is suggested, together with consistent environment temperature and humidity conditions (Janus et al 2014).

Interactions Between Replacement Hormones

Glucocorticoids and Growth Hormone

2.19 We suggest testing HPA axis functionality before and after starting GH replacement if patients are not receiving GC replacement and in patients who have demonstrated apparently normal pituitary-adrenal function. (2|ΦOOO)

Evidence

Many features of hypopituitarism, such as visceral obesity, insulin resistance, osteoporosis, and increased vascular mortality are reminiscent of Cushing’s syndrome. Patients with GHD in the setting of hypopituitarism demonstrate an increased cortisol/cortisone metabolite ratio and reduced circulating cortisol concentrations on HC replacement.
As GH suppresses the conversion of cortisone to cortisol, patients receiving glucocorticoid replacement may require higher doses once GH is initiated, and those with low adrenal reserve may be rendered hypo-adrenal (Giavoli JCEM 89:5397 2004) 52.

**Glucocorticoids and Thyroid**

2.20 We suggest that patients with CH should be evaluated for adrenal insufficiency prior to starting L-T4 therapy. If this is not feasible, patients with CH should receive empiric glucocorticoid therapy when starting L-T4 therapy until a definitive evaluation for adrenal insufficiency can be completed. (2[]OO)

**Evidence**

It is suggested that AI be conclusively excluded prior to initiating L-T4 therapy in CH. This is based on the fact that thyroid hormone accelerates endogenous cortisol clearance and could unmask insufficient cortisol production and precipitate adrenal crisis. If L-T4 therapy is started prior to evaluation, it is recommended that empiric glucocorticoid replacement therapy be initiated simultaneously until a definitive evaluation is completed (Persani L, 2012).

Physiologic and pharmacologic doses of GC suppress TSH levels (Haugen B, 2009). CH patients do not appear to require L-T4 dose adjustments based on glucocorticoid therapy (Alexopoulou O, 2004).

**Glucocorticoids and Estrogen**

2.21 We suggest considering that total serum cortisol level can be falsely elevated due to the effects of estrogen on cortisol-binding globulin (CBG) when assessing adrenal reserve or adequacy of hydrocortisone replacement. (2[]OO)
Evidence

About 95% of circulating cortisol is bound mainly to CBG and to a lesser extent to albumin, and unbound cortisol is the active fraction. Oral estrogen therapy increases circulating CBG (through a hepatic first pass effect) leading to increased total cortisol levels; this is not seen with transdermal estrogen therapy (Shifren et al., 2007; Qureshi et al., 2007).

Growth Hormone and Thyroid

2.22 We recommend that euthyroid patients with GHD be monitored for the risk of developing CH upon instituting GH therapy, and if fT4 levels decrease below the reference range, L-T4 should be initiated. CH patients with GHD who are already receiving L-T4 may require increased L-T4 doses when GH therapy is instituted to maintain fT4 levels within target ranges. (1|O O)

2.23 We suggest treating CH prior to GH stimulation testing because CH may impair the accurate diagnosis of GHD. (2|O O)

Evidence

Administering GH to GHD adults causes variable changes in thyroid hormone levels, with the most consistent effect being decreased fT4 levels (Jorgensen J, 1989, Porretti S, 2002, Martins M, 2007). Some studies also report increases of fT3 levels, with no significant effects on TSH levels. These effects can decrease fT4 levels into the hypothyroid range, suggesting that untreated GHD can mask CH by artificially maintaining fT4 levels in the reference range. In patients with GHD, 36-47% of euthyroid patients and 16-18% of treated CH patients developed low fT4 levels within 3-6 month of starting GH therapy (Jorgensen J, 1994, Agha A, 2007). Most patients at increased risk of developing CH while receiving GH had previously undergone surgery and/or radiation therapy for pituitary tumors, had lower
basal T4 levels and were more likely to have other multiple hormone deficiencies. GHD patients should be monitored for developing CH approximately 6 weeks after GH therapy is started or adjusted (Losa Thyroid 18:1249, 2008). Alexopoulou et al. reported that only men with CH required increased L-T4 doses after starting GH therapy (1.8 vs. 1.6 mcg/kg/day) (Alexopoulou O, 2004).

The hypothalamic-pituitary-thyroid axis also influences GH dynamics, with altered GH and IGF-I secretion observed in hypothyroidism (Behan L, 2011). IGF-I levels are reduced in hypothyroidism, and GH stimulation with insulin or GHRH may be blunted (Filipsson H, 2009, Schmid C, 2006). GH deficiency could be over diagnosed in the setting of CH, which should be treated prior to stimulation testing for GHD.

**Estrogen and Thyroid Hormones**

2.24 In patients with CH requiring changes in estrogen therapy, we recommend monitoring T4 levels and adjusting L-T4 doses to maintain fT4 levels in target ranges. (1|ΘΘΘΟ)

**Evidence**

Increased serum estrogen levels, whether endogenous (pregnancy), or exogenous (estrogen replacement therapy, oral contraceptives), result in increased L-T4 dose requirements in patients with primary hypothyroidism (Stagnaro-Green A, 2011). This is due to estrogen-dependent liver production of thyroid binding globulin (TBG). Estrogen therapy increased mean L-T4 dose requirements in patients with CH from 1.3 to 1.8 mcg/kg/day (Alexopoulou O, 2004).

**Growth Hormone and Estrogen**

2.25 We suggest that women on oral estrogen replacement receive higher GH doses compared with eugonadal females or males. (2|ΘΘΟΟ)
Evidence

Oral estrogen treatment leads to decreased circulating IGF-I levels in GH-deficient women resulting in increased postprandial lipid oxidation and decreased protein synthesis, thereby antagonizing metabolic actions of GH. This is not observed when estrogen is administered transdermally, suggesting a first-pass effect of estrogen and inhibition of hepatic GH actions (Gibney et al., 2005; Mah et al., 2005; Cook et al., 1999). Studies showed that women on oral estrogen might require a GH replacement dose up to 50% higher compared with women who are not on estrogen (Cook et al., 1999) or men. (Cook DM, 2004).

Glucocorticoids and Diabetes Insipidus

2.26 Because AI may mask the presence of partial DI, we suggest monitoring for the development of DI after starting GC replacement. Conversely, improved DI in a patient without the diagnosis of AI should prompt testing for this deficiency. (2|@OOO)

Evidence

Glucocorticoid deficiency induces impaired free renal water clearance, resulting in the masking of polyuria in DI (Linas SL et al., 1980).

Risk of Hormonal Overreplacement in Hypopituitarism

Bone Disease

2.27 GC replacement should be individually assessed and over-replacement avoided to reduce the risk of osteoporosis. We suggest low-dose HC replacement since this approach might be associated with increased bone formation and a positive bone remodeling balance. (2|@@@OOO)
2.28 In men with hypopituitarism overreplaced with GC and at risk for fractures, we suggest identifying patients with unsuspected vertebral fractures. (2|9|9|0|0)

2.29 We suggest L-T4 replacement should be monitored as recommended in previous sections, and over-replacement avoided to reduce the risk of fractures. (2|9|9|0|0)

Evidence

Very few studies have assessed the impact of GC dose optimization on markers of bone formation and resorption. 42

A post hoc analysis 56 from a prospective single-center study on 175 adult patients with hypopituitarism (including GHD) showed that patients with AI receiving near physiological doses of HC did not exhibit a greater therapeutic response to GH than their counterparts not on GC replacement. In patients with AI on three different replacement regimens (for at least 4 weeks), replacement was associated with low serum ionized calcium levels without evidence of compensatory increased parathyroid hormone (PTH) levels; this was consistent with the direct or indirect suppression of bone remodeling and suppression of PTH levels. 57

Another small open cross-over study in hypopituitary men randomized to three commonly used HC dose regimens, low-dose HC replacement (10 mg a.m. and 5 mg p.m.) was associated with increased bone formation and positive bone remodeling balance and with probable long-term beneficial effect on bone health. 58
Over-replacement with GC in male patients with pituitary dysfunction can increase vertebral fracture risk, despite the restoration of gonadal status. In a cross-sectional study also in male hypopituitary patients receiving a median daily doses of HC 30 mg and cortisone 35 mg, 60% of patients had vertebral fractures. The risk of fracture correlated with untreated GHD, urinary cortisol values, and cortisone doses. In patients on GH replacement, the prevalence of vertebral fractures was not influenced by either cumulative or current cortisone doses.

L-T4 over-replacement in patients with primary hypothyroidism may increase bone turnover and increase the fracture risk, especially in postmenopausal women. Similarly, in a cautionary study in adult CH patients treated with 1.1 mcg/kg/day L-T4, higher daily L-T4 doses were associated with a higher prevalence of vertebral fractures assessed by lateral spine x-rays (Mazziotti G, 2014). This finding raises the question of possible adverse effects of targeting higher fT4 levels. CH patients should be monitored for the development of low bone mass, although there are no studies that assess the risks and benefits of adjusting L-T4 doses in CH based on bone health in addition to other clinical parameters.

Cardiovascular Risks in Patients with Hypopituitarism on Replacement Therapy

Glucocorticoid Overreplacement

2.30 In patients with central AI we recommend using the lowest dose of HC replacement tolerated to potentially decrease risk of metabolic, cardiovascular, and thromboembolic disease.

Evidence

Higher GC replacement doses in patients with ACTH deficiency are associated with increased overall and cardiovascular mortality; the greatest risk is in patients receiving daily HC doses higher or equal to 30 mg. This highlights the importance of providing patients with an adjustable GC replacement therapy regimen.
In a randomized crossover study, peripheral and hepatic insulin resistance did not differ between treating with HC twice daily (15 mg with breakfast, 5 mg with evening meal) versus physiological HC infusion. Short-term GC replacement increase (7-day increase in HC to 30 mg/day) resulted in reduced endothelial function and improved left ventricular systolic loading. Endothelial dysfunction, likely a direct effect of higher GC doses, may contribute to excess cardiovascular mortality in treated ACTH-deficient patients.

A dose reduction might be also associated with clinical improvement. When GC dose was halved (from 20-30 mg to 10-15 mg HC daily), mean body weight decreased by 7.1 kg after 6-12 months. In a prospective study, 13 patients with hypopituitarism taking 30 mg HC did not exhibit improvement in weight, 24-hour UFC, glucose, and HbA1C.

Patients with partial central adrenal insufficiency might be more likely to be over-treated. There is no apparent dose-dependent difference in integrated cortisol daily curves between patients on half-dose or no HC replacement, suggesting that current conventional full GC replacement doses might over treat patients with partial ACTH deficiency.

Due to the known increased risk of thromboembolism in patients with Cushing’s syndrome, it is presumed that non-physiological GC replacement regimens might contribute to this risk. However, when comparing low-dose versus high GC regimens (17.5 mg HC vs. 30 mg daily) for 2 weeks, fibrinolytic-coagulation parameters were not altered.
Thyroid Replacement

2.31 To avoid possible long-term cardiovascular risks of insufficient or excess thyroid hormone
treatment, L-T4 doses should be adjusted to avoid low or elevated fT4 levels in CH. (Ungraded Best
Practice Statement)

Remarks

Long-term cardiovascular risks of CH have not been well studied. However, recent evidence
suggests that mild hyper- or hypothyroidism may increase overall and cardiovascular-specific mortality
and morbidity (Collet TH 2014, Rhee CM 2013, Asvold BD 2012, Tseng FY 2012, Selmer C 2014,
Collet TH 2012).

Estrogen and Testosterone Replacement

The overall impact of estrogen and T replacement on cardiovascular disease in patients with
central hypogoandism is unclear.

Treatment with estrogens through age 45 years or longer may reduce the risk of cardiovascular
disease and mortality (Lokkegaard et al., 2006; Rivera et al., 2009; Rocca et al., 2012). Results of the
Women’s Health Initiative (that included participants aged on average 63 years) showed that combined
hormone therapy increases the risk of cardiovascular events. These results cannot be extrapolated to
younger women with premature ovarian failure (Rossouw et al., 2002).
Testosterone therapy in males with central hypogonadism reduces fat mass and increases fat-free mass (Katznelson et al., 1996; Brodsky et al., 1996; Bhasin et al., 1997; McNicholas et al., 2003; Wang et al., 2004). An analysis of 19 studies on the effects of intramuscular administration of T esters (Whitsel et al., 2001) reported a small, dosage-dependent decrease in HDL cholesterol and a concomitant reduction in total and LDL cholesterol. Given the lack of long-term randomized placebo controlled trials in males with central hypogonadism, the overall impact of T replacement on cardiovascular disease or mortality is unclear.

3. Special Circumstances

Cushing’s Disease

3.1 GC replacement is recommended until full HPA axis recovery after surgical resection of ACTH-secreting tumors. (1|ΩΩΩ)

3.2 After curative surgery for Cushing’s disease, we recommend retesting thyroid and GH axes before starting replacement treatment. (1|ΩΩΩ)

Evidence

ACTH excess from a pituitary tumor will suppress normal pituitary corticotroph cells, and AI can persist for years after surgical tumor resection. In 16 studies assessing recovery of adrenal function after successful treatment for Cushing’s (Crowley et al., 2014), most patients recovered HPA axis by 2 years. GC replacement is recommended until full HPA axis recovery 37, 68.

In the context of multiple pituitary deficiencies associated with Cushing’s disease 69, 70, the need for hormonal replacement (thyroid, GH) should be re-assessed after surgery, and replacement should not be started before repeat testing of the HPA axis. (Nieman 2015, Link to Cushing’s guidelines).
Prolactinomas

3.3 We recommend reassessment of the gonadotroph axis in patients with macroprolactinoma and central hypogonadism who have been treated successfully with a dopamine agonist. (1|⊕⊕⊕O)

Evidence

Treatment with dopamine agonists leads to normoprolactinemia in 68% (range 40-100%) and tumor shrinkage in 62% (range 20-100%) of patients with macroprolactinoma (Melmed et al., 2011) leading to recovery of pituitary deficits. The reversal of hypogonadism has been reported in 44-62% of the cases usually within 6 months after starting treatment. (Colao et al., 2004; Karavitaki et al., 2013)

Furthermore, recovery of other hormonal axes has been reported following adenoma shrinkage (Warfield, 1984 and hormonal re-evaluation should be performed aiming to avoid unnecessary life-long hormone replacement.

GH Replacement in Cured Acromegaly after Surgery and/or Radiation

3.4 We suggest low-dose GH replacement in patients with cured acromegaly and documented GHD in the absence of known contraindications. (2|⊕OOO)

Evidence

Acromegaly patients, after rigorous GH dynamic testing and documentation of GHD, may benefit from low-dose GH replacement (Mazziotti trends in endo 2015). Features of accelerated GHD may develop in acromegaly patients after surgical resection of a GH-secreting adenoma. In patients undergoing GH secreting adenoma resection, immediate (72 hours) post-operative GH levels as well as bilaterality of intrasellar tumor involvement are significant determinants of subsequent GHD (seen in about 10% of patients) (Ku EJE 2014). In a large retrospective analysis, overall mortality was similar;
however, cardiovascular mortality was higher in GHD associated with treated acromegaly as compared to non-functioning pituitary adenomas (SMR 3.03, p < 0.02) (Tritos JCEM 2014).

In a randomized placebo-controlled study, mean GH doses of 0.58 mg/day resulted in decreased visceral fat mass and improvement in QOL indices (Miller k JCEM 2012). In 42 subjects prospectively studied, GH replacement was shown to enhance QOL and improve both body composition and lipid profiles (Giavoli JCEM 2014). These benefits appear to occur without incurring the risk of glucose intolerance.
Peri-operative Management of Hypopituitarism

Pituitary Surgery

3.5 We recommend using stress doses of steroids in AI before surgery and tapered doses after surgery until repeat testing is performed. (1|⊕⊕Ο)

3.6 We suggest short-term administration (until HPA axis can be evaluated) of prophylactic GC postoperatively in patients with normal preoperative adrenal function. (2|⊕ΟΟ)

3.7 With preoperative CH, we recommend L-T4 therapy be instituted for non-emergency surgery and continued through the peri-operative period. (1|⊕ΟΟ)

3.8 With intact pre-operative thyroid function, we recommend fT4 levels be measured 6-8 weeks post-operatively to assess for CH. (1|⊕ΟΟ)

3.9 We suggest that initial therapy for DI utilizes short-acting subcutaneous aqueous vasopressin, allowing for safer use in the vast majority of cases in whom DI resolves spontaneously. (2|⊕ΟΟ)

3.10 We suggest against pre-scheduled DDAVP dosages in the first week post-surgery because of risk of hyponatremia after transient DI resolves, and risk of SIADH risk that may occur 7-10 days after surgery. (2|ΟΟΟ)

3.11 We suggest oral or intranasal DDAVP after discharge, with clear instruction that the medication should be used only if significant polyuria occurs. (2|ΟΟΟ)
3.12 We suggest retesting all pituitary axes starting at 6 weeks post pituitary surgery then periodically for a year to monitor the development or resolution of pituitary deficiencies. (2|6|6|0)0

Evidence

Pituitary adenomas, as well as the surgical and radiation treatment, can cause hypopituitarism. Rates of pituitary axes recovery or new onset hypopituitarism after transphenoidal surgery TSS vary significantly between studies (Greenman, JCEM, 1995; Berg, EJE, 2010; Yedinak, Pituitary, 2015).

In pre-operative AI, stress doses of GC should be started before surgery, depending on clinical circumstances. Stress dose are tapered after surgery and discontinued if repeat testing shows a normal HPA axis. GC postoperatively in patients with normal preoperative adrenal function has been widely used. However, a postoperative AM cortisol level higher than 15 mcg/dL may mitigate the requirement for GC treatment (Marko, 2009).

Pre-operative CH should be treated with L-T4. If surgery is not urgent, it may be optimal to wait until CH is adequately treated to optimize surgical outcomes, however perioperative complications seem to be minor (Ladenson PW 1984, Weinberg A 1983). Replacement L-T4 should be continued through the peri-operative period, and fT4 levels checked 6 weeks later for adequacy of the L-T4 dose. If patients were not started on L-T4 pre-operatively, or L-T4 was not continued post-operatively, patients should be evaluated for the development of CH by measuring fT4 levels 6-8 weeks following surgery since the serum half-life of T4 is 7 days.

DI occurs commonly in the immediate (day 1-2) period after pituitary or hypothalamic surgery (Devin 2012). Post-surgical abundant diuresis may also be caused by steroid–induced hyperglycemia, abundant intra-operative fluid administration, and (in the case of acromegaly) abrupt reduction of serum GH levels. (Zada G 2010) The incidence of postoperative DI is increased by high-dose perioperative
glucocorticoids, possibly mediated by an increased glomerular filtration rate (Rajaratnam et al 2003), and reduced ADH secretion and renal sensitivity to the hormone (Raff H Am J Physiol. 1987; Baylis C, Semin Nephrol. 1990; Raff, H., American Journal of Physiology, 1990).


Non-Pituitary Surgery

3.13 Day of surgery: we recommend adjusting glucocorticoid dose according to the severity of illness and magnitude of the stressor. (1|⊗⊗⊗O)

3.14 Minor to moderate surgical stress: we suggest HC 25-75 mg/24 h (usually 1 to 2 days). (2|⊗⊗ΟΟ)

3.15 Major surgical stress: we suggest Hydrocortisone 100 mg per IV injection followed by continuous IV infusion of 200 mg hydrocortisone/24 hours (alternatively 50 mg q6h IV or IM). (2|⊗⊗ΟΟ)

Evidence

Adults secrete 75-100 mg of cortisol/day in response to major surgery and 50 mg/day in response to minor surgery (Salem et al, 1994). Cortisol secretion in the first 24 hours after surgery rarely exceeds 200 mg and correlates with the duration and extent of surgery (Salem et al, 1994). Lower doses of hydrocortisone (25-75 mg/24 hour) have been suggested for surgical stress in secondary AI (Salem et al, 1994; Glowniak, Loriaux, 1997).
Management of Hypopituitarism in Pregnancy

As fertility is often impaired in hypopituitarism, natural pregnancy is rare. A multidisciplinary team is required for fertility induction and the management of hypopituitary women.

Glucocorticoids

The diagnosis of AI may be missed in the first trimester due to confounding symptoms of normal pregnancy. A low morning cortisol <3 ug/dL is diagnostic of AI. Plasma cortisol can be falsely “normal” because of increased cortisol-binding globulin in the second and third trimesters. Normal pregnancy ranges are available for cortisol values.

HC is the preferred GC replacement in pregnancy and represents physiologic replacement; it is degraded by the enzyme 11beta-HSD2 and does not cross the placenta. Using a replacement dose of 12-15 mg/m² with adjustments based on clinical judgment is suggested. During labor and delivery, women require stress dose GC (50 mg intravenous HC in the second stage of labor). For cesarean section, a dose of 100 mg every 6-8 hours is recommended.

Management of PAI in pregnancy is reviewed in the Endocrine Society guidelines; GC recommendations are similar in central AI and PAI. Notably, patients with central adenal insufficiency do not require mineralocorticoid replacement (Bornstein S. et al., JCEM, to be published 2015).

Thyroid

3.16 We recommend that women with CH who become pregnant should have monitoring of fT4 or total T4 levels every 4-6 weeks, and may require increased L-T4 doses to maintain levels within target ranges. (1│0│0│0)
Evidence

Treatment of hypothyroidism is critical for optimal pregnancy outcomes and fetal brain development. Many women with primary hypothyroidism require significant (20-50%) increases in L-T4 doses early in pregnancy to maintain normal thyroid hormone levels (Stagnaro-Green A, 2011) due to increased TBG levels secondary to high serum estradiol levels. Current recommendations include increasing L-T4 doses by two extra pills (at previous dose) per week upon confirmation of pregnancy with further dose adjustments based on thyroid hormone and TSH levels. However, women with CH may not require the same degree of L-T4 dose escalation due to hCG stimulation of an intact thyroid gland, at least during the first trimester. It is prudent to monitor pregnant women with CH closely with L-T4 dose adjustments based on thyroid hormone levels. L-T4 doses should be reduced back to pre-pregnancy levels immediately after delivery to avoid iatrogenic hyperthyroidism.

In contrast to primary hypothyroidism, serum TSH levels in CH are not useful for monitoring L-T4 doses in pregnancy. Therefore, either fT4 or total T4 levels should be used depending on local experience with fT4 assay performance in pregnant patients. Many fT4 assays are imprecise in pregnant samples; an alternative approach is to monitor total T4 levels, adjusting the non-pregnant reference range upward by 50% to account for TBG effects (Stagnaro-Green A, 2011).

**DDAVP**

3.17 In pregnant women with pre-existing DI, we suggest continuing DDAVP during pregnancy and adjusting doses if required. (2|0|0|0)
Evidence

During pregnancy, serum sodium and osmolarity are reduced due to a decreased threshold for vasopressin release and thirst mechanism (Durr & Lindheimer 1996). The placenta produces large amounts of the enzyme vasopressinase, which degrades endogenous vasopressin, requiring an increased secretion. Pregnancy may unmask mild forms of DI, which often occurs with subsequent pregnancies.

In general, the DDAVP requirement is unchanged but sometimes might be slightly higher (Ball 2007). Exposure to DDAVP during pregnancy is safe (Kallen et al 1995), and DDAVP is generally considered safe for the newborn in lactating mothers (Durr & Lindheimer 1996).

Growth Hormone

3.18 We suggest discontinuing GH replacement during pregnancy, as there is no clear evidence yet for efficacy or safety. (2|⊕⊕ΟΟ)

Pituitary Apoplexy

3.19 We recommend testing for acute pituitary insufficiency in all patients with pituitary apoplexy. (1|⊕⊕ΟΟ)

3.20 As acute AI is a major cause of mortality, we recommend GC therapy until laboratory diagnosis is established and normal pituitary function is maintained. (1|⊕⊕ΟΟ)

3.21 We recommend monitoring pituitary axes after the acute episode with surgical decompression or conservative management, as reversibility of panhypopituitarism may occur after both. (1|⊕⊕ΟΟ)
Evidence

Pituitary apoplexy is a life-threatening acute pituitary infarction, hemorrhage, and/or necrosis presenting as rapid onset headache, and may include vomiting, fever, meningismus, vision abnormalities, and changes in mental status\(^73\). Partial or complete hypopituitarism is a prominent feature and contributes to high mortality\(^74,75\). Pituitary apoplexy should be diagnosed early and treated promptly (Capatina et al, 2014).

Pituitary dysfunction may be due to preexisting deficiencies\(^16-18\) or occur quickly from a rapid increase of intrasellar pressure\(^74\). Patients present with variable decreases in pituitary hormones, although diabetes insipidus is uncommon\(^74\), with an incidence of 4% for transient and 2% for persistent DI. Differences in anterior and posterior pituitary blood supply may explain the relative sparing of antidiurectic hormone secretion\(^75\).

Transsphenoidal decompression and immediately instituting high-dose intravenous corticosteroid replacement therapy are the standard of care\(^76-78\). However, conservative management in a carefully selected group of patients is also advocated\(^79\).

Recognizing acute secondary AI is critical, and prompt GC therapy should be started to prevent AC. High dose GC may also improve visual outcomes\(^76\). When patients cannot tolerate oral medications, they should be started on 100-200 mg of intravenous HC bolus followed by 2-4 mg per hour by continuous infusion or 50-100 mg injections every 6 hours\(^80\). Hydrocortisone should be quickly tapered and standard oral maintenance doses of 15-30 mg per day initiated with clinical improvement. High doses of dexamethasone have also been used for the treatment of pituitary apoplexy.
Hypopituitarism may be permanent or transient after pituitary apoplexy, with recovery occurring from weeks to months from the initial event. More than 50% of patients eventually require hormonal replacement. There is no consensus on whether surgical treatment improves pituitary function, but an increased incidence of hormonal deficiencies was reported with conservative management. In one study, transsphenoidal surgery achieved a return of normal pituitary function in most patients in the immediate postoperative period, although these findings have not been replicated in larger studies. Advocates of conservative management argue that there is no difference in long-term hypopituitarism rates between surgically managed and carefully selected conservatively treated patients.

Treatment of Hypopituitarism in Patients Receiving Antiepileptic Medications

3.22 In patients with AI on non-dexamethasone GCs who start enzyme-inducing antiepileptic drugs (AED), we suggest education about early signs and symptoms of AI.

3.23 In patients with AI on dexamethasone, we suggest increasing dexamethasone replacement doses if enzyme induced AED are co-administered.

3.24 In CH patients receiving L-T4, we recommend checking fT4 at least 6 weeks after starting an AED, and increasing L-T4 doses if fT4 levels decrease below the target range.

3.25 We suggest assessment of AED dose in women starting estrogen replacement.

3.26 We suggest monitoring of DDAVP dose and further adjustments as needed.
Evidence

Some AEDs enhance hepatic CYP450 isoenzyme activity (e.g., phenytoin, carbamazepine, oxcarbazepine, and topiramate), accelerating the hepatic metabolism of hormonal preparations and decreasing serum concentrations of relevant hormones. Effects depend on the type of GC.

Dexamethasone is metabolized primarily by hepatic CYP3A4, and dexamethasone doses may need to be increased (Paragliola, 2014). AEDs only modestly decrease the concentrations of prednisone and prednisolone. CYP3A4-mediated 6β-hydroxylation may not contribute significantly to the breakdown of cortisol; therefore, while AED are less likely to be clinically significant in patients treated with Hydrocortisone, caution is always needed when patients with adrenal insufficiency are treated with any type of GC.

AEDs accelerate thyroxine and sex hormone clearance, and patients may require compensatory increases in hormone replacement doses (Carl 2008). As FT4 measurements may be impaired by phenytoin, a equilibrium dialysis FT4 assay is preferred. Other AEDs increase SHBG leading to the reduced bioavailability of estradiol and T (Paragliola et al., 2014) and may compromise the efficacy of hormonal treatment. Combined estrogen and progesterone may decrease lamotrigine levels (Harden et al., 2006), and endogenous and exogenous sex steroids may affect seizure activity and epilepsy in women (Erel et al., 2010).

The addition of carbamazepine, oxcarbazepine, lamotrigine, perapanel, or felbamate to DDAVP therapy can cause hypotremia by increasing DDAVP renal responsiveness (Paragliola et al 2014).
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