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

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Objective: To formulate clinical practice guidelines for hormonal replacement in hypopituitarism in adults.

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

Evidence: The Task Force developed this evidence-based guideline 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 in adults, including appropriate biochemical assessments, specific therapeutic decisions to decrease the risk of co-morbidities due to hormonal over-replacement or under-replacement, and managing hypopituitarism during pregnancy, pituitary surgery, and other types of surgeries. **(*J Clin Endocrinol Metab* 101: 3888–3921, 2016)**

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Abbreviations: AC, adrenal crisis; ADH, antidiuretic hormone; AED, antiepileptic drug; AGHD, adult GHD; AI, adrenal insufficiency; BMD, bone mineral density; BMI, body mass index; CBG, corticosteroid-binding globulin; CH, central hypothyroidism; CI, confidence interval; DI, diabetes insipidus; DDAVP, desmopressin; E2, estradiol; fT3, free T_3; fT4, free T_4; GC, glucocorticoid; GHD, GH deficiency; HC, hydrocortisone; HDL, high-density lipoprotein; HPA, hypothalamic-pituitary-adrenal; HRT, hormonal replacement therapy; LC-MSMS, liquid chromatography-mass spectrometry; LDL, low-density lipoprotein; L-T3, levotriiodothyronine; L-T4, levothyroxine; MRI, magnetic resonance imaging; PRL, prolactin; QOL, quality of life; SMR, standard mortality ratio; TBG, thyroid-binding globulin.

Summary of Recommendations

1.0 Diagnosis of hypopituitarism

Central adrenal insufficiency

1.1 We suggest measuring serum cortisol levels at 8–9 AM as the first-line test for diagnosing central adrenal insufficiency (AI). (2|⊕◯◯◯)

1.2 We recommend against using a random cortisol level to diagnose AI. (1|⊕⊕◯◯)

1.3 We suggest that a cortisol level <3 μg/dL is indicative of AI and a cortisol level >15 μg/dL likely excludes an AI diagnosis. (2|⊕◯◯◯)

1.4 We suggest performing a corticotropin stimulation test when morning cortisol values are between 3 and 15 μg/dL to diagnose AI. Peak cortisol levels <18.1 μg/dL (500 nmol/L) at 30 or 60 minutes indicate AI. (2|⊕⊕◯◯)

1.5 We suggest that clinicians perform biochemical testing for the hypothalamic-pituitary-adrenal (HPA) axis at least 18–24 hours after the last hydrocortisone (HC) dose or longer for synthetic glucocorticoids (GCs). (2|⊕⊕◯◯)

Central hypothyroidism

1.6 We recommend measuring serum free T_4 (fT4) and TSH to evaluate central hypothyroidism (CH). An fT4 level below the laboratory reference range in conjunction with a low, normal, or mildly elevated TSH in the setting of pituitary disease usually confirms a CH diagnosis. (1|⊕⊕⊕⊕)

1.7 In patients with pituitary disease and low-normal fT4 levels suspected to have mild CH, we suggest starting levothyroxine (L-T4) if suggestive symptoms are present or following fT4 levels over time and starting treatment if the fT4 level decreases by 20% or more. (2|⊕◯◯◯)

1.8 We suggest against using dynamic TSH-secretion testing to diagnose CH. (2|⊕⊕⊕◯)

GH deficiency

1.9 In patients with suspected GH deficiency (GHD), we recommend GH stimulation testing. Single GH measurements are not helpful. (1|⊕⊕⊕◯)

1.10 We recommend using appropriately controlled body mass index (BMI) cutoffs to assess peak GH values. (1|⊕⊕◯◯)

1.11 We suggest against biochemical testing for GHD in patients with clear-cut features of GHD and three other documented pituitary hormone deficits. (2|⊕⊕⊕◯)

Central hypogonadism in males

1.12 In males with suspected hypogonadism, we recommend measuring serum T, FSH, and LH to diagnose central hypogonadism. (1|⊕⊕◯◯)

1.13 We recommend that clinicians perform hormonal testing for central hypogonadism in males in the absence of acute/subacute illness and before 10 AM (after overnight fast) combined with serum prolactin (PRL). (1|⊕⊕◯◯)

Central hypogonadism in females

1.14 In the presence of oligomenorrhea or amenorrhea, we recommend measuring serum estradiol (E2), FSH, and LH. Clinicians should exclude other causes of menstrual irregularities related to impaired ovulation (hyperprolactinemia, hyperandrogenism, and thyroid disease), particularly if no other pituitary hormone deficits are present. In cases of amenorrhea, clinicians should also exclude pregnancy. (1|⊕⊕◯◯)

1.15 We suggest against dynamic testing with GnRH, which offers no useful diagnostic information. (2|⊕⊕◯◯)

1.16 We recommend that in postmenopausal women, the absence of high serum FSH and LH is sufficient for a diagnosis of gonadotrope dysfunction (provided the patient is not on hormonal replacement therapy [HRT]). (1|⊕⊕⊕◯)

Central diabetes insipidus

1.17 We recommend simultaneously measuring serum and urine osmolarity in patients with polyuria (more than 50 mL/kg of body weight/24 hours, 3.5 L/d 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 ratio should be ≥2), whereas urine dipstick should be negative for glucose. (1|⊕⊕⊕◯)

2.0 Treatment

Hormonal replacement in panhypopituitarism

Glucocorticoid replacement

2.1 We recommend using HC, usually 15–20 mg total daily dose in single or divided doses. Patients using divided doses should take the highest dose in the morning at awakening and the second in the afternoon (two-dose regime) or the second and third at lunch and late afternoon, respectively (three-dose regime). (1|⊕⊕⊕◯)

2.2 We suggest using longer-acting GCs in selected cases (eg, nonavailability, poor compliance, convenience). (2|⊕◯◯◯)

2.3 We recommend that clinicians teach all patients with AI regarding stress-dose and emergency GC administration and instruct them to obtain an emergency card/bracelet/necklace regarding AI and an emergency kit containing injectable high-dose GC (1|⊕⊕⊕◯)

2.4 We recommend against using fludrocortisone in patients with secondary AI. (1|⊕⊕⊕◯)

Adrenal crisis

2.5 We recommend that clinicians treat patients with suspected adrenal crisis (AC) due to secondary AI with an immediate parenteral injection of 50–100 mg HC. (1|⊕⊕⊕◯)

Thyroid hormone replacement

2.6 We recommend 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 μg/kg/d, with dose adjustments based on clinical context, age, and fT4 levels. (1|⊕⊕⊕◯)

2.7 We suggest against treating CH with levotriiodothyronine (L-T3), thyroid extracts, or other formulations of thyroid hormones. (2|⊕⊕◯◯)

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

Testosterone replacement

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

Estrogen replacement in premenopausal women

2.10 We recommend gonadal hormone treatment in premenopausal women with central hypogonadism, provided there are no contraindications. (1|⊕⊕⊕◯)

GH 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/d for patients younger than 60 years and 0.1–0.2 mg/d for patients older than 60 years. (1|⊕⊕⊕◯)

2.12 We recommend titrating GH doses and maintaining IGF-1 levels below the upper limit of normal and reducing the dose if side effects manifest. (1|⊕◯◯◯)

2.13 We suggest against administering GH to elderly adults with age-adjusted low IGF-1 levels and no history of pituitary or hypothalamic disease. (2|⊕◯◯◯)

2.14 We recommend against using GH to enhance athletic performance because this practice is illegal in the United States, has poor scientific or ethical justification, and does not have substantiated efficacy. (Ungraded Good Practice Statement)

Diabetes insipidus

2.15 When administering desmopressin (DDAVP) in diabetes insipidus (DI), we suggest individualized therapeutic schedules. Although clinicians should offer therapy to all patients, 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 clinicians educate all patients receiving DDAVP about the risk of overdosing. Periodically (at least weekly), patients should experience a phase of polyuria during which the effect of the medication has obviously worn off. (Ungraded Good Practice Statement)

2.16 In postpituitary surgery DI, we suggest that clinicians should make at least one attempt to discontinue DDAVP during the weeks/months after surgery to determine whether posterior pituitary function has recovered. (Ungraded Good Practice Statement)

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

2.18 We suggest that all patients with DI wear an emergency bracelet or necklace to inform clinicians of the patient's health problem if incapacitated. (Ungraded Good Practice Statement)

Interactions between replacement hormones

Glucocorticoids and GH

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

Glucocorticoids and thyroid hormone

2.20 We suggest evaluating patients with CH for AI before starting L-T4 therapy. If this is not feasible, clinicians should prescribe empiric GC therapy in patients with CH who are starting L-T4 therapy until there is a definitive evaluation for AI. (2|⊕⊕◯◯)

Glucocorticoids and estrogen

2.21 We suggest that when clinicians assess adrenal reserve or the adequacy of HC replacement, they take into consideration that total serum cortisol level can be elevated due to the effects of estrogen on corticosteroid-binding globulin (CBG). (2|⊕⊕⊕◯)

GH and thyroid hormones

2.22 We recommend that clinicians monitor euthyroid patients with GHD who begin GH therapy for the risk of developing CH, and if fT4 levels decrease below the reference range, these patients should begin L-T4 therapy. CH patients with GHD who are already receiving L-T4 may require increased L-T4 doses when they begin GH

therapy to maintain fT4 levels within target ranges. (1|⊕⊕◯◯)

2.23 We suggest clinicians treat CH before performing GH stimulation testing because CH may impair the accurate diagnosis of GHD. (2|⊕⊕◯◯)

Estrogen and thyroid hormones

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

GH and estrogen

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

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, patients with improved DI without an AI diagnosis should undergo AI testing. (2|⊕◯◯◯)

Risk of hormonal over-replacement in hypopituitarism

Bone disease

2.27 Clinicians should individually assess GC replacement and avoid over-replacement to reduce the risk of osteoporosis. We suggest low-dose HC replacement because this approach might be associated with increased bone formation and a positive bone-remodeling balance. (2|⊕⊕◯◯)

2.28 In men with hypopituitarism over-replaced with GC and at risk for fractures, we suggest vertebral fracture assessment (baseline plain spinal x-rays or dual-energy x-ray absorptiometry) to identify patients with unsuspected vertebral fractures. (2|⊕⊕◯◯)

2.29 We suggest clinicians monitor L-T4 replacement, as recommended in previous sections, and avoid over-replacement to reduce the risk of fractures. (2|⊕⊕◯◯)

Cardiovascular risks in patients with hypopituitarism on replacement therapy

Glucocorticoid over-replacement

2.30 In patients with central AI, we recommend using the lowest tolerable dose of HC replacement to potentially decrease the risks of metabolic and cardiovascular disease. (1|⊕⊕⊕◯)

Thyroid replacement

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

3.0 Special circumstances

Cushing's disease

3.1 We recommend GC replacement until full HPA axis recovery after surgically resecting ACTH-secreting tumors. (1|⊕⊕⊕◯)

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

Prolactinomas

3.3 We recommend reassessing all pituitary axes in patients with macroprolactinoma and central hypogonadism who have had successful dopamine agonist treatments. (1|⊕⊕⊕◯)

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|⊕◯◯◯)

Perioperative management of hypopituitarism

Pituitary surgery

3.5 We recommend using stress doses of steroids in AI before surgery and tapered doses after surgery before repeating testing. (1|⊕⊕⊕◯)

3.6 In patients with normal preoperative adrenal function, we suggest an individualized clinical approach for postoperative GC administration until the HPA axis can be evaluated. (2|⊕⊕◯◯)

3.7 With preoperative CH, we recommend using L-T4 therapy before nonemergency surgery and throughout the perioperative period. (1|⊕⊕⊕◯)

3.8 With intact preoperative thyroid function, we recommend measuring fT4 levels 6–8 weeks postoperatively to assess for CH. (1|⊕⊕◯◯)

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

3.10 We do not suggest prescheduled DDAVP dosages in the first week postsurgery because of the risk of hyponatremia after transient DI resolves and the risk of syndrome of inappropriate ADH secretion that may occur 7–10 days after surgery. (2|⊕◯◯◯)

3.11 We suggest oral or intranasal DDAVP after discharge, with clear instructions that patients should only

use the medication if significant polyuria occurs. (2|⊕◯◯◯)

3.12 We suggest retesting all pituitary axes starting at 6 weeks after pituitary surgery and then periodically to monitor the development or resolution of pituitary deficiencies. (2|⊕⊕◯◯)

Non-pituitary surgery

3.13 On the day of surgery, we recommend adjusting GC doses according to the severity of illness and magnitude of the stressor. (1|⊕⊕⊕◯)

3.14 In cases of minor to moderate surgical stress, we suggest 25–75 mg HC per 24 hours (usually for 1–2 days). (2|⊕⊕◯◯)

3.15 In cases of major surgical stress, we suggest a 100-mg HC per iv injection followed by a continuous iv infusion of 200 mg HC per 24 hours (alternatively 50 mg every 6 hours iv or im). (2|⊕⊕◯◯)

Management of hypopituitarism in pregnancy

Glucocorticoids

3.16 We suggest using HC as the preferred GC in pregnancy and increasing the dose based on the individual clinical course; higher doses may be required, in particular during the third trimester. (Ungraded Good Practice Statement)

3.17 We suggest that pregnant patients with central AI be closely monitored for clinical symptoms and signs of GC over- and under-replacement (eg, normal weight gain, fatigue, postural hypotension or hypertension, hyperglycemia). (Ungraded Good Practice Statement)

3.18 We recommend against using dexamethasone in pregnancy because it is not inactivated in the placenta. (1|⊕⊕◯◯)

3.19 We recommend HC stress dosing during the active phase of labor, similar to that used in major surgical stress. (1|⊕⊕◯◯)

Thyroid

3.20 We recommend that clinicians monitor fT4 or total T_4 levels every 4–6 weeks for women with CH who become pregnant, and that these women may require increased L-T4 doses to maintain levels within target ranges for pregnancy. (1|⊕⊕◯◯)

Desmopressin

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

Growth hormone

3.22 We suggest discontinuing GH replacement during pregnancy because there is no clear evidence yet for efficacy or safety, and the placenta produces GH. (2|⊕⊕◯◯)

Management of hypopituitarism in pituitary apoplexy

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

3.24 Because acute AI is a major cause of mortality, we recommend GC therapy until a laboratory diagnosis is established and the patient maintains normal pituitary function. (1|⊕⊕◯◯)

3.25 We recommend that clinicians monitor pituitary axes in pituitary apoplexy patients treated with either surgical decompression or conservative management because hypopituitarism may develop over time. (1|⊕⊕◯◯)

Treatment of hypopituitarism in patients receiving antiepileptic medications

3.26 We suggest clinicians educate AI patients that are taking nondexamethasone GCs and who start enzyme-inducing antiepileptic drugs (AEDs) about the early signs and symptoms of AI. (2|⊕⊕◯◯)

3.27 In patients with AI on dexamethasone, we suggest increasing dexamethasone replacement doses if enzyme-induced AEDs are coadministered. (2|⊕◯◯◯)

3.28 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. (1|⊕⊕◯◯)

3.29 In women who have started estrogen replacement, we suggest evaluating AED levels and adjusting AED doses as required. (2|⊕⊕◯◯)

3.30 We suggest monitoring DDAVP doses and making further adjustments as needed in patients who are started on AEDs. (2|⊕⊕◯◯)

Method of Development of Evidence-Based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee (CGS) of the Endocrine Society deemed hormonal replacement in hypopituitarism 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 (1). A detailed description of the grading scheme has been published elsewhere (2). 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 recom-

mend" 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 ⊕◯◯◯ denotes very low quality evidence; ⊕⊕◯◯, low quality; ⊕⊕⊕◯, moderate quality; and ⊕⊕⊕⊕, 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 the Task Force considered in making the recommendation. In some instances there are remarks, a section in which the Task Force offers 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 Task Force and its values and preferences; therefore, one should consider these remarks as 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. The Task Force labeled these as "Ungraded Good Practice Statement." Direct evidence for these statements was either unavailable or not systematically appraised; therefore, the Task Force considers these statements out of the scope of this guideline. The intention of these statements is to draw attention to and remind providers of these principles; one should not consider these statements as graded recommendations (3).

The Endocrine Society maintains a rigorous conflict-of-interest review process for developing clinical practice guidelines. All Task Force members must declare any potential conflicts of interest by completing a conflict-of-interest form. The CGS reviews all conflicts of interest before the Society's Council approves the members to participate on the Task Force and periodically during the development of the guideline. All those participating in the guideline's development must also disclose any conflicts of interest in the matter under study, and a majority of these participants must be without any conflicts of interest. 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 commercial interest(s) in the form of grants; research support; consulting fees; salary; ownership interest (eg, stocks, stock options [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; the Task Force received no funding or remuneration from commercial or other entities.

Commissioned systematic reviews

The guideline Task Force commissioned two 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 (RR, 1.55; 95% confidence interval [CI], 1.14–2.11). Factors associated with increased mortality were female gender, younger age at diagnosis, an underlying diagnosis of a craniopharyngioma or aggressive tumor, the presence of DI, 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 a risk of pituitary tumor recurrence, secondary malignancy, or stroke. The review included seven 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.

Each review 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 AI, hypothyroidism, hypogonadism, GHD, and (more rarely) DI. Not all disorders that affect anterior pituitary function may cause DI, and DI can occur without anterior pituitary dysfunction. Hypopituitarism 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 (4). Considering evidence

from the commissioned systematic review and other evidence extracted mostly from contemporary studies on the management of hypopituitarism due to heterogeneous etiologies, it seems that mortality associated with hypopituitarism is indeed high (5–10). Recently published evidence indicates that pituitary hormonal deficits managed with the currently used replacement protocols (including nonsupraphysiological doses of HC and appropriate thyroid and gonadal hormone replacement) might not adversely affect mortality (11).

Hypopituitary patients exhibit increased incapacitation and sick days, lower health status, and higher cost of care (12, 13). Those with GHD are less often working full time, more often on sick leave/disability, and often live alone or with parents (14). Despite receiving long-term GH replacement, the working capacity of hypopituitary patients remains lower than the general population (14).

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

Central adrenal insufficiency

Central AI represents inadequate cortisol secretion due to ACTH deficiency. It can be secondary, when pituitary disease impairs the release of ACTH, or tertiary from inadequate hypothalamic CRH (15).

The prevalence of central AI (excluding exogenous steroid use) is 150–280 per million inhabitants (16); almost one-third of the patients with pituitary failure may have AI (17–19). The reported prevalence after pituitary surgery varies (20–22), with up to 90% after craniopharyngioma surgery (23). Patients who have undergone cranial radiation for nonpituitary tumors have a high prevalence of hypopituitarism (24, 25). The timing of the onset of new pituitary deficiencies after radiation varies, but in most cases it may take a few years to develop (26). A high index of suspicion is required for diagnosing AI (27) because delaying treatment can result in AC and death (16, 28–30). Mild ACTH deficiency may manifest as clinically important AI with stress (31).

Central hypothyroidism

CH is caused by insufficient TSH stimulation of a normal thyroid gland due to the inadequate secretion or action of TSH-releasing hormone and/or TSH (32, 33). Acquired CH is usually associated with other pituitary hormone deficiencies.

Approximately 50% of CH cases are caused by pituitary macroadenomas, whereas craniopharyngiomas are the most common extrasellar cause, especially in younger patients (33). The frequency of CH with nonfunctioning pituitary adenomas may reach 43% preoperatively and 57% postoperatively (34). CH occurs in up to 65% of patients irradiated for brain tumors and up to half of patients 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 T levels and features of T 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 is also high for patients who have had cranial irradiation for nonsellar lesions (35–39). Hyperprolactinemia attributed to tumors or medications is also a common cause of hypogonadism (40).

Untreated gonadotropin deficiency is an independent factor affecting mortality (hazard ratio, 1.86 [99% CI, 1.15–2.45]), and sex steroid replacement has been associated with a significantly reduced standard mortality ratio (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) (9). Androgen deprivation therapy in prostate cancer is associated with an increased incidence of myocardial infarctions and cardiovascular mortality (41–43) due to increased body weight, decreased lean body mass, increased serum low-density lipoprotein (LDL) and triglycerides, and reduced insulin sensitivity (43–46).

Early menopause is associated with increased risk of cardiovascular and cerebrovascular disease (47–50). Accordingly, bilateral oophorectomy without estrogen replacement before the age of 45 years increases cardiovascular mortality (51). One study reported a SMR of 2.09 (95% CI, 0.94–4.65) in females with untreated gonadotropin deficiency and an SMR of 0.94 (95% CI, 0.35–2.49) in those with treated hypogonadism (52).

Central (neurogenic) diabetes insipidus

Central (neurogenic) DI occurs when the secretion of ADH (also called 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 (53). DI can be congenital or acquired; it can be secondary to a variety of pathological processes including tumors (mostly craniopharyngioma and germinomas), head trauma, and inflammatory, autoimmune,

granulomatous, infectious diseases involving the hypothalamus and/or posterior pituitary. Sometimes the cause of DI is unknown ("idiopathic DI") and is thought to be autoimmune in nature. In some of these cases, periodical follow-up imaging may unveil the cause, particularly in young patients (54). DI is very rarely encountered in nonoperated pituitary adenomas (55).

Adult GH deficiency

Adult GHD (AGHD) may be present at childhood or may occur during adulthood as an acquired condition. About 6000 cases of AGHD are reported each year in the United States, with an estimated 50 000 diagnosed adults (56). In European reports, AGHD occurs at an annual incidence of 12–19 cases per million (57, 58). The prevalence after traumatic brain injury is estimated at 12% (59). Whether or not adult GH replacement in patients with proven AGHD reduces mortality is not clear because long-term controlled trials are lacking. However, GH replacement may reduce 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 (60). Untreated congenital GHD does not lead to shortened life expectancy (61).

Prolactin deficiency

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 (62). However, many cases of hypopituitarism are associated with hyperprolactinemia that occurs due to stalk interruption (63) and the absence of dopamine inhibition.

Etiology and clinical manifestations

We list the most frequent causes of acquired adult hypopituitarism in Table 1.

The most common cause of central AI is exogenous GCs that suppress ACTH; however, this review focuses on endogenous 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 to this order (eg, hypophysitis). Therefore, it can be challenging to ascribe specific features to a single hormone deficiency. We list relevant clinical features for each pituitary hormone deficiency in Table 2.

1.0 Diagnosis of hypopituitarism

Establishing the diagnosis and monitoring therapy of hypopituitarism requires an understanding of hormonal assay characteristics and limitations (Appendix A or Supplemental Table 1).

In several instances where data were lacking on the central deficiency state, we extrapolated it from studies on primary gland failure. However, this evidence may or may not be directly applicable to central pituitary deficiencies.

Table 1. Causes of Acquired Adult Hypopituitarism

Neoplastic	**Infectious**
Pituitary adenoma	Bacterial
Craniopharyngioma	Fungal
Meningioma	Parasites
Cysts (Rathke's cleft, arachnoid, epidermoid, dermoid)	Tuberculosis
Germinoma	Syphilis
Glioma	**Vascular**
Astrocytoma	Pituitary tumor apoplexy
Ganglioneuroma	Sheehan's syndrome
Paraganglioma	Intrasellar carotid artery aneurysm
Teratoma	Subarachnoid hemorrhage
Chordoma	**Traumatic**
Pituicytoma	Head injury
Ependymoma	Medications
Pituitary carcinoma	Opiates (primarily gonadotropin ACTH, GH)
Metastases	GCs (ACTH only)
Treatment of sellar, parasellar, and hypothalamic diseases	Megestrol acetate (ACTH only)
Surgery	Somatostatin analogs (GH, ACTH, TSH)
Radiotherapy	CTLA-4 blockers (ACTH, TSH, LH/FSH)
Infiltrative/inflammatory disease	Empty sella
Autoimmune (lymphocytic hypophysitis, pituitary and POUF-1 antibodies)	Idiopathic
Hemochromatosis	
Granulomatous (granulomatosis with polyangiitis, sarcoidosis)	
Langerhans cell histiocytosis	
Giant cell granuloma	
Xanthomatous hypophysitis	

Abbreviation: CTLA-4, cytotoxic T-lymphocyte antigen 4. [Derived from Carmichael JD. Anterior Pituitary Failure, Melmed S, editor, The Pituitary 3rd edition, Elsevier; 2011:343–381 with permission, © Elsevier (64).]

Central adrenal insufficiency

Clinicians can assess central AI using insulin tolerance and low-dose and standard-dose ACTH stimulation tests (Table 3). Limitations include interpreting test cutoff values and thresholds required for GC replacement (17, 25, 64, 66–71). Although assays have evolved, cortisol levels <18.1 μg/dL (500 nmol/L) poststimulation are indicative of AI (Table 3). The Endocrine Society clinical practice guideline for primary AI includes details on additional tests (72).

Table 2. Clinical Manifestations of Hypopituitarism

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

Derived from S. Melmed and J. L. Jameson: Disorders of the anterior pituitary and hypothalamus. In: Jameson JL, ed. *Harrison's Endocrinology.* 2nd ed. Chap 2. New York, NY: McGraw-Hill Professional; 2010:16–49 (65), with permission.

1.1 We suggest measuring serum cortisol levels at 8–9 AM as the first-line test for diagnosing central AI. (2|⊕◯◯◯)

1.2 We recommend against using a random cortisol level to diagnose AI. (1|⊕⊕◯◯)

1.3 We suggest that a cortisol level <3 μg/dL is indicative of AI and a cortisol level >15 μg/dL likely excludes an AI diagnosis. (2|⊕◯◯◯)

1.4 We suggest performing a corticotropin stimulation test when morning cortisol values are between 3 and 15 μg/dL to diagnose AI. Peak cortisol levels <18.1 μg/dL (500 nmol/L) at 30 or 60 minutes indicate AI. (2|⊕⊕◯◯)

1.5 We suggest that clinicians perform biochemical testing for the HPA axis at least 18–24 hours after the last HC dose or longer for synthetic GCs. (2|⊕⊕◯◯)

Evidence

The Endocrine Society has published a guideline on the diagnosis of primary AI (72). Although high ACTH values are diagnostic of primary AI, the finding of a random low-normal ACTH level may not be helpful in diagnosing central AI (73).

A meta-analysis (74) identified 30 studies assessing the diagnostic performance of the ACTH stimulation test in 1437 patients with suspected secondary AI. Both high- and low-dose tests had moderate accuracy overall, primarily because of low sensitivity. Notably, the prevalence of AI in the included studies was 36%. There was no statistically significant difference between the accuracy of the high-dose and low-dose tests, but the analysis was associated with significant heterogeneity. Understanding the pretest probability of disease and knowledge of the test limitations are essential to properly diagnosing AI.

Because GCs suppress the HPA axis and there are interferences in cortisol measurements, clinicians should perform biochemical testing at least 18–24 hours after the last HC dose or longer for synthetic GCs (75). Clinicians should also consider the duration of GC treatment and the influence of oral estrogen on total serum cortisol levels, which can increase CBG.

Central hypothyroidism

1.6 We recommend measuring serum fT4 and TSH to evaluate CH. An fT4 level below the laboratory reference range in conjunction with a low, normal, or mildly elevated TSH in the setting of pituitary disease usually confirms a CH diagnosis. (1|⊕⊕⊕⊕)

1.7 In patients with pituitary disease and low-normal fT4 levels suspected to have mild CH, we suggest starting L-T4 if suggestive symptoms are present or following fT4 levels over time and starting treatment if the fT4 level decreases by 20% or more. (2|⊕◯◯◯)

1.8 We suggest against using dynamic TSH-secretion testing to diagnose CH. (2|⊕⊕⊕◯)

Evidence

TSH levels in CH may be low, normal, or slightly elevated, reflecting decreased 24-hour secretion and altered

Table 3. Dynamic Tests for Diagnosing Suspected Hypopituitarism

Hormone Test	Procedure	Interpretation/Expected Normal Response
GH		
Insulin tolerance	Administer insulin, 0.05–0.15 U/kg iv. Sample blood at − 30, 0, 30, 60, 120 min for GH and glucose.	Glucose should drop <40 mg/dL, (2.2 mmol/L). GH should be >3–5 μg/L. Cutoffs for GH response are BMI related.
GHRH[a] + arginine	Administer GHRH, 1 μg/kg (max 100 μg) iv followed by an arginine infusion 0.5 g/kg (max 35 g) over 30 min. Sample blood at 0, 30, 45, 60, 75, 90, 105, and 120 min for GH.	Can give false normal GH response if GHD is due to hypothalamic damage (eg, after radiation). GH >4 μg/L, but cutoffs for GH response should be correlated to BMI. (Obesity may blunt GH response to stimulation.)
Glucagon	Administer glucagon, 1 mg (1.5 mg if weight >90 kg) im. Sample blood at 0, 30, 60, 90, 120, 150, 180, 210, and 240 min for GH and glucose.	GH >3 μg/L, but cutoffs for GH response should be correlated to BMI. (Obesity may blunt GH response to stimulation.)
ACTH		
Insulin tolerance	Administer insulin, 0.05–0.15 U/kg iv. Sample blood at −30, 0, 30, 60, and 120 min for cortisol and glucose.	Glucose should drop <40 mg/dL (2.2 mmol/L). Peak cortisol should be >500–550 nmol/L (>18.1–20 μg/dL) depending on assay.
Corticotropin standard dose (250 μg)	Administer ACTH 1–24 (cosyntropin), 250 μg im or iv. Sample blood at 0, 30, and 60 min for cortisol.	Cortisol should be at 30 or 60 min >500–550 nmol/L (>18.1–20 μg/dL) depending on assay.
Corticotropin low dose (1 μg)	Administer ACTH 1–24 (cosyntropin), 1 μg iv. Sample blood at 0 and 30 min for cortisol.	Cortisol should be at 30 min >500 nmol/L (18.1 μg/dL) depending on assay.
ADH		
Water deprivation test	Initiate fluid deprivation for 8h (starting from 8 AM). Weigh patient at beginning of testing, then measure weight and urine volume hourly during the test. Measure plasma and urine osmolality every 2–3 h. At 4 PM administer DDAVP 2 μg im and allow patient to drink freely. Notes: If plasma osmolality >305 mOsm/kg or if 3% loss of body weight with plasma osmolality >305 mOsm/kg, proceed to DDAVP administration earlier. If urine output has not decreased and/or urine osmolality/plasma osmolality ratio <2, but the plasma osmolality has not concentrated to >295 mOsm/kg, continue water deprivation for a further hour and measure plasma and urine osmolality. Offer DDAVP after this. Continue measuring urine osmolality hourly for the next 4 h (after DDVAP administration) and measure hourly urine volumes. Stop test if >3% weight loss occurs.	Plasma osmolality >295 mOsm/L with inappropriately hypotonic urine (urine osmolality/plasma osmolality ratio <2) during the fluid deprivation confirms DI (test is discontinued). After administering DDVAP, urine concentrates >800 mOsm/kg with central DI and <300 mOsm/kg with nephrogenic DI. With partial DI or primary polydipsia, urine concentrates partially during the water deprivation test (300–800 mOsm/kg), and further investigation is required including a prolonged water deprivation test or DDVAP therapeutic trial.

[Derived from: Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, Merke DP, Murad MH, Stratakis CA, Torpy DJ. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2016; 101:364–389 (72); Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Vance ML. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011; 96:1587–1609 (85); Melmed S, Jameson JL. Disorders of the anterior pituitary and hypothalamus. In: Jameson JL, ed. *Harrison's Endocrinology*. 2nd ed. Chap 2. New York, NY: McGraw-Hill Professional; 2010:16–49 (65); Webb R, Singer M. Oxford handbook of Critical Care. Oxford; New York: Oxford University Press, 2005, with permission, © Oxford University Press (88).]

[a] Presently unavailable in the United States.

bioactivity with relatively preserved immunoactivity (76–78). In contrast to primary hypothyroidism, TSH and fT4 levels do not correlate (33). Accordingly, clinicians cannot use TSH levels alone to diagnose or monitor CH.

The combination of a low fT4 and a nonmarkedly elevated TSH in patients with known pituitary disease is diagnostic of CH, unless a patient is severely ill and could have nonthyroidal illness-induced changes in thyroid hormone levels. However, this approach may miss a significant number of patients with mild CH, as some pituitary patients with low-normal fT4 levels may have mild CH. Because patients with primary hypothyroidism usually

require high-normal or slightly elevated fT4 levels to normalize TSH levels (79), low-normal fT4 levels in hypopituitary patients may suggest the presence of CH. However, it is difficult to confirm this because many healthy subjects have fT4 levels in the lower part of the laboratory reference range, and there are no validated measures of thyroid function in hypopituitary patients. Studies have suggested that 10–18% of high-risk pituitary patients have unrecognized CH with low-normal fT4 levels (78, 80). These patients often have a blunted or absent nocturnal surge in TSH levels, but this is impractical for diagnostic use (33). 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% (78). However, these recommendations have not been systematically investigated.

Serum T_3 or free T_3 (fT3) levels are generally not helpful in diagnosing CH; most patients with CH have low fT3 levels, but there is considerable overlap between CH and non-CH patients with pituitary disease (76, 78). Peripheral indices of thyroid hormone action lack sufficient sensitivity and specificity for diagnosing or monitoring (33, 81–83).

Past studies have attempted to categorize CH based on TSH responsiveness to exogenous TSH-releasing hormone administration (84), but this has not proven to be useful in clinical practice.

GH deficiency

1.9 In patients with suspected GHD, we recommend GH stimulation testing. Single GH measurements are not helpful. (1|⊕⊕⊕◯)

1.10 We recommend using appropriately controlled BMI cutoffs to assess peak GH values. (1|⊕⊕◯◯)

1.11 We suggest against biochemical testing for GHD in patients with clear-cut features of GHD and three other documented pituitary hormone deficits. (2|⊕⊕⊕◯)

Evidence

GHD is measured via insulin tolerance, glucagon, and (if available) GHRH + arginine tests. The Endocrine Society guidelines extensively reviewed these tests (85), and they are listed them in Table 3.

Diagnosing adults who have a prior diagnosis of childhood-onset GHD (congenital or acquired) is relatively straightforward because these patients had short stature. However, because clinical features of acquired AGHD are often subtle, are not necessarily specific to an underlying pituitary disorder, and are commonly encountered in the general population, these patients should all be retested 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, and age, all of which may influence pituitary GH secretion (86, 87).

Unlike GH, IGF-1 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-1 levels, particularly males (86).

Remarks

Because most GH reserve tests are associated with high false-positive rates, patients should have a rigorous biochemical evaluation only when there is 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 during childhood (isolated GHD with normal pituitary imaging) should all be retested as adults before continuing adult GH replacement. Many of these patients prove to be GH-sufficient on subsequent retesting.
- Patients should exhibit evidence for pituitary damage, including a 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.

Central hypogonadism in males

1.12 In males with suspected hypogonadism, we recommend measuring serum T, FSH, and LH to diagnose central hypogonadism. (1|⊕⊕◯◯)

1.13 We recommend that clinicians perform hormonal testing for central hypogonadism in males in the absence of acute/subacute illness and before 10 AM (after overnight fast) combined with serum PRL. (1|⊕⊕◯◯)

Evidence

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

Testosterone levels (total, free, and bioavailable) demonstrate a circadian rhythm with maximum serum values between 5:30 and 8 AM and trough levels approximately 12 hours later (89–91). Acute/subacute illness alters T levels acting at various levels of the hypothalamo-pituitary-gonadal axis (92, 93). Systemic diseases, eating disorders, extensive exercise, and a number of medications or recreational drugs (eg, GCs, opiates, ketoconazole, bar-

biturates, cocaine) affect T levels (94, 95). Hyperprolactinemia can cause hypogonadotropic hypogonadism, and clinicians need to take into account the possibility of a prolactinoma because dopamine agonist treatment can reverse the hypogonadism. Two measurements performed with the same assay are preferred for borderline low T values (96, 97).

Remarks

Testosterone levels demonstrate an age-related decline (98, 99). 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 (98). The level of serum T below which symptoms of hypogonadism occur has not been clearly established.

About 2% of circulating T is free (unbound), 44% is bound to SHBG, and 54% is bound to albumin and other proteins (100). Total T levels at the low end of the reference range are associated with conditions or medications affecting SHBG and albumin (eg, hypothyroidism/hyperthyroidism, obesity, diabetes mellitus, nephrotic syndrome, liver disease, HIV infection, GCs, or anticonvulsants). When assessing fertility is required, clinicians should perform semen analysis before starting T replacement. Notably, one study reported cases of males with acquired hypogonadotropic hypogonadism remaining fertile after T treatment (101).

Central hypogonadism in females

1.14 In the presence of oligomenorrhea or amenorrhea, we recommend measuring serum E2, FSH, and LH. Clinicians should exclude other causes of menstrual irregularities related to impaired ovulation (hyperprolactinemia, hyperandrogenism, and thyroid disease), particularly if no other pituitary hormone deficits are present. In cases of amenorrhea, clinicians should also exclude pregnancy. (1|⊕⊕◯◯)

1.15 We suggest against dynamic testing with GnRH, which offers no useful diagnostic information. (2|⊕⊕◯◯)

1.16 We recommend that in postmenopausal women, the absence of high serum FSH and LH is sufficient for a diagnosis of gonadotrope dysfunction (provided the patient is not on HRT). (1|⊕⊕⊕◯)

Evidence

The diagnosis of central hypogonadism in females requires the exclusion of other conditions causing impaired ovulation and menstrual irregularities, including hyperprolactinemia, hyperandrogenism, and thyroid dysfunction (40). The value of GnRH testing provides no extra diagnostic information over that derived from baseline gonadotropin values measured by currently available ultrasensitive assays (102). Furthermore, one study proposed that in patients with hypogonadotropic hypogonadism, the GnRH responses are variable and depend on the severity of gonadotropin deficiency, which is often reflected by the clinical phenotype (102).

HRT invariably causes a reduction in circulating FSH and LH levels (103). Clinicians could observe reductions of up to 60% for FSH and 50% for LH.

Central diabetes insipidus

1.17 We recommend simultaneously measuring serum and urine osmolarity in patients with polyuria (more than 50 mL/kg of body weight/24 hours, 3.5 L/d 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 ratio should be ≥2), whereas urine dipstick should be negative for glucose. (1|⊕⊕⊕◯)

Evidence

The presence of DI may be obvious with severe forms in the appropriate clinical scenario (eg, after surgery for hypothalamic or pituitary lesion). More subtle cases require a water deprivation test to document partial inability to concentrate urine. The diagnosis may be particularly challenging when DI is partial and magnetic resonance imaging (MRI) does not show an obvious pathology. However, in most cases of isolated DI, MRI of the sellar area shows a progressive loss of the posterior pituitary bright spot (104).

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), sample stability, and interference from replacement hormonal therapies and their analogs (eg, prednisolone and HC in cortisol assays).

We reviewed the performance characteristics (sensitivity, specificity, variability [precision], and sample limitations) of widely used assays for GH, IGF-1, PRL, FSH, LH, TSH, fT4, T, E2, cortisol, and ACTH (Appendix A or Supplemental Table 1). All assays exhibited adequate sensitivity and acceptable intra-assay variability at <20% (Appendix A or Supplemental Table 1). However, some analytes, such as E2, T, GH, fT4, and to a lower extent gonadotropins, had large interassay variability; therefore, clinicians should consider differences among assays and use the same assay for serial and longitudinal measurements (Appendix A or Supplemental Table 1) (105).

Clinicians need to follow precautions for sample integrity and should consider sample storage and handling (freeze-thaw) when reviewing questionable results.

Clinicians are increasingly using liquid chromatography-mass spectrometry (LC-MSMS) assays with suggested improved sensitivity and reduced interference. In contrast to immunoassays that measure hormones intact, LC-MSMS separates and molecularly fragments hormones via liquid chromatography and ionizes these fragments via mass spectrometry, respectively. Variable electrical fields allow analysts to filter out ionized fragments of interest and identify and quantify them by their charge-to-mass ratios. Separation and fragmentation eliminates the problem with interferences due to autoantibodies that we see with immunoassays. Furthermore, filtering for selected charge-to-mass ratios affords a very high level of specificity. This allows analysts, for example, to distinguish between cortisol and prednisolone—something that is not possible with most immunoassay methods. It also makes it easier to detect steroids, namely E2, T (106, 107), and thyroid and peptide hormones (79, 108).

In addition, LC-MSMS allow us to measure more than one analyte in a single measurement, such as T and dihydrotestosterone. Finally, LC-MSMS provides improved comparability between different laboratories. This is not possible between different immunoassays, which are laboratory-developed tests that lack standardization and require extensive validation and expertise.

2. Treatment

Hormonal replacement in panhypopituitarism

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

Glucocorticoid replacement

2.1 We recommend using HC, usually 15–20 mg total daily dose in single or divided doses. Patients using divided doses should take the highest dose in the morning at awakening and the second in the afternoon (two-dose regime) or the second and third at lunch and late afternoon, respectively (three-dose regime). (1|⊕⊕⊕◯)

2.2 We suggest using longer-acting GCs in selected cases (eg, nonavailability, poor compliance, convenience). (2|⊕◯◯◯)

2.3 We recommend that clinicians teach all patients with AI regarding stress-dose and emergency GC administration and instruct them to obtain an emergency card/bracelet/necklace regarding AI and an emergency kit containing injectable high-dose GC. (1|⊕⊕⊕◯)

2.4 We recommend against using fludrocortisone in patients with secondary AI. (1|⊕⊕⊕◯)

Evidence

Total daily dose. Daily physiological cortisol production in healthy individuals is about 5–10 mg per square meter of body surface area (109), corresponding to a replacement dose of approximately 15–20 mg/d. Many believe that a dose in this range may avoid under- or overtreatment. Because no reliable marker to determine exact GC needs is available, initial dose requirements are largely estimated. Further dose adjustments depend on clinical status, patient preference, and comorbidities.

Researchers have used a cortisol day curve (110), but it has little value for routine clinical use (28). Prednisolone cross-reacts in many cortisol assays, whereas dexamethasone exhibits limited cross-reactivity. Urine-free cortisol measurements have wide inter- and intra-variability, and thus are rarely useful (111, 112). For patients with suspected malabsorption or increased steroid metabolic clearance, serial measurements of blood cortisol might be useful (28).

Stress doses of GC replacement for intercurrent illnesses and minor stress are similar to those used in primary AI (72). A recent guideline reviewed the prevention of AC and the importance of patient education (72).

Circadian rhythm-multiple daily dosing. Cortisol secretion exhibits a distinct circadian rhythm: low at the time of sleep onset, rising in early morning, peaking just after the time of waking, then falling during the day (28, 109). No currently available GC treatment regimen is capable of accurately simulating the normal cortisol circadian rhythm. Clinicians currently prescribe several regimens, either weight-based (113) or multiple fixed doses two or three times per day (28, 112, 114). Weight-adjusted, three-times-daily dosing using HC reduces GC overexposure and represents the most refined regime available, although it does not replicate the normal cortisol rhythm (115). Clinicians also frequently prescribe single daily HC doses in patients with central AI (116, 117).

Type of GC replacement. Published surveys of current practice for GC replacement therapy include mostly patients with primary AI; however, some studies also include patients with central AI (118). HC is the most common GC used for replacement, followed by prednisone, cortisone, and dexamethasone. 11β-Hydroxysteroid dehydrogenase-1 converts cortisone acetate to biologically active cortisol, which might reduce circulating cortisol fluctuations (112). One can compare GCs of different potencies by calculating the HC equivalence based on anti-inflammatory effects (Table 4) (28, 112, 119–121). However, this method might sometimes overestimate the calculation of a replacement dose.

Table 4. Dose Equivalence for GCs

Equivalent Dose	GCs
20 mg	HC
5 mg	Prednisone
0.75 mg	Dexamethasone
4 mg	Methylprednisolone
5 mg	Prednisolone
25 mg	Cortisone

[Derived from S. Melmed and J. L. Jameson: Disorders of the anterior pituitary and hypothalamus. In: Jameson JL, ed. *Harrison's Endocrinology*. 2nd ed. Chap 2. New York, NY: McGraw-Hill Professional; 2010:16–49 (65); Webb R, Singer M. Oxford handbook of Critical Care. Oxford; New York: Oxford University Press, 2005, with permission, © Oxford University Press (88).]

A high proportion of patients on "conventional" corticosteroid replacement therapy for AI are overtreated or on inappropriate replacement regimens (122). Few studies have compared different replacement regimens for central AI. However, a lower dose of HC seems to correlate with improved QOL, health status, and mood. In a randomized, double-blind, crossover design (123), patients received varying multiple doses of HC vs prednisone for 4 weeks at each dose. The HC 10 mg AM/5 mg PM 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 (27), HC doses above 30 mg/d were associated with adverse health status by validated self-assessment questionnaires. Three-times-daily intake of HC was not superior to two-times-daily intake. In 2737 adult hypopituitary patients (124), those receiving the equivalent of ≤ 10 mg HC had the best QOL, 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 the GC doses to address unexplained QOL deficits.

New GC preparations (not U.S. Food and Drug Administration 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 rise in early morning cortisol is not well mimicked (125–127). The primary AI guideline reviewed the new GC preparations (72).

Androgen replacement in women

Recent Endocrine Society guidelines have reviewed the risks and benefits of androgen replacement in women (128). 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 (128).

Adrenal crisis

2.5 We recommend that clinicians treat patients with suspected AC due to secondary AI with an immediate parenteral injection of 50–100 mg HC. (1|⊕⊕⊕◯)

Evidence

AC 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 AC (19, 29–31, 112, 114). Excess cardiovascular mortality might be specifically related to AC (30). Crisis incidence is not influenced by educational status, BMI, GC dose, dehydroepiandrosterone treatment, age at diagnosis, hypogonadism, hypothyroidism, or GHD. Interestingly, the female sex and the presence of DI in AC correlated with hospital admission in one study (29).

The need for immediate GC replacement and fluid resuscitation is the same in central AI as it is in primary AI (72). Patient education is considered the key to preventing 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 GCs for emergency administration. These include im or sc HC preparations designed for self-injection (72).

Thyroid hormone replacement

2.6 We recommend 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 μg/kg/d, with dose adjustments based on clinical context, age, and fT4 levels. (1|⊕⊕⊕◯)

2.7 We suggest against treating CH with L-T3, thyroid extracts, or other formulations of thyroid hormones. (2|⊕⊕◯◯)

Evidence

The standard therapy for CH is L-T4 (~1.6 μg/kg/d). In a randomized, double-blind, crossover study, 32 hypopituitary CH patients received L-T4 doses previously adjusted by endocrinologists using the best clinical judgment (81). Increasing the L-T4 dose from a mean of 1.0 to a mean of 1.6 μg/kg/d led to mild weight loss; improvements in hypothyroid symptom scores; and decreases in BMI, total and LDL cholesterol levels, and serum creatine kinase levels. When clinicians substituted L-T3 for some of the L-T4, working memory was slightly better but at the expense of T_3 levels above the reference range. Based on these results, the authors recommended an L-T4 dose of 1.6 μg/kg/d in CH, with a target fT4 level 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 (76, 78, 129–131). One cross-sectional study of CH patients reported that mean L-T4 doses of 1.9 μg/kg led to fT4 levels in the upper half of the normal range (132). However, a recent publication reported that increased risk of vertebral fracture in hypopituitary patients receiving higher daily doses of L-T4 correlated with higher fT4 levels (133). Therefore, clinicians should adjust L-T4 doses for age, estrogen status (including pregnancy, see below), comorbidities, and clinical context, including potential risks of overtreatment (33). Some investigators recommend following fT3 levels or peripheral indicators of thyroid function during L-T4 therapy because elevated fT3 levels can indicate overtreatment, although studies have not validated this (33, 78).

Few studies have examined the use of L-T3 or other formulations of thyroid hormone for CH (81); 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 (76). Alternate preparations of thyroid hormones or nutraceuticals are not recommended for treating CH.

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

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 (76, 81, 129, 131). Therefore, clinicians should not interpret undetectable TSH levels 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 in the morning before taking their daily L-T4 dose or at random times during the day. 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 of CH (81) measured fT4 levels 2 hours after dose ingestion and reported slightly elevated mean fT4 levels with adequate doses. Therefore, we recommend checking fT4 before the L-T4 dose.

Testosterone replacement

2.9 We suggest T replacement for adult males with central hypogonadism and no contraindications in order to prevent anemia related to T deficiency; reduce fat mass; and improve BMD, libido, sexual function, energy levels, sense of well-being, and muscle mass and strength. (2|⊕⊕◯◯)

Evidence

Central hypogonadism in males leads to adverse manifestations and sequelae, which T replacement may reverse. Studies on this topic are limited in that they employed various T formulations with different regimes, were usually short in duration with a small number of patients, and were not randomized and placebo controlled.

Treatment increases BMD (134–137) and improves trabecular structure (138) and bone mechanical properties (139). Nevertheless, data on the impact on fracture risk are not currently available.

Testosterone replacement increases libido, sexual motivation and sexual function (136, 137, 140–145), mood (146), sense of well-being, concentration (137, 141, 145, 147, 148), self-reported sense of energy (136, 137), muscle mass and strength (134, 149, 150), and the recovery from anemia related to T deficiency (136). Men with nonreplaced hypogonadism due to nonfunctioning pituitary adenomas scored significantly worse in parameters of health-related QOL questionnaires compared to those with an intact gonadotroph axis or on hormone replacement (37).

The choice of T formulations depends on numerous factors, including the risk of specific adverse effects, the cost, patient convenience, and patient preference. For information regarding T therapy, potential adverse effects, available T formulations, and treatment monitoring (151), we recommend the most recent Endocrine Society guidelines (97).

Estrogen replacement in premenopausal women

2.10 We recommend gonadal hormone treatment in premenopausal women with central hypogonadism, provided there are no contraindications. (1|⊕⊕⊕◯)

Evidence

For premenopausal women with central hypogonadism, clinicians should prescribe 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, primarily in women close to or after the natural age of menopause, have shown that oral estrogen or combined estrogen/progestogen therapy is very effective in alleviating vasomotor symptoms of hypoestrogenism (hot flushes and night sweats) (152) and improving vaginal atrophy (153), urinary frequency, and dysuria (154). Because there are no studies on premenopausal women with

central hypogonadism, for this group of female patients, clinicians often refer to the published results from women with primary hypogonadism.

Treatment with estrogens until age 45 years or longer may reduce the risk of cardiovascular disease and mortality (47, 49, 51).

Primary ovarian failure is associated with reduced BMD and increased risk of fractures (155–157), and estrogen replacement protects against fractures (155, 158, 159). Other pituitary hormone deficits and/or their treatment also affect BMD and the risk of fracture in central hypogonadism (133, 160, 161). 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, clinicians should prescribe other general measures optimizing BMD (including lifestyle changes, weight-bearing exercises, adequate calcium and vitamin D supplementation, and avoiding smoking).

Remarks

The combined estrogen-progestin contraceptive pill (compared with HRT) may be more acceptable for younger females; however, studies comparing the 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 patient preference (162).

Follow-up of gonadal hormone replacement includes evaluating symptoms and monitoring for side effects. Measuring serum E2 levels is not beneficial; moreover, some estrogens are not detected by the assays.

Studies have not associated HRT in women 40–49 years old with increased risk of breast cancer (163), and there is no evidence that estrogen replacement in women with premature ovarian failure relates to a higher risk of breast cancer (164).

It is prudent to replace gonadal hormones until the mean age of natural menopause (165). Clinicians should base decisions about estrogen replacement after menopause on relevant recent guidelines (162).

GH 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/d for patients younger than 60 years and 0.1–0.2 mg/d for patients older than 60 years. (1|⊕⊕⊕◯)

Table 5. GH Replacement Therapy for AGHD

Starting dose	
Age <60 y	0.2–0.4 mg/d
Age >60 y	0.1–0.2 mg/d
Dose titration	
Increase by 0.1–0.2 mg/d	6-wk intervals
Dose determinants	
Mid-normal age-adjusted IGF-1 level	

Abbreviation: DXA, dual-energy x-ray absorptiometry. [Derived from S. Melmed: Idiopathic adult growth hormone deficiency. *J Clin Endocrinol Metab*. 2013;98:2187–2197 (167), with permission. ©The Endocrine Society.].

2.12 We recommend titrating GH doses and maintaining IGF-1 levels below the upper limit of normal and reducing the dose if side effects manifest. (1|⊕◯◯◯)

2.13 We suggest against administering GH to elderly adults with age-adjusted low IGF-1 levels and no history of pituitary or hypothalamic disease. (2|⊕◯◯◯)

2.14 We recommend against using GH to enhance athletic performance because this practice is illegal in the United States, has poor scientific or ethical justification, and does not have substantiated efficacy. (Ungraded Good Practice Statement)

Evidence

GH replacement therapy (Tables 5 and 6) is approved for adults with rigorously proven GHD or for treating HIV-related muscle wasting (166). Younger patients require higher doses, especially if serum IGF-1 levels are particularly low.

Initial low GH replacement doses are preferred because fluid retention is dose-dependent. As women exhibit features of relative GH resistance, they usually require higher starting and maintenance replacement GH doses, as do women receiving oral estrogens (168). Morbid obesity may also require increased GH dosing.

Table 6. Patient Monitoring After Initiating Adult GH Replacement

1. Measure IGF-1 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 BMD by DXA every 18 months.
6. Periodically assess residual pituitary mass via a pituitary MRI.
7. Assess QOL.

Abbreviation: DXA, dual-energy x-ray absorptiometry. [Derived from S. Melmed: Idiopathic adult growth hormone deficiency. *J Clin Endocrinol Metab*. 2013;98:2187–2197 (167), with permission. ©The Endocrine Society.].

Remarks

Once the dose has been stabilized, clinicians should monitor for efficacy. The 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 (169), whereas lean body mass improves by up to 7% during the first year of GH replacement (170, 171). Muscle strength improvement is sustained for at least 10 years (171). A meta-analyses of 11 randomized trials reported that adult GH replacement resulted in significantly enhanced maximum oxygen uptake and muscle power (172). Although the beneficial effects of weight loss confound the impact of GH on insulin sensitivity, GH itself is an insulin antagonist. Serum lipoprotein profiles improve with reduced total and LDL cholesterol and increased high-density lipoprotein (HDL) cholesterol, triglycerides, and apolipoprotein B 100 levels (173). Lean body mass cardiac stroke volume and left ventricular mass are increased (173). However, research has not consistently reported cardiovascular risk profile improvement (174). The effects of GH replacement on BMD are more beneficial in men (175) and with patients that have severe bone loss. Increased bone mass occurs after 12 months (176), and fracture development is slowed in patients with no previous osteoporosis (160).

Side effects of GH replacement at the recommended doses manifest in about 20% of patients and are usually reversible by lowering the GH dose. Reported side effects include fluid retention, arthralgias, myalgias, paresthesias, carpal tunnel syndrome, sleep apnea, sleep disturbances, and dyspnea. If replacement doses are too high, insulin resistance with diabetes may occur. Although the development of new cancers and new-onset diabetes is of concern, the safety profile for GH treatment (using appropriate replacement doses) appears favorable in long-term surveillance studies (177). GH administration does not appear to increase the rate of pituitary adenoma recurrence (RR, 0.887; 95% CI, 0.56–1.33) (178).

Diabetes insipidus

2.15 When administering DDAVP in DI, we suggest individualized therapeutic schedules. Although clinicians should offer therapy to all patients, 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 clinicians educate all patients receiving DDAVP about the risk of overdosing. Periodically (at least weekly), patients should experience a phase of polyuria during which the effect of the medication has obviously worn off. (Ungraded Good Practice Statement)

2.16 In postpituitary surgery DI, we suggest that clinicians should make at least one attempt to discontinue DDAVP during the weeks to months after surgery to determine whether posterior pituitary function has recovered. (Ungraded Good Practice Statement)

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

2.18 We suggest that all patients with DI wear an emergency bracelet or necklace to inform clinicians of the patient's health problem if incapacitated. (Ungraded Good Practice Statement)

Evidence

DDAVP, a longer-acting analog of ADH, acts mostly on the V2 receptor and thus has only minimal vasopressor activity. When treating DI patients in the outpatient setting who have an intact thirst mechanism, clinicians should use the lowest DDAVP dose that allows adequate rest at night and causes minimal disruption of individual daytime activities. About one-fourth 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 (179). Because of differences in work or travel schedules, and because of the high variability of medication response (180), clinicians must individualize and tailor treatments to meet patient requirements and practical needs.

Clinicians can administer DDAVP sc, orally, intranasally, or sublingually as a melt (the latter form is not available in all countries). In all forms, clinicians must carefully monitor treatment to prevent overdosing, which can result in potentially dangerous hyponatremia (181). This is particularly important in elderly individuals who may have increased renal sensitivity to the drug and/or may have abnormalities in osmoregulation (182). Oral and sublingual DDAVP absorption rates are $<1\%$, whereas intranasal is approximately 6% (183). Oral DDAVP is available in 100-, 200-, and, in some countries, 400-μg tablets. Sublingual melts and nasal preparations include a spray (usually 10 μg per squirt) and a rhinal tube (dose range, 1–10 μg). The mean dose ratio of sublingual to intranasal DDAVP is 1:24 (182); we list dose comparisons in Table 7.

Sometimes hypothalamic pathology or surgery may alter the thirst mechanism due to damaged hypothalamic osmoreceptors. In these cases, there is a high risk of both hypernatremia and hyponatremia because patients cannot adjust fluid intake according to thirst (179). After careful

Table 7. Dose Comparisons of Available Desmopressin Formulations

	Melts	Tablets	Spray	Drops	Injections
Bioavailability	0.25% (95% CI, 0.21–0.31%)	0.16 ± 0.17%	6.0 ± 2.29%	Similar to spray?*	NA
Dose equivalence	60 μg	100 μg	2.5 μg	2.5 μg	NA
	120 μg	200 μg	5.0 μg	5.0 μg	<0.5 μg
	240 μg	400 μg	10.0 μg	10.0 μg	<1.0 μg

Abbreviations: *?, unclear; NA, not applicable. [Derived from Y. Oiso et al: Clinical review: treatment of neurohypophyseal diabetes insipidus. *J Clin Endocrinol Metab.* 2013;98:3958–3967 (183), with permission. © Endocrine Society.].

titration (requiring frequent weighing and sodium measurements), we suggest a fixed dose of DDAVP and a constant amount of fluid intake together with consistent environmental temperature and humidity conditions (184).

Interactions between replacement hormones

Glucocorticoids and GH

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

Evidence

Many features of hypopituitarism, such as visceral obesity, insulin resistance, osteoporosis, and increased vascular mortality, are reminiscent of Cushing's syndrome (185, 186). Patients with GHD in the setting of hypopituitarism demonstrate an increased cortisol/cortisone metabolite ratio (187, 188).

Because GH suppresses the conversion of cortisone to cortisol, patients receiving GC replacement may require higher doses once GH is initiated, and those with low adrenal reserve may be rendered hypoadrenal by the GH therapy (185, 189).

Glucocorticoids and thyroid

2.20 We suggest evaluating patients with CH for AI before starting L-T4 therapy. If this is not feasible, clinicians should prescribe empiric GC therapy in patients with CH who are starting L-T4 therapy until there is a definitive evaluation for AI. (2|⊕⊕◯◯)

Evidence

Data suggest that AI should be conclusively excluded before initiating L-T4 therapy for CH. This is because thyroid hormone accelerates endogenous cortisol clearance and could unmask insufficient cortisol production and precipitate AC. If patients start L-T4 therapy before evaluation, clinicians should initiate empiric GC replacement therapy simultaneously until they complete a definitive evaluation for AI (33).

Physiological and pharmacological doses of GC suppress TSH levels (190). CH patients receiving GC therapy do not appear to require L-T4 dose adjustments (78).

Glucocorticoids and estrogen

2.21 We suggest that when clinicians assess adrenal reserve or the adequacy of HC replacement, they take into consideration that total serum cortisol level can be elevated due to the effects of estrogen on CBG. (2|⊕⊕⊕◯)

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 does not occur with transdermal estrogen therapy (191, 192).

GH and thyroid

2.22 We recommend that clinicians monitor euthyroid patients with GHD who begin GH therapy for the risk of developing CH, and if fT4 levels decrease below the reference range, these patients should begin L-T4 therapy. CH patients with GHD who are already receiving L-T4 may require increased L-T4 doses when they begin GH therapy to maintain fT4 levels within target ranges. (1|⊕⊕◯◯)

2.23 We suggest clinicians treat CH before performing GH stimulation testing because CH may impair the accurate diagnosis of GHD. (2|⊕⊕◯◯)

Evidence

Administering GH to adults with GHD causes variable changes in thyroid hormone levels—the most consistent effect being decreased fT4 levels (82, 193, 194). Some studies also report increased 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 months of starting GH therapy (193, 195). Most patients, who were at in-

creased risk of developing CH while receiving GH and who had previously undergone surgery and/or radiation therapy for pituitary tumors, had lower basal T_4 levels and were more likely to have other multiple hormone deficiencies. Clinicians should monitor GHD patients for developing CH approximately 6 weeks after they start or adjust GH therapy (196). Alexopoulou et al reported that only men with CH required increased L-T4 doses after starting GH therapy (1.8 vs 1.6 μg/kg/d) (78).

The hypothalamic-pituitary-thyroid axis also influences GH dynamics, with altered GH and IGF-1 secretion occurring in hypothyroidism (34). IGF-1 levels are reduced in hypothyroidism, and GH stimulation with insulin or GHRH may be blunted (187, 197). Clinicians could overdiagnose GHD in the setting of CH and should treat CH before performing stimulation tests for GHD.

Estrogen and thyroid hormones

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

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 (198). This is due to the 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 μg/kg/d (78).

GH and estrogen

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

Evidence

Oral estrogen treatment leads to decreased circulating IGF-1 levels in GHD women resulting in increased postprandial lipid oxidation and decreased protein synthesis, which antagonizes the metabolic actions of GH. This does not occur with transdermally administered estrogen, suggesting a first-pass effect of estrogen and the inhibition of hepatic GH actions (199–201). One study showed that women on oral estrogen might require a GH replacement dose up to 50% higher compared with women or men who are not on estrogen (201).

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, patients with improved DI without an AI diagnosis should undergo AI testing. (2|⊕◯◯◯)

Evidence

GC deficiency induces impaired free renal water clearance, resulting in the masking of polyuria in DI (202).

Risk of hormonal over-replacement in hypopituitarism

Bone disease

2.27 Clinicians should individually assess GC replacement and avoid over-replacement to reduce the risk of osteoporosis. We suggest low-dose HC replacement because this approach might be associated with increased bone formation and a positive bone-remodeling balance. (2|⊕⊕◯◯)

2.28 In men with hypopituitarism over-replaced with GC and at risk for fractures, we suggest vertebral fracture assessment (baseline plain spinal x-rays or dual-energy x-ray absorptiometry) to identify patients with unsuspected vertebral fractures. (2|⊕⊕◯◯)

2.29 We suggest clinicians monitor L-T4 replacement, as recommended in previous sections, and avoid over-replacement to reduce the risk of fractures. (2|⊕⊕◯◯)

Evidence

Very few studies have assessed the impact of GC dose optimization on markers of bone formation and resorption (122).

A post hoc analysis (203) 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 any evidence of compensatory increased PTH levels; this was consistent with the direct or indirect suppression of bone remodeling and suppression of PTH levels (204).

Another small open crossover study in hypopituitary men randomized to three commonly used HC dose regimens reported that low-dose HC replacement (10 mg AM and 5 mg PM) was associated with increased bone formation and positive bone-remodeling balance and with probable long-term beneficial effects on bone health (205).

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 (161) of male hypopituitary patients receiving median daily doses of 30 mg HC and 35 mg cortisone, 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, neither cumulative nor current cortisone doses influenced the prevalence of vertebral fractures.

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 74 adult CH patients treated with 1.1 μg/kg/d L-T4, higher daily L-T4 doses were associated with a higher prevalence of vertebral fractures (assessed by lateral spine x-rays) (133). This finding raises the question of possible adverse effects associated with targeting higher fT4 levels. Clinicians should monitor CH patients for developing 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 over-replacement

2.30 In patients with central AI, we recommend using the lowest tolerable dose of HC replacement to potentially decrease the risks of metabolic and cardiovascular disease. (1|⊕⊕⊕◯)

Evidence

Higher GC replacement doses in patients with ACTH deficiency were associated with increased overall and cardiovascular mortality; the greatest risk was in patients receiving daily HC doses higher or equal to 30 mg (8). This highlights the importance of providing patients with an adjustable GC replacement therapy regimen (206).

In a randomized crossover study (207), peripheral and hepatic insulin resistance did not differ between patients treated with HC twice daily (15 mg with breakfast, 5 mg with evening meal) vs those receiving physiological HC infusions. A short-term GC replacement increase (7-day increase in HC to 30 mg/d) (208) 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 (209). It has also been suggested that lower HC doses (15 mg/d) may result in lower arterial stiffness and a more physiological nocturnal blood pressure dip (210).

Dose reduction might also be associated with clinical improvement. When patients cut their GC dose in half (from 20–30 mg to 10–15 mg HC daily), mean body weight decreased by 7.1 kg after 6–12 months (211). However, a small prospective study of patients with hypopituitarism taking 30 mg HC did not report improvements in weight, 24-hour urine-free cortisol, glucose, or glycosylated hemoglobin (212).

Patients with partial central AI might be more likely to be overtreated. There is no apparent dose-dependent difference in integrated cortisol daily curves between patients on half-doses or no HC replacement (213), suggesting that current conventional full GC replacement doses might overtreat patients with partial ACTH deficiency.

Due to the known increased risk of thromboembolism in patients with Cushing's syndrome, it is presumed that nonphysiological GC replacement regimens might contribute to this risk. However, when comparing low-dose vs high GC regimens (17.5 vs 30 mg HC daily) for 2 weeks, fibrinolytic-coagulation parameters did not change (214).

Thyroid replacement

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

Remarks

The long-term cardiovascular risks of CH have not been well studied. However, recent evidence suggests that mild hyperthyroidism or hypothyroidism may increase overall and cardiovascular-specific mortality and morbidity (215–220).

Estrogen and testosterone replacement

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

Treatment with estrogens through age 45 years or longer may reduce the risk of cardiovascular disease and mortality (47, 49, 51). Results of the Women's Health Initiative (average participant age, 63 years) showed that combined hormone therapy increases the risk of cardiovascular events. However, we cannot extrapolate these results to younger women with premature ovarian failure (221).

Testosterone therapy in males with central hypogonadism reduces fat mass and increases fat-free mass (134, 137, 142, 149, 150). An analysis of 19 studies on the effects of administering T esters im (222) 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 We recommend GC replacement until full HPA axis recovery after surgically resecting ACTH-secreting tumors. (1|⊕⊕⊕◯)

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

Evidence

ACTH excess from a pituitary tumor will suppress normal pituitary corticotroph cells, and AI can persist for years after surgical tumor resection. Hormonal replacement after curative surgery for Cushing's disease has been recently reviewed in an Endocrine Society guideline (223). In 16 studies assessing the recovery of adrenal function after successful treatment for Cushing's disease (114), most patients recovered HPA axis by 2 years. We recommend GC replacement until full HPA axis recovery (114, 116).

In the context of multiple pituitary deficiencies associated with Cushing's disease (224, 225), clinicians should reassess the need for hormonal replacement (thyroid, GH) after surgery and should not start replacement before repeat testing of the HPA axis (223).

Prolactinomas

3.3 We recommend reassessing all pituitary axes in patients with macroprolactinoma and central hypogonadism who have had successful dopamine agonist treatments. (1|⊕⊕⊕◯)

Evidence

Administering dopamine agonists to patients with macroprolactinoma leads to normoprolactinemia in 68% (range, 40–100%) and tumor shrinkage in 62% (range, 20–100%) (226). Studies have reported that 44–62% of cases experience a reversal of hypogonadism, usually within 6 months after starting treatment (227, 228). Further research has reported the recovery of other hormonal axes after adenoma shrinkage (229); therefore, patients should have hormonal re-evaluation to avoid unnecessary lifelong 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|⊕◯◯◯)

Evidence

Acromegaly patients, after rigorous GH dynamic testing and documented GHD, may benefit from low-dose GH replacement (230). Features of accelerated GHD may develop in acromegaly patients who have had a GH-secreting adenoma surgically resected. In these patients, immediate (72 hours) postoperative GH levels, as well as the bilaterality of intrasellar tumor involvement, are significant determinants of subsequent GHD (seen in about 10% of patients) (231). In a large retrospective analysis, overall mortality was similar; however, cardiovascular mortality was higher in GHD associated with treated acromegaly vs GHD associated with nonfunctioning pituitary adenomas (SMR, 3.03; $P < .02$) (232).

In a randomized placebo-controlled study, mean GH doses of 0.58 mg/d resulted in decreased visceral fat mass and improved QOL indices (233). A prospective study of 42 subjects reported that GH replacement enhanced QOL and improved both body composition and lipid profiles (234). These benefits appear to occur without incurring the risk of glucose intolerance.

Perioperative management of hypopituitarism

Pituitary surgery

3.5 We recommend using stress doses of steroids in AI before surgery and tapered doses after surgery before repeating testing. (1|⊕⊕⊕◯)

3.6 In patients with normal preoperative adrenal function, we suggest an individualized clinical approach for postoperative GC administration until the HPA axis can be evaluated. (2|⊕⊕◯◯)

3.7 With preoperative CH, we recommend using L-T4 therapy before nonemergency surgery and throughout the perioperative period. (1|⊕⊕⊕◯)

3.8 With intact preoperative thyroid function, we recommend measuring fT4 levels 6–8 weeks postoperatively to assess for CH. (1|⊕⊕◯◯)

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

3.10 We do not suggest prescheduled DDAVP dosages in the first week postsurgery because of the risk of hyponatremia after transient DI resolves and the risk of syndrome of inappropriate ADH secretion that may occur 7–10 days after surgery. (2|⊕◯◯◯)

3.11 We suggest oral or intranasal DDAVP after discharge, with clear instructions that patients should only use the medication if significant polyuria occurs. (2|⊕◯◯◯)

3.12 We suggest retesting all pituitary axes starting at 6 weeks after pituitary surgery and then periodically to monitor the development or resolution of pituitary deficiencies. (2|⊕⊕◯◯)

Evidence

Pituitary adenomas, as well as the associated surgical and radiation treatments, can cause hypopituitarism. Rates of pituitary axes recovery or new-onset hypopituitarism after transsphenoidal surgery vary significantly between studies (117, 235, 236).

A meta-analysis showed that morbidity of early postoperative AI ranged from 0.96–12.90%, with an overall morbidity of 5.55% (237).

Depending on circumstances, clinicians start stress doses of GC before surgery in patients with preoperative AI. Stress doses are tapered after surgery and discontinued if repeat testing shows a normal HPA axis. In patients with normal preoperative adrenal function, clinicians often prescribe GC in the immediate postoperative period until the HPA axis can be evaluated (117, 235, 236).

However, a postoperative morning cortisol level higher than 15 μg/dL may mitigate the requirement for postoperative GC treatment (238). A morning cortisol measurement might be useful even after intraoperative administration of dexamethasone (239). Other steroid-sparing regimens have also been suggested (240), but further research is needed, especially for patients that are discharged from the hospital on postoperative day 1.

Clinicians should treat preoperative CH 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 (241, 242). Patients should continue replacement L-T4 throughout the perioperative period and have fT4 levels checked 6 weeks after surgery to gauge the adequacy of the L-T4 dose. If patients do not start L-T4 preoperatively or continue L-T4 postoperatively, clinicians should evaluate patients for CH by measuring fT4 levels 6–8 weeks after surgery because the serum half-life of T_4 is 7 days.

DI occurs commonly in the immediate period (days 1–2) after pituitary or hypothalamic surgery (243). Other causes of postsurgical abundant diuresis include steroid-induced hyperglycemia, abundant intraoperative fluid administration, and (in the case of acromegaly) an abrupt reduction of serum GH levels (244). High-dose perioperative GCs increase the incidence of postoperative DI, possibly mediated by an increased glomerular filtration rate (245), reduced ADH secretion, and reduced renal sensitivity to GCs (246–248).

The risk of developing new-onset, postoperative pituitary failure depends on tumor size, surgical expertise, and the extent of surgery (249).

Non-pituitary surgery

3.13 On the day of surgery, we recommend adjusting GC doses according to the severity of illness and magnitude of the stressor. (1|⊕⊕⊕◯)

3.14 In cases of minor to moderate surgical stress, we suggest 25–75 mg HC per 24 hours (usually for 1–2 days). (2|⊕⊕◯◯)

3.15 In cases of major surgical stress, we suggest a 100-mg HC per iv injection followed by a continuous iv infusion of 200 mg HC per 24 hours (alternatively 50 mg every 6 hours iv or im). (2|⊕⊕◯◯)

Evidence

Adults secrete 75–100 mg of cortisol per day in response to major surgery and 50 mg per day in response to minor surgery (250). Cortisol secretion in the first 24 hours after surgery rarely exceeds 200 mg and correlates with the duration and extent of surgery (250). Studies have suggested lower doses of HC (25–75 mg/24 hours) for surgical stress in secondary AI (250, 251).

Management of hypopituitarism in pregnancy

Because fertility is often impaired in hypopituitarism, natural pregnancy is rare. Women require a multidisciplinary team for fertility induction and the management of hypopituitarism. However, with appropriate hormonal replacement, women with hypopituitarism can expect an uneventful pregnancy and a healthy infant.

Glucocorticoids

3.16 We suggest using HC as the preferred GC in pregnancy and increasing the dose based on the individual clinical course; higher doses may be required, in particular during the third trimester. (Ungraded Good Practice Statement)

3.17 We suggest that pregnant patients with central AI be closely monitored for clinical symptoms and signs of GC over- and under-replacement (eg, normal weight gain, fatigue, postural hypotension or hypertension, hyperglycemia). (Ungraded Good Practice Statement)

3.18 We recommend against using dexamethasone in pregnancy because it is not inactivated in the placenta. (1|⊕⊕◯◯)

3.19 We recommend HC stress dosing during the active phase of labor, similar to that used in major surgical stress. (1|⊕⊕◯◯)

The diagnosis of AI may be missed in the first trimester due to confounding symptoms of normal pregnancy. A low morning cortisol <3 μg/dL in the presence of typical clinical presentation is diagnostic of AI (252). Plasma cortisol can be falsely "normal" because of increased CBG in the second and third trimesters (253). One study suggests new normal ranges for cortisol in pregnancy (254).

HC is the preferred physiological GC replacement in pregnancy because it is degraded by the enzyme 11β-hydroxysteroid dehydrogenase 2 and does not cross the placenta.

The best regimen of GC replacement in pregnancy is not well defined; therefore, we recommend adjusting dose regimes based on clinical judgment. Another approach is to increase HC doses by 20–40% in the third trimester (16,

72). Lower doses of HC might be needed in women with hypopituitarism (compared with primary AI) who are not treated with GC replacement (28, 112, 114, 185, 186).

During labor and delivery, clinicians should administer a stress dose of GC (50 mg iv HC in the second stage of labor). For cesarean section, we recommend a dose of 100 mg every 6–8 hours (28, 253). Endocrine Society guidelines reviewed the management of primary AI in pregnancy (72). GC recommendations are relatively similar in central AI and primary AI; however, patients with central AI do not require mineralocorticoid replacement.

Thyroid

3.20 We recommend that clinicians monitor fT4 or total T_4 levels every 4–6 weeks for women with CH who become pregnant and that these women may require increased L-T4 doses to maintain levels within target ranges for pregnancy. (1|⊕⊕◯◯)

Evidence

Treating 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 (198) due to increased TBG levels secondary to high serum E2 levels. Current recommendations include increasing L-T4 doses by two extra pills per week (based on previous dose) upon confirming pregnancy and making 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 human chorionic gonadotropin 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. It should be noted that many fT4 assays do not perform well during pregnancy; if pregnancy-specific fT4 reference ranges are not available, clinicians can use total T_4 reference ranges adjusted upward by 50% (198). Clinicians should reduce L-T4 doses back to prepregnancy 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, clinicians should use either fT4 or total T_4 levels, depending on local experience with fT4 assay performance in pregnant patients. Many fT4 assays from pregnant patients are imprecise; an alternative approach is to monitor total T_4 levels, adjusting the nonpregnant reference range upward by 50% to account for TBG effects (198).

Desmopressin

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

Evidence

During pregnancy, serum sodium and osmolarity are reduced due to a decreased threshold for ADH release and thirst mechanism (255). The placenta produces large amounts of the enzyme vasopressinase, which degrades endogenous ADH and thus requires increased secretion. Pregnancy may unmask mild forms of DI, which often occurs with subsequent pregnancies.

In general, the DDAVP requirement is unchanged, but it sometimes might be slightly higher (256). Exposure to DDAVP during pregnancy is safe (257), and DDAVP is generally considered safe for the newborn in lactating mothers (255).

Growth hormone

3.22 We suggest discontinuing GH replacement during pregnancy because there is no clear evidence yet for efficacy or safety, and the placenta produces GH. (2|⊕⊕◯◯)

Remarks

An observational study on 201 pregnancies in hypopituitary patients reported that >50% of patients continued GH replacement during pregnancy. GH use before and during pregnancy was not related to pregnancy outcomes; however, there are no prospective studies on this (258).

Management of hypopituitarism in pituitary apoplexy

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

3.24 Because acute AI is a major cause of mortality, we recommend GC therapy until a laboratory diagnosis is established and the patient maintains normal pituitary function. (1|⊕⊕◯◯)

3.25 We recommend that clinicians monitor pituitary axes in pituitary apoplexy patients treated with either surgical decompression or conservative management because hypopituitarism may develop over time. (1|⊕⊕◯◯)

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 (259). Partial or complete hypopituitarism is a prominent feature and contributes to high mortality (260, 261). Pituitary apoplexy should be diagnosed early and treated promptly (262).

Pituitary dysfunction may be due to pre-existing deficiencies (20–22) or may occur quickly from a rapid increase of intrasellar pressure (260). Patients present with variable decreases in pituitary hormones; however, DI is uncommon (261), 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 ADH secretion (261).

Transsphenoidal decompression and immediate high-dose iv corticosteroid replacement therapy are the standard of care (263–265). However, we also advocate conservative management in a carefully selected group of patients (266).

Recognizing acute secondary AI is critical, and patients should begin GC therapy promptly to prevent AC. High-dose GC may also improve visual outcomes (263). When patients cannot tolerate oral medications, they should begin with a 100–200 mg iv HC bolus followed by 2–4 mg/h by continuous infusion or 50–100 mg injections every 6 hours (267). Clinicians should quickly taper HC as indicated and initiate standard oral maintenance doses. Clinicians have also used high doses of dexamethasone to treat pituitary apoplexy.

Hypopituitarism may be permanent or transient after pituitary apoplexy, with recovery occurring from weeks to months from the initial event (268). More than 50% of patients eventually require hormonal replacement (260, 261, 264). There is no consensus on whether surgical treatment improves pituitary function, but one study reported an increased incidence of hormonal deficiencies with conservative management (269). In one study of eight patients, transsphenoidal surgery achieved a return of normal pituitary function in most patients in the immediate postoperative period (260), although larger studies have not replicated these findings (266). Advocates of conservative management argue that there is no difference in long-term hypopituitarism rates between surgically managed and carefully selected, conservatively treated patients (266, 270).

Treatment of hypopituitarism in patients receiving antiepileptic medications

3.26 We suggest clinicians educate AI patients that are taking nondexamethasone GCs and who start enzyme-inducing AEDs about the early signs and symptoms of AI. (2|⊕⊕◯◯)

3.27 In patients with AI on dexamethasone, we suggest increasing dexamethasone replacement doses if enzyme-induced AEDs are coadministered. (2|⊕◯◯◯)

3.28 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. (1|⊕⊕◯◯)

3.29 In women who have started estrogen replacement, we suggest evaluating AED levels and adjusting AED doses as required. (2|⊕⊕◯◯)

3.30 We suggest monitoring DDAVP doses and making further adjustments as needed in patients who are started on AEDs. (2|⊕⊕◯◯)

Evidence

Some AEDs enhance hepatic CYP450 isoenzyme activity (eg, phenytoin, carbamazepine, oxcarbazepine, and topiramate), accelerating the hepatic metabolism of hormonal preparations and decreasing serum concentrations of relevant hormones (271). Effects depend on the type of GC. Dexamethasone is metabolized primarily by hepatic CYP3A4 (272), and patients may need to increase dexamethasone doses (271). AEDs only modestly decrease the concentrations of prednisone and prednisolone (273). CYP3A4-mediated 6β-hydroxylation may not contribute significantly to the breakdown of cortisol; therefore, AEDs are less likely to be clinically significant in patients treated with HC (274–276). However, a recent report found that oxcarbazepine increases cortisol elimination in normal subjects (275), suggesting that attention should also be paid to symptoms of underdosing in patients on HC. In conclusion, clinicians should always exercise caution when treating AI patients with any type of GC if patients are also taking AEDs.

AEDs accelerate T_4 and sex hormone clearance, and patients may require compensatory increases in hormone replacement doses (277). Some AEDs also displace thyroid hormones from their binding protein, resulting in observed normal or even decreased free hormone levels (278). Because phenytoin may impair fT4 measurements, an equilibrium dialysis fT4 assay is preferred.

Other AEDs increase SHBG, leading to the reduced bioavailability of E2 and T (271), which may compromise the efficacy of hormonal treatment. Combined estrogen and progesterone may decrease lamotrigine levels (279), and endogenous and exogenous sex steroids may affect seizure activity and epilepsy in women (280).

The addition of carbamazepine, oxcarbazepine, lamotrigine, perampanel, or felbamate to DDAVP therapy can cause hyponatremia by increasing DDAVP renal responsiveness (271).

Financial Disclosures of the Task Force*

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Appendix A or Supplemental Table 1: Assay Characteristics of Common Automated Immunoassays

Hormone	Assays Detectable Level	Sample Stability	Remarks	Mean Variability (% Imprecision) at Stated Concentrations	
				Within Method	Between Methods
GH (mcg/liter)	0.002 (b) 0.01 (c) 0.030 (d)	Rfg. <8 h. Frz. >8 h (undetermined duration or about 2 months). Avoid frz.-thawing (activity lost after repeated cycles).	Exhibits adequate assays sensitivity. Some assays (4) indicate detection of both 20 and 22 kDa forms. All assays use IRP 98/574 (lower GH results when compared with earlier standard). Varied conversion factors were applied when converting mIU/liter to ug/liter. All used BMI-related cut-off values. Variability between assays was assessed at 3.4 ng/ml.	6.9%	23.1%
IGF-1 (ng/ml)	20 (c)	Rfg. <24 h. Frz. up to 12 months.	It is preferable to measure IGF-BP-3 on the same sample. Variability between assays was assessed at 75 ng/ml.	13.2%	NA
PRL (ng/ml)	0.6 (a) 0.25 (b) 0.3 (c) 0.047 (d) 1.4 (e)	RT <8 h. If >24 h (remove serum/plasma from gel/cells). Rfg. <48 h (up to 7 days). Frz. up to 12 months. Avoid repeated frz.-thawing.	There is adequate agreement among assays (variability assessed at 7.2 ng/ml).	7.2%	7.1%
FSH (mIU/ml)	0.05 (a) 0.2 (b) 0.3 (c) 0.1 (d) 0.66 (e)		There is variability between assays (variability assessed at 7.9 mIU/liter).	8.1%	8.9%
LH (mIU/ml)	0.5 (a) 0.2 (b) 0.07 (c) 0.1 (d) 0.216 (e)		There is variability between assays (variability assessed at 3.9 mIU/liter).	7.7%	8.9%
TSH (mcIU/ml)	0.0038 (a) 0.015 (b) 0.004 (c) 0.005 (d) 0.015 (e)		There is variability between assays (variability assessed at 0.73 mcIU/ml).	6.1%	8.3%
fT4 (ng/dl)	0.4 (a) 0.25 (b) 0.1 (c) 0.023 (d) 0.07 (e)	RT <8 h. If >24 h remove from gel/cells. Rfg. <48 h (up to 7 days). Frz. >48 h (up to 30 days). Avoid repeated frz.-thawing.	There is variability between assays (variability assessed at 0.73 ng/dl).	12.2%	11.2%
Estradiol (pg/ml)	25 (a) 20.0 (b) 7 (c) 5.0 (d) 6.36 (e)	RT <8 h. If >24 h remove from serum/plasma from gel / cells. Rfg. <48 h (up to 7 days). Frz. (up to 6 months). Avoid more than one freeze-thaw cycle.	There is variable between assays (variability assessed at 141 pg/ml).	16.9%	64.9%
T (ng/dl)	4.33 (a) 10.0 (b) 10 (c) 2.0 (d) 4.9 (e)	RT <8 h. Remove from gel/cells immediately. Rfg. <48 h (up to 7 days). Frz. (up to 60 days). Avoid more than one freeze-thaw cycle.	There is high variability between assays (up to 54%) (variability assessed at 113 ng/dl).	11.4%	15.6%

(*Continued*)

Appendix A or Supplemental Table 1: Continued

Hormone	Assays Detectable Level	Sample Stability	Remarks	Mean Variability (% Imprecision) at Stated Concentrations	
				Within Method	Between Methods
ADH			There are limited assays available.	NA	NA
11-deoxycortisol		Rfg. if <7 days. Frz. If <14 days.	An 8 a.m. specimen is preferred.	NA	NA
Cortisol (micg/dl)	1.0 (a)	RT <8 h.	There is adequate assays sensitivity for diagnosis.	9.5%	10.6%
	0.4 (b)	If >8 h, remove serum/plasma from gel/cells.	There is significant and variable cross-reactivity with prednisolone and fludrocortisone.		
	0.2 (c)	Rfg. <48 h (up to 14 days).	There is little or no cross reactivity with dexamethasone.		
	0.1 (d) 0.16 (e)	Frz. >48 h (up to 30 days).	Variability between assays was assessed at 4.1 mcg/liter.		
ACTH (pg/ml)	1.0 (d)	Collect sample in ice-cooled EDTA-tube. Centrifuge immediately in refrigerated centrifuge. Store frozen in plastic container (binds to non-siliconized glass). Stable if frozen for 14 days.	ACTH 1–24 medication causes negative interference. Variability between assays was assessed at 17.4 pg/ml.	19.5%	NA

T, testosterone; PRL, prolactin; IRP, international reference preparation; fT4, free T4; ADH, anti-diuretic hormone; RT, room temperature; Rfg., refrigeration; Frz., freeze; NA, data not available; (a), Abbott Diagnostics, Chicago, IL; (b), Beckman Coulter, Brea, CA, USA; (c), Siemens Healthcare Diagnostics Inc., Tarrytown, NY; (d), Roche Diagnostics, Indianapolis, IN.; (e), Ortho-Clinical Diagnostics, Inc., Rochester, NY; Assay variability (imprecision) was calculated as 100 × (standard deviation/ mean analyte concentration). Only assays with adequate available data are reviewed here. Variability was calculated using available data for the lowest analyte concentration (281).

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281. Raw variability data was obtained with permission from published BioRad Unity quality control data (Bio-Rad Laboratories I 9500 Jeronimo Road, Irvine, CA 92 618). Information on sample stability was summarized from respective manufacturers' published information.