Hormone replacement in patients with hypopituitarism

A practical approach

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Hypopituitarism affects about one in 2000 people and requires long-term, often lifelong, management. Implementing a practical, stepwise approach to hormone assessment and replacement is important for all clinicians and can prevent life-threatening complications. This includes an understanding of the sequence and method of central adrenal insufficiency, central hypothyroidism and hypogonadism treatment, but also extends more broadly to cardiovascular and bone health.

Pituitary hypofunction affects about one in 2000 people, and its incidence is on the rise, at least partly due to the increasing use of cancer immunotherapy, which frequently results in hypophysitis.[1-4] Treatment of hypopituitarism can span decades and is often lifelong. It is therefore valuable for primary care physicians to have a practical approach to hormone evaluation and appropriate replacement. This article provides an overview of the pathophysiology of hypopituitarism, with an emphasis on the importance of appropriate hormone evaluation and replacement therapy.

Key points

- **Hypopituitarism is characterised by the inadequate secretion of pituitary hormones.**
- **The sequence of anterior pituitary hormone replacement is an important consideration. Cortisol should be replaced first, followed by thyroxine, sex hormones and, lastly, growth hormone. This avoids the onset of a life-threatening adrenal crisis and incorrect interpretation of hormone studies based on other untreated deficiencies.**
- **Corticosteroid replacement in pituitary disease should not be discontinued without endocrinologist input. On sick days, corticosteroid doses should be doubled or tripled depending on the degree of symptom severity.**
- **Thyroid-stimulating hormone evaluation is not helpful to guide thyroxine replacement; instead, the treatment goal is a free thyroxine level in the upper half of the normal range.**
- **There is no evidence that testosterone replacement to physiological ranges increases the risk of prostate cancer.**
- **Symptoms of growth hormone deficiency can be subtle. Some patients will not experience symptom improvement with treatment.**
- **Patients with arginine vasopressin deficiency receiving desmopressin replacement should drink to thirst to maintain normal sodium levels. The lowest dose should be prescribed to control polyuria or polydipsia.**

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Pituitary function and hypopituitarism

The pituitary is often referred to as the master gland, mostly acting as an intermediary between the hypothalamus and end-organ glands (primary glands), which produce the hormones that are active in body tissues. The anterior pituitary (adenohypophysis) produces six hormones: adrenocorticotropin hormone (ACTH), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinising hormone (LH), growth hormone (GH) and prolactin. When an anterior pituitary hormone deficiency causes deficiency of end-organ hormone production, the condition is considered 'secondary' or 'central'.[5] The posterior pituitary (neurohypophysis) releases two hormones that are synthesised in the hypothalamus: arginine vasopressin (AVP) and oxytocin (Figure).

Hypopituitarism arises because of pituitary or hypothalamic disease, such as pituitary, suprasellar or parasellar tumours; surgery; irradiation; traumatic brain injury; infiltrative disease; vascular insult; or drug effects (Box 1). Hypopituitarism is associated with increased mortality.[6,7] Loss of hormonal function can be singular but is often progressive depending on the aetiology. When managing the condition, it is important that hormones be replaced in a certain sequence to avoid potentially life-threatening consequences. A full assessment of pituitary function is therefore necessary in all patients with a suspected or confirmed pituitary hormone abnormality.[7] Changes in one type of hormone replacement may affect the other axes, necessitating an integrated approach to replacement regimens. The significance of low prolactin and oxytocin levels is currently unclear, and there is no role for replacement of these hormones.

1. Aetiology of hypopituitarism[5]

- Discrete mass
  - pituitary, suprasellar or parasellar mass (e.g. pituitary neuroendocrine tumour [formerly known as pituitary adenoma], craniopharyngioma, meningioma, sellar metastasis)
  - Rathke's cleft cyst
- Surgery
  - extensive surgical removal of a pituitary tumour or base-of-skull lesion
  - hypophysectomy
- Infiltrative or inflammatory disease
  - autoimmune
  - lymphocytic hypophysitis
  - immune checkpoint inhibitor-related hypophysitis
  - histiocytosis
  - granulomatous disease
  - haemochromatosis
- Vascular factors
  - pituitary apoplexy
  - Sheehan's syndrome
  - subarachnoid haemorrhage
- Cranial irradiation
- Traumatic brain injury
- Rare genetic causes
- Medications
  - e.g. opioids, chronic or high-dose corticosteroids, immune checkpoint inhibitors

Hypothalamic–pituitary–adrenal axis

Cortisol, a glucocorticoid stress hormone, is essential in human physiology, and its deficiency is life threatening. The lowest tolerated dose of glucocorticoid replacement is recommended to mimic physiological patterns and avoid detrimental effects of over-replacement, while minimising the risk of inadequate replacement in times of stress, which may otherwise result in an adrenal crisis.[8] Central adrenal insufficiency, characterised by low ACTH levels and resulting in hypocortisolism, is present in up to one-third of patients with hypopituitarism. It differs from primary adrenal insufficiency (e.g. Addison's disease) in that, typically, only glucocorticoid (and not mineralocorticoid) replacement is required.[6] This is because ACTH primarily controls cortisol production, whereas aldosterone production is also regulated by the renin–angiotensin system.

When to suspect central adrenal insufficiency

Features suggestive of adrenal insufficiency include fatigue, nausea, weight loss and postural hypotension. Cortisol levels less than 100 nmol/L, measured at 8.00 to 9.00 am, are convincing for the presence of hypocortisolism, whereas intermediate levels are suggestive and should precede confirmatory testing with a short Synacthen (tetracosactide acetate) test.[8] A borderline level in our local practice is a morning cortisol level of 100 to 250 nmol/L, but there is considerable variation between assays and so the upper threshold may be as high as 360 nmol/L, depending on local protocols.[9] A short Synacthen test can be conducted to assess the adrenal response to a large dose (250 mcg) of synthetic ACTH over 60 minutes. This test relies on the presence of adrenal atrophy, which is a feature of chronic ACTH deficiency. Short Synacthen testing for central hypocortisolism should therefore only be performed after a six-week lag from hypothalamic–pituitary–adrenal insult. A typical cortisol response exceeds 400 to 450 nmol/L.[8,10]

Hypocortisolism can be fatal, particularly during times of increased physiological stress when the cortisol demand is increased

It is crucial to ensure the correct timing of cortisol tests and adhere to local reference ranges, as there is considerable diurnal and interassay variation; older-generation cortisol assays typically yield high readings.[9,11] The diagnosis of central, rather than primary, adrenal insufficiency is established by subsequently demonstrating

Table. Expected findings in patients with hypopituitarism based on the affected pituitary axis and suggested management approaches

Pituitary axis (hormone)	Suggestive clinical findings	Expected biochemical findings	Differences from primary organ insufficiency	Typical replacement regimen	Monitoring
Anterior pituitary					
Adrenal (cortisol)	• Fatigue • Nausea • Weight loss • Presyncope • Postural hypotension	• Low or inappropriately normal ACTH level at 8.00 am to 9.00 am • Low cortisol level (e.g. <100 to 250 nmol/L) at 8.00 am to 9.00 am – borderline cortisol level requires confirmatory testing (e.g. short Synacthen test)	• No loss of mineralocorticoid function, which remains primarily under the control of RAAS • No hyperpigmentation (related to high ACTH levels in PAI)	• Hydrocortisone 0.20 to 0.25 mg/kg in two to three divided doses with the largest in the morning (e.g. 10 mg 8.00 am + 8 mg 2.00 pm) • Alternatives: – cortisone acetate 25 mg 8.00 am + 5 mg 2.00pm – prednisolone 5 to 7 mg in the morning	• Clinical features of adrenal insufficiency *vs* hypercortisolism, including blood pressure
Thyroid (thyroxine)	• Dry skin • Constipation • Cold intolerance • Fatigue • Weight gain	• Low or inappropriately normal TSH level • Low free thyroxine level • Low free triiodothyronine level	• TSH levels unhelpful for monitoring; low TSH levels should not be confused for hyperthyroidism	• Levothyroxine 1.6 mcg/kg/day	• Free thyroxine levels, aiming for the upper half of the normal range
Gonadal (testosterone)	• Reduced libido • Erectile dysfunction • Reduced muscle strength • Fatigue	• Low or inappropriately normal FSH and LH levels • Low (multiple occasions) fasting testosterone level at 8.00 am to 9.00 am		• Testosterone 1% gel 5 g (50 mg testosterone) daily • Testosterone undecanoate 1000 mg IM every 12 weeks	• Blood pressure • Total testosterone sex hormone-binding globulin levels at 8.00 am to 9.00 am one week prior to IM testosterone • Haematocrit ± prostate-specific antigen • Bone densitometry

Abbreviations: ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; GH = growth hormone; IGF-1 = insulin-like growth factor-1; IM = intramuscular; LH = luteinising hormone; PAI = primary adrenal insufficiency; RAAS = renin–angiotensin–aldosterone system; TSH = thyroid-stimulating hormone.

a low or inappropriately normal ACTH level (the sample of which must be collected on ice).[8]

Managing hypocortisolism in pituitary disease

Hydrocortisone is the preferred glucocorticoid for replacement, as it is bioidentical to endogenous cortisol.[12] The leading alternatives are cortisone acetate, which also allows for variable dosing to mimic normal endogenous variations, and prednisolone, which does not allow for diurnal variations but may aid compliance due to its single daily dosing (Table).

The typical dose of hydrocortisone in adults with hypocortisolism is 15 to 20 mg daily.[6] Body weight is the most important predictor of hydrocortisone clearance in adults.[13] A weight-based calculation may be used, with evidence that a dose in the range of 0.20 to 0.25 mg/kg body weight is associated with the lowest cardiometabolic risk.[14] It is helpful to note that hydrocortisone is available in 20 mg and 4 mg tablets, and that cortisol follows a diurnal rhythm with a peak on waking and a nadir overnight.[12] Hence, a typical regimen for an adult with a body weight of 70 kg is 10 mg in the morning and 4 to 8 mg in the early afternoon, or 10 mg in the morning, 4 mg in the early afternoon and 4 mg in the early evening.

Stress dosing of corticosteroids

Hypocortisolism can be fatal, particularly during times of increased physiological stress when the cortisol demand is increased.[15] All patients with adrenal insufficiency, regardless of the aetiology, should have a written sick day management plan and carry a medical alert bracelet (or equivalent). Ideally, a close contact will have been

Table. Expected findings in patients with hypopituitarism based on the affected pituitary axis and suggested management approaches *continued*

Pituitary axis (hormone)	Suggestive clinical findings	Expected biochemical findings	Differences from primary organ insufficiency	Typical replacement regimen	Monitoring
Anterior pituitary					
Gonadal (oestrogen and progesterone)	• Menstrual disturbance • Vaginal dryness • Fatigue • Mood disturbance • Hot flushes (rare)	• Low or inappropriately normal (e.g. normal despite menopause) FSH and LH levels • Low oestrogen or progesterone levels	• Consider effect of oral oestrogen on GH levels – will reduce GH signalling and therefore increase GH requirements • Vasomotor symptoms less common	• Until the age of menopause • Progesterone: required if uterus is intact • Combined transdermal patch • Transdermal oestrogen + levonorgestrel	• Blood pressure • Bone densitometry
GH	• Reduced muscle strength • Altered body composition	• Low IGF-1 level – confirmatory testing required (e.g. glucagon stimulation test)		• GH: – age <60 years: 0.2 to 0.4 mg/day – age ≥60 years: 0.1 to 0.2 mg/day – dose adjustments: 0.1 mg/day	• IGF-1 levels six weeks after dose adjustments and every six months thereafter • Lipid levels every six months • HbA_{1c} every six months • Bone densitometry
Posterior pituitary					
Arginine vasopressin	Polyuria and polydipsia, particularly overnight	• 24-hour urine collection confirming hypotonic polyuria (>50 mL/kg/day, urine osmolality/plasma osmolality ratio <2) • Paired with serum sodium/osmolality • Low copeptin level • Confirmatory testing may be required (e.g. hypertonic saline copeptin test)		• Desmopressin: – intranasal: 10 to 20 mcg – oral: 100 to 400 mcg – at night or twice daily	• Titrate to reach manageable urine output • Drink to thirst • Serum sodium levels

Abbreviations: ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; GH = growth hormone; IGF-1 = insulin-like growth factor-1; IM = intramuscular; LH = luteinising hormone; PAI = primary adrenal insufficiency; RAAS = renin–angiotensin–aldosterone system; TSH = thyroid-stimulating hormone.

trained in parenteral hydrocortisone administration, and patients should always have an in-date kit on hand. Patients are instructed to double or triple their corticosteroid dose for two to three days, depending on the degree of illness. If they are unable to take oral tablets or if the illness progresses, urgent parenteral corticosteroid administration and hospital admission is required.

Increased demand for cortisol is also observed in the perioperative period. A dose of 50 mg intravenous hydrocortisone should be given at the time of anaesthetic induction or at procedure commencement (if no anaesthetic is given). Postoperative requirements depend on the degree of surgery. Information on precise dosing is available from Hormones Australia (https://www.hormones-australia.org.au/patient-resources/).

Hypothalamic–pituitary–thyroid axis

Central hypothyroidism is caused by inadequate TSH signalling to the thyroid. This is demonstrated by a notably low or inappropriately normal TSH level with low thyroid hormone levels. If the results do not correspond to the clinical picture or are obtained after a recent illness, sick euthyroid syndrome should be considered, and measurements of TSH, free thyroxine and free triiodothyronine levels should be repeated.[16]

Management of central hypothyroidism

Adrenal insufficiency must be excluded before starting thyroid hormone replacement. Starting thyroxine in the setting of untreated adrenal insufficiency can accelerate the metabolism of the low residual

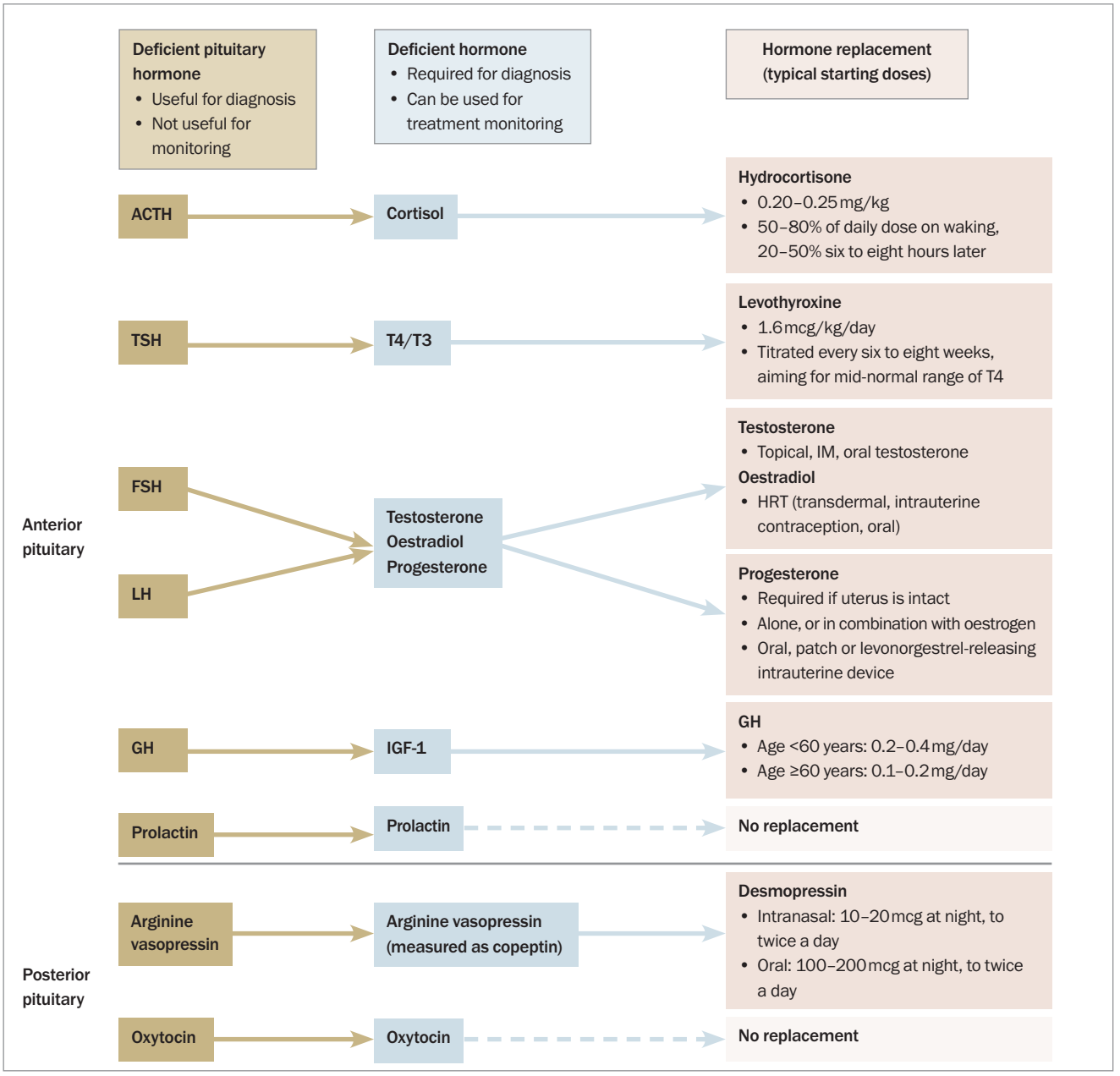

Figure. Hormone replacement approaches for hypopituitarism

Abbreviations: ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; GH = growth hormone; HRT = hormone replacement therapy; IGF-1 = insulin-like growth factor-1; IM = intramuscular; LH = luteinising hormone; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

cortisol and precipitate adrenal crises.[6]

Thyroid hormone replacement is similar to hormone replacement for primary hypothyroidism (e.g. associated with Hashimoto's thyroiditis), using an estimated dose of 1.6 mcg/kg/day of levothyroxine. Patients taking levothyroxine are usually advised to take their tablets at least 30 minutes before or after taking other tablets and other oral intake (apart from water). However, this is often impractical in the setting of panhypopituitarism, as patients require hydrocortisone on waking for symptomatic relief. In such cases, thyroxine and hydrocortisone should be consistently taken together and at least 30 minutes before or after other oral intake. The dose of thyroxine can then be titrated according to the results of repeated blood tests, accepting that the dose requirement may be higher to compensate for theoretically reduced absorption.

Monitoring of central hypothyroidism

The major difference between primary and central hypothyroidism is in monitoring. By definition, TSH levels are inadequate in central

hypothyroidism and are therefore not useful to monitor.[16] A low TSH level should not be confused with levothyroxine over-replacement. Free thyroxine should be used for titration, aiming for a target level in the mid to upper half of the normal range.[6]

Hypothalamic–pituitary–gonadal axis

Hypogonadism typically manifests as reduced energy, muscle strength and libido in men; menstrual irregularities, or oligomenorrhoea or amenorrhoea in women; and subfertility or infertility, and low bone density in either sex.[6] Central hypogonadism should be suspected if low sex hormone levels are accompanied by inappropriately normal or low FSH and LH levels.[17] Functional hypogonadism should be excluded if a clear pituitary disorder is not present.[18] This may result from acute or critical illness, anorexia nervosa, obesity (in men), obstructive sleep apnoea or the use of certain medications (e.g. opioids).

A note on hyperprolactinaemia

Hyperprolactinaemia should be excluded as a cause of central hypogonadism.[18] If detected, the cause of hyperprolactinaemia should be investigated, and the role of treatment (e.g. antipsychotic medication withdrawal, dopamine agonist therapy or surgical resection) should be considered after endocrinological review. If irregular prolactin levels are the primary cause, normalisation will usually restore the hypothalamic–pituitary–gonadal axis. If hypogonadism persists despite prolactin normalisation, testosterone or oestrogen/progesterone replacement may be required.

Free thyroxine should be used for titration, aiming for a target level in the mid to upper half of the normal range

Management of central hypogonadism in men

In Australia, oral, transdermal (creams, gels and patches) and intramuscular injection testosterone preparations are available. The choice of therapy is based on individual requirements.[18] GPs can prescribe testosterone via the PBS, after endorsement by a treating endocrinologist, urologist or sexual health physician (Fellow of the Australasian Chapter of Sexual Health Medicine).

The monitoring of patients on testosterone therapy is guided by routine clinical review with thorough history taking and examination.[18] Routine assessments of serum testosterone levels with sex hormone-binding globulin and haematocrit is recommended.

Bone densitometry, sleep study and prostate-specific antigen (PSA) level monitoring may be tailored to individual patient needs after baseline screening.[5,6] Restoration of physiological testosterone levels is not thought to cause prostate cancer; however, existing prostate cancer can progress with testosterone exposure. Hence, PSA levels should be measured at baseline before starting testosterone therapy to rule out high PSA levels requiring urological evaluation. However, the decision to pursue ongoing PSA monitoring should be based on the same considerations as in the general population.[18]

Measurements of serum testosterone levels in patients taking daily treatments should be acquired two to three hours after their usual dose. Three-monthly monitoring of intramuscular testosterone levels is performed the week before the next scheduled dose (trough level), but this does not delay the dose. Therapeutic targets incorporate both patients' physical needs and achieving testosterone levels in the middle of the normal range.[18] An elevated haematocrit level (≥0.54%) should prompt a reduction in testosterone dosage. Other strategies for managing polycythaemia include switching from intramuscular to transdermal testosterone preparations and, ultimately, venesection.

Management of central hypogonadism in women

Female hypogonadism may be associated with premature cardiovascular disease, reduced BMD and reduced quality of life.[6,7] Current recommendations include the use of sex hormone replacement until the natural age of menopause.

In the hypopituitary setting, transdermal oestrogen replacement is preferred, as first-pass metabolism of oral oestrogen attenuates GH and insulin-like growth factor-1 (IGF-1) action and metabolism.[19] Furthermore, transdermal oestrogen has been shown to yield greater gains in BMD than oral oestrogen in central hypogonadism.[20] If oral oestrogen is used, higher dose requirements for GH should be anticipated.[6] The Australasian Menopause Society provides a discussion of oestrogen and progesterone replacement options (https://www.menopause.org.au/hp/management). Evidence does not currently support the routine use of androgen therapy (testosterone or dehydroepiandrosterone) in women.[21,22]

Monitoring following the initiation of replacement therapy is primarily symptom based. BMD should be measured periodically if it is low at baseline (e.g. biannually, or 12 months after the treatment changes).

Fertility in hypopituitarism

Both male and female fertility are impaired in central hypogonadism. Assisted reproductive treatments (i.e. ovulation induction or in vitro fertilisation) are often required for conception, with pregnancy rates ranging from 47 to 76% in small observational studies.[17,21] Women with central hypogonadism who wish to conceive should be offered ovulation induction with gonadotropins. In men with central hypogonadism who wish to conceive, testosterone replacement should be paused, as this directly inhibits spermatogenesis, and human chorionic gonadotropin with or without FSH should be used instead to induce spermatogenesis. Several months of treatment may be required to induce adequate sperm counts.[23,24]

Growth hormone

Adult-onset GH deficiency can be clinically subtle but impact metabolic health and cardiovascular risk.[7] Because of interactions between the various pituitary hormones and given that GH is the least critical hormone to replace, the other pituitary axes should be investigated and any abnormalities treated before GH is assessed.[25]

2. Resources for patients and healthcare practitioners

- **The Australian Pituitary Foundation:** hypopituitarism patient fact sheets and links to cortisol replacement resources and patient support – https://pituitary.asn.au/
- **Hormones Australia:** fact sheets on various hormone deficiencies – https://www.hormones-australia.org.au/endocrine-diseases/
- **Endocrine Society of Australia:** adrenal insufficiency resources – https://www.endocrinesociety.org.au/reseources-adrenal-insufficency-resources.asp
- **The Pituitary Foundation (UK):** sick day management for central diabetes insipidus (AVP-D) – https://www.pituitary.org.uk/information/publications/diabetes-insipidus/
- **Australasian Menopause Society:** information for healthcare professionals regarding menopause management (broadly applicable to the central hypogonadism setting) – https://www.menopause.org.au/hp/management

IGF-1 levels may be used to screen for GH deficiency; a definitive diagnosis is made based on the results of an insulin tolerance test or glucagon stimulation test, with assessment of the peak GH level.[6] GH replacement consists of daily subcutaneous injections of recombinant human GH. Weekly preparations exist but are not yet available via the PBS.[26] Recombinant human GH is not recommended in patients with active malignancy or during pregnancy.[25] The GH dose is titrated to symptoms of GH deficiency or excess and the IGF-1 level, which should be mid-normal.

During pregnancy, placental GH production mitigates the need for exogenous GH replacement. Although GH replacement is typically ceased on confirmation of pregnancy, some experts advocate for weaning after the first trimester.[21,27] Limited data suggest that GH continuation in pregnancy is not harmful, but prospective studies are needed.[28]

Arginine vasopressin

AVP, also known as antidiuretic hormone, is released from the posterior pituitary in response to increased serum osmolality and acts on the renal tubules to retain water. AVP deficiency (AVP-D), previously termed central diabetes insipidus, may be complete or partial, causing renal water wasting and significant polyuria.[29]

Most patients with AVP-D retain their sense of thirst, which is important for salt and water balance. Provided patients are able to drink to thirst to replace urinary losses, AVP-D management is straightforward.[30] Adipsic AVP-D is rare, being found only with extensive sellar masses or injuries that involve the hypothalamic regions responsible for thirst.

Initial investigations for polyuria-polydipsia syndrome include measurements of 24-hour urine volume and osmolality with paired serum osmolality, sodium, glucose, calcium and copeptin. Confirmatory testing (e.g. via the hypertonic saline-stimulated copeptin test) may be required to differentiate AVP-D from primary polydipsia.[29,31,32]

The treatment of AVP-D involves the use of desmopressin, which is a synthetic analogue of vasopressin with a longer half-life. The aim of treatment is to provide relief from the excessive urination and thirst, which otherwise interfere with daily activities and sleep. Dosing is titrated to relieve symptoms while avoiding excessive water retention leading to hyponatraemia. Overtreatment with desmopressin can cause dangerous hyponatraemia, hence, erring on the side of lower desmopressin doses and drinking to thirst is typically the safest option.[29] Withholding desmopressin periodically until breakthrough polyuria develops has been shown to lower rates of hospitalisation for hyponatraemia.[32-34]

Sick day management of AVP-D

Sick days can generally be managed using the usual rule of drinking to thirst and aiming for equal fluid input and output. This can be difficult with gastrointestinal illnesses, such as diarrhoea, and inpatient management may be required under the care of an endocrinologist.[35]

Broader considerations in hypopituitarism

Patients with hypopituitarism have an increased cardiovascular risk. Modifiable cardiovascular risk factors should therefore be considered routinely and optimised where possible, including smoking cessation and lipid assessment.[6]

Bone density is negatively affected by hypogonadism, GH deficiency and supraphysiological replacement of cortisol and thyroxine, but typically improves, or at least stabilises, with appropriate hormonal replacement, adequate calcium and vitamin D consumption and engaging in weightbearing exercise.[6] Bone densitometry should be considered in these settings.

Conclusion

Hypopituitarism affects a broad range of physiological systems and necessitates stepwise investigation and management. Identification and treatment of central adrenal insufficiency prior to starting other therapies is key, as is recognising the differences between primary and central hormone deficiencies. Box 2 lists some resources for patients and GPs. **ET**

References

A list of references is included in the online version of this article (www.endocrinologytoday.com.au).

COMPETING INTERESTS: None.

Don't miss

The case study about management of a 53-year-old woman with postmenopausal symptoms on page 34.

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