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REVIEW

Interpretation of the endocrinology of hospital inpatients

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Abstract

Blood tests to assess the endocrine system are commonly performed in patients admitted to hospital. This may be because an endocrinopathy is thought to be aetiological in the presenting disease or suspected as an incidental occurrence by the clinician. Many patients, in addition to the pathology leading to admission, frequently have one or more comorbidities, a change in nutritional status and polypharmacy. Added to this, presentation with acute illness is a major life stress. All of these are likely to impact on one or more endocrine axes, although often only transiently. Endocrine evaluation in the vast majority of cases can be safely deferred to the outpatient setting. This article considers the most common endocrine anomalies discovered in hospital, the confounders, and provides guidance on how to investigate these further.

Key words: Adrenal insufficiency; Hypogonadism; Hyponatraemia; Stress; Thyroid

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Introduction

Endocrinology is a speciality commonly practiced in outpatient settings. However, an endocrinology opinion is commonly sought for many patients admitted acutely to hospital for non-endocrine-related reasons (eg infection, surgery, dialysis) and less commonly for endocrine emergencies (eg adrenal crisis, malignant hypercalcaemia, thyrotoxic storm). It is well recognised that both acute illness and chronic disease can affect endocrine function and thus interpretation of hormone levels. Therefore it is essential to recognise potential confounders to avoid unnecessary investigations, which in turn can lead to inappropriate treatment.

Investigation and management of acute endocrine emergencies have been extensively covered in the literature and are not reviewed in this article.

Thyroid function tests

Many patients have a thyroid function test performed during their hospital stay. This may be because of direct suspicion of thyroid disorders (eg atrial fibrillation), but in many cases a routine screen for disorders including dementia, hyponatraemia or fractures triggers the test. In the absence of pre-existing thyroid disorders, thyroid function tests are frequently abnormal during acute illness (eg severe infection, myocardial infarction), surgery or trauma. The observed changes were previously termed 'sick euthyroid syndrome', but it is increasingly recognised that these individuals likely have a degree of central and peripheral hypothyroidism and therefore a more appropriate term is 'non-thyroidal illness' syndrome.

Acute illness can affect the thyroid axis via a number of different mechanisms. Non-thyroidal illness inhibits deiodinase enzymes (D1 and D2), which are responsible for conversion of thyroxine (T4) to active liothyronine (T3), resulting in low T3 level. Non-thyroidal illness also increases D3 enzyme activity responsible for conversion of T4 to the inactive form of T3 (reverse T3). Cytokines play an additional role in non-thyroidal illness through inhibition of thyrotropin-releasing hormone and thyroid-stimulating hormone secretion and inhibition of D1 activity (Vries et al, 2015).

Low T3 and high reverse T3 levels are the hallmark of non-thyroidal illness. Thyroid-stimulating hormone and free T4 levels depend on the acuity and duration of illness (Table 1). During recovery from illness, thyroid-stimulating hormone levels can show a modest increase, which can be confused with primary hypothyroidism should free T4 levels remain

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Degree of illness	Thyroid-stimulating hormone	Free T4	Can be mistakenly diagnosed as
Mild–moderate illness	Normal or low	Normal, low or high	Primary hyperthyroidism (low thyroid-stimulating hormone, high T4) Secondary hypothyroidism (low thyroid-stimulating hormone, low T4)
Severe or prolonged illness	Low	Low	Secondary hypothyroidism
Recovery	High	Low	Primary hypothyroidism

Table 1. Thyroid function tests during non-thyroidal illness

From Lee and Farwell (2016); Salvatore et al (2016)

low. Thyroid function tests normalise several weeks after resolution of illness (DeGroot, 2015). There is no robust evidence that thyroid hormone replacement, either T4 or T3, administered to normalise thyroid hormone levels during non-thyroidal illness will improve outcomes. Therefore, at present thyroid hormone replacement is not recommended, and thyroid function tests should be re-checked 3 months after recovery of illness to ensure they normalise.

Where an elevated thyroid-stimulating hormone level is detected while an inpatient but in the absence of acute illness, the higher the thyroid-stimulating hormone level the greater the probability that this represents primary hypothyroidism (thyroid-stimulating hormone ≥10 miu/litre) and thyroid hormone replacement can be considered. Epidemiological studies of longitudinal changes in thyroid-stimulating hormone and T4 values in healthy individuals frequently show values outside of the reference ranges, which may not necessarily evolve (Vanderpump et al, 1995). This is particularly true where thyroid-stimulating hormone values are above the reference range but <10 miu/litre (subclinical hypothyroidism). Thyroid function tests should be repeated along with measurement of thyroid peroxidase antibodies after at least 3 months (National Institute for Health and Care Excellence, 2019) and requirement for replacement considered at that time.

Male hypogonadism

Men admitted to the hospital might have their testosterone level checked as a part of investigation of an osteoporotic fracture or unexplained anaemia. However, functional hypogonadism commonly occurs as a result of acute systemic illness, organ failure or medications (opioids and glucocorticoids) (Bhasin et al, 2018). Acute illness including sepsis, burns, respiratory tract infection, myocardial infarction or stroke can cause reversible hypogonadism. Importantly, testosterone has a significant diurnal rhythm and levels are reduced by consumption of carbohydrates. Testosterone levels should only ever be checked between 8 and 10 am after an overnight fast.

In a study of older (age >65 years) male patients admitted to geriatric units, just over half (53.3%) showed evidence of hypogonadism. Of these, 43.7% were felt to represent primary hypogonadism (Iglesias et al, 2014). In contrast, within the community setting, the European Male Aging Study followed 2736 men aged ≥40 years for 4.4 years and found that over 80% of men in their 7–8th decade had normal testosterone levels (Tajar et al, 2010). Therefore, it can be hypothesised that hypogonadism in older male inpatients mostly relates to coexisting acute medical conditions. In keeping with these observations, within the European Male Aging Study population two distinct groups of older men with low total testosterone levels were demonstrated (Wu et al, 2010). The majority were characterised by low testosterone and low–normal luteinising hormone levels associated with age-related non-gonadal comorbidities but not age, whereas a minority had low testosterone levels associated with high luteinising hormone levels, in keeping with primary testicular insufficiency.

Thus, although late-onset hypogonadism relating to reduced Leydig cell function, and characterised biochemically by reduced total and free testosterone in association with a compensatory rise in luteinising hormone levels does occur with ageing, the majority of hypogonadism in older individuals relates to acute illnesses and associated comorbidities (ie diabetes mellitus, cardiovascular disease, inflammatory disease, obesity) and is characterised by low testosterone levels and lack of a compensatory increase in luteinising hormone levels. Investigation of hypogonadism should be delayed in the inpatient as hypogonadism is highly prevalent. Where undertaken and testosterone levels are found to be low, a repeat blood test for testosterone, sex hormone-binding globulin, gonadotropins and prolactin should be performed as an outpatient 2–3 months after resolution of any acute illness and care of comorbidities has been optimised.

Hyponatraemia

Hyponatraemia (Na <135 mmol/litre) occurs in at least 15% of acute admissions and is associated with increased risk of mortality irrespective of the underlying cause (Holland-Bill et al, 2015). It is the commonest reason for referral of inpatients to the endocrine team. Hyponatraemia can be the first sign of serious underlying pathology (eg cancer) and, if severe, can cause seizures and death, so accurate assessment and management is essential. There are a number of suitable published algorithms for managing hyponatraemia. Some commence with assessment of extracellular volume status (Grant et al, 2015) while others start with measurement of urine osmolality and urine sodium in order to narrow the differential diagnosis (Spasovski et al, 2014). In general, management is directed at the cause of the hyponatraemia so it is imperative to establish the aetiology.

In routine practice, the authors suggest using the following approach:

Step 1: Assess the severity of hyponatraemia

Severe hyponatraemia (hyponatraemia associated with vomiting, confusion, somnolence, seizures and/or coma) is a medical emergency that requires urgent treatment with hypertonic saline irrespective of the underlying cause. The authors recommend following the Society for Endocrinology protocol for hypertonic saline infusion (Ball et al, 2016). A study found that the use of bolus infusion of hypertonic saline led to faster improvement in serum sodium levels and symptoms compared with continuous infusion in the treatment of severe hyponatraemia (Garrahy et al, 2019).

Step 2: Rule out non-hypotonic hyponatraemia

- Measure serum glucose and calculate corrected sodium using the following formula

$$\text{Corrected Na (mmol/litre)} = \text{measured Na (mmol/litre)} + 2.4 \times \frac{\text{glucose (mmol/litre)} - 5.5}{5.5}$$

- Consider pseudohyponatraemia, which can be caused by hypertriglyceridaemia or multiple myeloma.

Step 3: Assess causes of hyponatraemia from the clinical context

Patients can be split into three categories, depending on the cause of hyponatraemia:

- Patients who are clinically dehydrated with an obvious cause, eg vomiting, diarrhoea
- Patients who are clinically overloaded with an obvious cause, eg nephrotic syndrome, cardiac, renal or hepatic failure
- Patients on thiazide diuretics (and to a lesser extent loop diuretics).

Step 4: Assess fluid status and undertake screening tests

In patients with euvolaemic hyponatraemia, measure spot plasma and urine osmolality and electrolytes, 9.00 am cortisol and thyroid function tests to identify the cause (Table 2) (Grant et al, 2015). Concurrent diuretic use increases urinary sodium levels and should be discontinued before assessing urine electrolytes and osmolality. Sometimes interpretation of these tests can be difficult, particularly where two or more concomitant causes are

Table 2. Differential diagnosis of hyponatraemia

Cause	Urine osmolality	Urine sodium	Volume status
Primary polydipsia Tea and toast hyponatraemia Beer potomania	Low (<100 mOsm/kg)	N/A	Euvolaemic
Heart failure Liver failure Nephrotic syndrome	High (>100 mOsm/kg)	<30 mmol/litre	Overloaded
Diarrhoea Third space loss	High (>100 mOsm/kg)	<30 mmol/litre	Dehydrated
Vomiting Addison's disease	High (>100 mOsm/kg)	>30 mmol/litre	Dehydrated
Syndrome of inappropriate antidiuretic hormone secretion Secondary adrenal failure Severe hypothyroidism	High (>100 mOsm/kg)	>30 mmol/litre	Euvolaemic

From Spasovski et al (2014)

responsible for the hyponatraemia (eg dehydration in patients with syndrome of inappropriate antidiuretic hormone secretion). Therefore, these tests might need to be repeated if diagnosis remains unclear or hyponatraemia persists despite initial treatment.

Step 5: Rule out adrenal insufficiency and hypothyroidism before diagnosing syndrome of inappropriate antidiuretic hormone secretion

Both adrenal insufficiency and hypothyroidism can cause hyponatraemia with paired serum and urine osmolality and sodium values that are indistinguishable from syndrome of inappropriate antidiuretic hormone secretion. Therefore these conditions must be excluded before syndrome of inappropriate antidiuretic hormone secretion can be diagnosed. Cuesta et al (2016) identified that 3.8% of patients with euvolaemic hyponatraemia initially diagnosed as syndrome of inappropriate antidiuretic hormone secretion actually had secondary adrenal insufficiency.

Adrenal insufficiency

Precipitation of adrenal crisis has long been recognised in patients with adrenal insufficiency who have not received appropriate steroid cover during surgery. The adrenal gland secretes ~10 mg cortisol daily. Surgical stress results in a transient increase in endogenous cortisol production, up to 50 mg/day and 150 mg/day in minor and major surgery respectively (Liu et al, 2017). Therefore, it is important that all patients with adrenal insufficiency receive appropriate glucocorticoid cover during periods of surgical stress. The UK Addison's disease self-help group (www.addisons.org.uk), working with experts in the field of adrenal insufficiency, has developed protocols (Tables 3–5) for steroid cover during surgery, labour and invasive procedures. This protocol has been endorsed by European expert consensus statement (Husebye et al, 2014).

As previously mentioned, a new diagnosis of adrenal insufficiency can be the cause of hyponatraemia, but also so can failure to increase the dose of glucocorticoids during times of intercurrent stresses (ie infections, cardiac events, trauma) in patients with known adrenal insufficiency. Furthermore, failure to appropriately increase maintenance glucocorticoid dosage can risk development of a life-threatening adrenal crisis. For patients on physiological replacement dosage of steroids (ie hydrocortisone 15–20 mg/day, prednisolone 3–4 mg/day)

<table>
<tr><th colspan="3">Table 3. Steroid cover for patients with adrenal insufficiency undergoing surgery</th></tr>
<tr><th>Type of surgery</th><th>Preoperative and intraoperative dose</th><th>Postoperative dose</th></tr>
<tr><td>Major surgery with long recovery time (eg cardiac surgery, major bowel surgery, procedures requiring stay in intensive care)</td><td rowspan="2">Hydrocortisone 100 mg intravenous (or intramuscular) just before anaesthesia followed by either:

Hydrocortisone continuous intravenous infusion of 200 mg over 24 hours, or

Hydrocortisone 100 mg intravenous (or intramuscular) every 6 hours</td><td>Immediate postoperative:
■ Continue parenteral hydrocortisone (100 mg intravenous every 6 hours or continuous intravenous infusion 200 mg over 24 hours)
If patient becomes well, able to eat and drink and discharged from intensive care unit:
■ Double oral dose for >48 hours
■ Then return to normal dose</td></tr>
<tr><td>Major surgery with rapid recovery (eg caesarean section, joint replacement)</td><td>Immediate postoperative:
■ Continue parenteral hydrocortisone (100 mg intravenous every 6 hours or continuous intravenous infusion 200 mg over 24 hours) for 24–48 hours
If patient becomes well, able to eat and drink:
■ Double oral dose for 24–48 hours
■ Then return to normal dose</td></tr>
<tr><td>Minor surgery (eg cataract surgery, hernia repairs, laparoscopy with local anaesthetic)</td><td>Hydrocortisone 100 mg intramuscular just before anaesthesia</td><td>Double oral dose for 24 hours

Then return to normal dose</td></tr>
<tr><td>Minor procedure (eg skin mole removal with local anaesthetic)</td><td>Take extra oral dose (eg hydrocortisone 10 mg orally) 1 hour before procedure</td><td>Take another extra dose (eg hydrocortisone 10 mg orally) 1 hour after the procedure

Then return to normal dose</td></tr>
</table>

From Addison's Disease Self-Help Group (2017)

<table>
<tr><th colspan="2">Table 4. Steroid cover for women with adrenal insufficiency undergoing vaginal delivery</th></tr>
<tr><td>At onset of active labour (cervical dilation >4 cm)</td><td>Give hydrocortisone 100 mg intravenous (or intramuscular) just before anaesthesia followed by either:
■ Hydrocortisone 100 mg intravenous (or intramuscular) every 6 hours or
■ Hydrocortisone continuous intravenous infusion 200 mg over 24 hours until delivery</td></tr>
<tr><td>After delivery</td><td>Double oral dose for 24–48 hours then return to normal dose (if well)</td></tr>
</table>

From Addison's Disease Self-Help Group (2017)

a two–three fold increase in steroid dosage for 3–4 days is adequate for most situations, but if the patient is acutely unwell (ie severe pneumonia, sepsis) intravenous steroids may be necessary (eg hydrocortisone 50 mg four times a day). Where there is doubt, it is generally safer to give a higher dose of steroids than too little.

Weaning from steroids

Synthetic glucocorticoids are very commonly prescribed to treat various immune, inflammatory and malignant diseases. It is estimated that 1–2% of the UK population is receiving glucocorticoids in one form or another. Chronic use of exogenous glucocorticoids can suppress adrenocorticotropic hormone release thereby causing secondary adrenal insufficiency (Bancos et al, 2015). Failure to recognise this on withdrawal of glucocorticoids can lead to occurrence of life-threatening adrenal crises. Questions commonly asked of the endocrinologist regarding patients on exogenous corticosteroids are:

1. Is it safe to stop steroids suddenly?
2. Does the hypothalamo–pituitary–adrenal axis need to be assessed before stopping steroids?

Table 5. Steroid cover for patients with adrenal insufficiency undergoing invasive procedures

Type of procedure	Preprocedure	Postprocedure
Invasive bowel procedures requiring laxatives, eg colonoscopy, barium enema	Hospital admission overnight Give intravenous fluids and hydrocortisone 100 mg intramuscular during preparation Give hydrocortisone 100 mg intramuscular at start of procedure	Double oral dose for 24 hours, then return to normal dose
Other invasive procedures, eg upper gastrointestinal endoscopy	Hydrocortisone 100 mg intramuscular just before commencing	

From Addison's Disease Self-Help Group (2017)

Despite significant individual variability in response to glucocorticoids, there are general rules that can be followed to aid decision making (**Figure 1**) (Liu et al, 2017).

Diagnosing adrenal insufficiency in critically ill patients

Patients admitted to the intensive care unit for vital organ support develop functional changes in their hypothalamo–pituitary–adrenal axis. A review by Téblick et al (2019) suggested three phases of hypothalamo–pituitary–adrenal axis response to severe stresses. In the first minutes–hours after the insult, there is an increase in the total and free cortisol levels, mainly driven by increased adrenocorticotropic hormone secretion. In the second phase (hours–days), adrenocorticotropic hormone secretion is suppressed by increased plasma cortisol level. However, total and free cortisol levels remain elevated as a result of decreased metabolism of cortisol. Most prolonged stresses also cause a decrease in cortisol-binding globulin levels, which in turn increases free cortisol but reduces total cortisol levels. If the stressor remains for weeks, prolonged suppression of adrenocorticotropic hormone will result in marked decrease in cortisol production that cannot be compensated for by the concurrent decrease in cortisol metabolism.

Critical illness-related corticosteroid insufficiency is a term used to describe a unique condition in which cortisol level and/or action is not adequate for the severity of critical illness (ie relative adrenal insufficiency). There is no consensus on which test should be used to diagnose critical illness-related corticosteroid insufficiency. Some authors suggest using a random cortisol level of <276 nmol/litre (<10 ug/dl), while others suggest using the short synacthen test (250 ug Cosyntropin) with critical illness-related corticosteroid insufficiency diagnosed if the 60-minute cortisol level fails to increase by 248 nmol/litre (9 ug/dl) from the baseline level (Annane et al, 2017). Shock unresponsive to fluid resuscitation and/or vasopressors should signal the presence of critical illness-related corticosteroid insufficiency, and a low threshold for treatment with glucocorticoids applied to the clinical context.

Using corticosteroids in treating patients with sepsis or septic shock is controversial. A Cochrane review (Annane et al, 2015) and subsequent meta-analysis (Rochwerg et al, 2018) showed that corticosteroid treatment was associated with reduction of mortality in patients with sepsis. This has been reflected in guidelines that currently recommend using corticosteroids in patients with septic shock unresponsive to fluid resuscitation and vasopressors (Annane et al, 2017; Rhodes et al, 2017). Furthermore, BMJ guidelines recommended using corticosteroids in all patients with sepsis with or without shock (Lamontagne et al, 2018).

An initial study showed that the short synacthen test can predict the mortality benefit of corticosteroid treatment in patients with sepsis (Annane et al, 2002). However, the subsequent APROCCHSS trial did not show a difference in 90-day mortality between responders and non-responders to the short synacthen test who were given corticosteroids in sepsis (Annane et al, 2018). Moreover, the short synacthen test is not an accurate test to assess adrenal reserve in critically ill patients consequent on an increased cortisol distribution volume, which can lead to low incremental total cortisol response to synacthen even in patients with good adrenal reserve (Peeters et al, 2018).

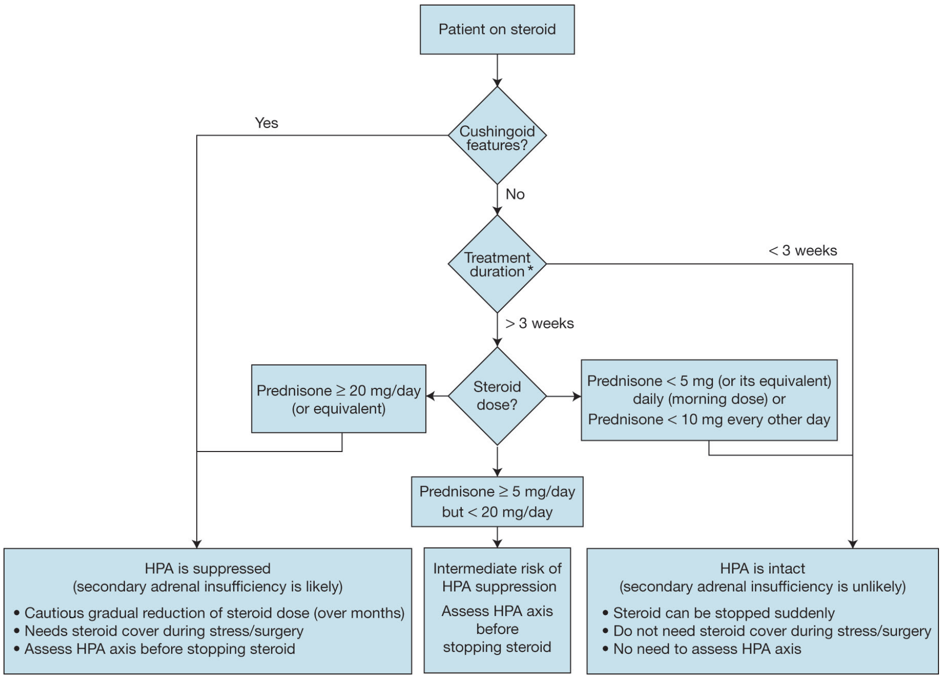

Figure 1. Suggested algorithm for safely stopping exogenous glucocorticoids. *Patients who received frequent short courses of steroid can develop hypothalamo–pituitary–adrenal axis (HPA) suppression. Adapted from Liu et al (2017).

It is very important to differentiate between critical illness-related corticosteroid insufficiency (a state of relative adrenal insufficiency) and acute adrenal insufficiency caused by structural pituitary lesions or adrenal lesions that can present acutely during times of increased cortisol demand. Moreover, drugs commonly used in the intensive care unit (eg etomidate, ketoconazole, propofol and opioids) can affect the hypothalamo–pituitary–adrenal axis, leading to low plasma cortisol levels (Téblick et al, 2019).

Anorexia nervosa, weight loss and malnutrition

Anorexia nervosa is an eating disorder that more commonly affects women. It is characterised by very low body mass index and altered perception of body image. Many of these patients undergo endocrine tests to investigate for hyperthyroidism and adrenal insufficiency as potential contributors to weight loss. As a sequela of weight loss and malnutrition, anorexia nervosa results in dysregulation of several endocrine axes. The results of hormonal tests can be confusing and can create unnecessary biochemical and/or radiological investigations. Similar but less marked abnormalities are observed with significant weight loss through dieting, low body mass index,and malnutrition, the most frequent being suppression of the gonadotropins with a picture of secondary hypogonadism.

Table 6 summarises the endocrine abnormalities commonly seen in patients with anorexia nervosa (Schorr and Miller, 2017).

Endocrine dysfunction in liver disease

Hepatic impairment impacts on multiple endocrine systems, including the growth hormone/insulin-like growth factor-1, gonadal and thyroid axes, as well as having adverse effects on skeletal integrity and glucose homeostasis. Serum thyroid hormone levels can fall, analogous to non-thyroidal illness. Type 1 deiodinase (D1) activity, which is responsible for up to 80% of circulating T3, is reduced in liver disease, resulting in impaired hepatic conversion of T4 to T3 (DeGroot, 2015).

The function of the hypothalamic–pituitary–gonadal axis is impaired at several levels in patients with chronic liver disease, making hypogonadism a frequent clinical feature of these individuals. Men present with gynaecomastia, decreased libido, testicular atrophy and oligospermia. These features are more prominent in patients with alcoholic liver disease as a result of the additional direct toxic effects of ethanol on the testes. There is reduction in serum testosterone and dihydroepiandrosterone levels with inappropriately low or normal gonadotropin production and pulsatility (Zacharias et al, 2014). Mild elevation of oestradiol levels and hyperprolactinaemia also occur, leading to an increase in the oestrogen:androgen ratio (Zacharias et al, 2014). Sex hormone-binding globulin levels are increased in liver disease and this binds testosterone with high affinity, lowering free testosterone concentrations. Women with cirrhosis can also suffer menstrual disturbances.

The growth hormone/insulin-like growth factor-1 axis is deranged in patients with chronic liver disease, leading to a state of functional growth hormone resistance (Wallace et al, 2002). The majority of circulating insulin-like growth factor-1 is produced by the liver after stimulation by growth hormone. In patients with chronic liver disease, serum insulin-like growth factor-1 levels are diminished secondary to reduced hepatocyte mass, decreased peripheral growth hormone receptors in the cirrhotic liver and insulin-like growth factor binding proteins. Serum growth hormone concentration is increased, reflecting reduced insulin-like growth factor-1 feedback inhibition of growth hormone secretion at the hypothalamus and pituitary. These alterations in the growth hormone/insulin-like growth factor-1 axis are believed to contribute to disorders of lipid and carbohydrate metabolism, insulin resistance and low bone mass in patients with chronic liver disease (Gariani et al, 2016; Wallace et al, 2002).

Hepatic osteodystrophy manifests with osteoporosis and osteopenia in patients with liver disease (Gatta et al, 2014) and is multifactorial. Risk factors for osteoporosis include malnutrition, hypogonadism, low insulin-like growth factor-1, low body mass index and

Table 6. Endocrine manifestations in patients with anorexia nervosa

System or hormone	Effect of anorexia nervosa	Notes
Growth hormone	↑ Growth hormone ↓ Insulin-like growth factor 1	Anorexia is a state of growth hormone resistance Growth hormone normalises on weight regain
Hypothalamo–pituitary–adrenal axis	↑ Cortisol (usually < 2 times the upper limit of normal)	Patients with anorexia do not exhibit classic clinical features of Cushing's syndrome (however, low bone mineral density, proximal muscle wasting and depression are common in both conditions) Hypercortisolaemia in anorexia does not require any further investigations or treatment
Thyroid function tests	Euthyroid sick syndrome picture: Thyroid-stimulating hormone: normal or ↓ Free T4: normal or ↓ Free T3: ↓	No further monitoring of thyroid function is needed Treatment with levothyroxine is not required
Hypothalamo–pituitary–gonadal axis	Hypothalamic amenorrhoea and infertility in women ↓ Oestradiol ↓ or normal luteinising hormone and follicle-stimulating hormone ↓ Testosterone	Weight regain and increase percentage of body fat are very important to restore regular menses. However, up to 15% may remain amenorrhoeic despite achieving normal weight
Water balance	Hyponatraemia (secondary to syndrome of inappropriate anti-diuretic hormone) ↓ Plasma osmolality ↑ Urine osmolality ↑ Urine Na	Monitoring serum sodium levels is essential in patients with hyponatraemia

From Misra and Klibanski (2014); Schorr and Miller (2017) chronic alcohol excess. Vitamin D deficiency is frequent in patients with chronic liver disease, in part as a result of reduced 25-hydroxylase activity.

Glucose disturbances are frequent in patients with chronic liver disease. Hypoglycaemia is a recognised complication in patients with cirrhosis caused by chronically impaired gluconeogenesis and significantly reduced glycogen stores; further amplified by malnutrition and the effects of acute alcohol on gluconeogenesis. Hypoglycaemia is significantly associated with increased short-term mortality in patients with acutely decompensated liver cirrhosis. Impaired glucose tolerance and hyperglycaemia leading to hepatogenous diabetes also occur as a result of insulin resistance.

Endocrine disorders in patients with renal disease

Chronic renal disease is associated with widespread endocrine dysfunction affecting the growth hormone/insulin-like growth factor-1, gonadal, prolactin and thyroid axes, as well as having adverse effects on maintenance of bone integrity. Plasma concentrations of many hormones can be abnormal and may be of limited value in chronic renal disease (Kuczera et al, 2015).

There is reduced production of 1,25-dihydroxyvitamin D (calcitriol), the active form of vitamin D, in the kidney because of the decline in activity of 1-α hydroxylase. The prevalence of calcitriol deficiency increases with progression of chronic renal disease, reaching 80% in patients with chronic renal disease stage 5 (Kuczera et al, 2015). Calcitriol deficiency leads to development of hypocalcaemia and secondary hyperparathyroidism. Levels of parathyroid hormone also increase as a result of reduced metabolic clearance. These biochemical disturbances result in renal osteodystrophy characterised by abnormalities in bone turnover and mineralisation as well as soft tissue calcification.

Approximately 50% of euthyroid patients with chronic renal disease have an enlarged thyroid gland, if not a palpable goitre. The prevalence of hypothyroidism is increased 2.5-fold, paralleling an increase in levels of thyroid peroxidase antibodies. Low T3 levels are the most common laboratory finding in patients with chronic renal disease, followed by subclinical hypothyroidism (Mohamedali et al, 2014). Serum thyroid-stimulating hormone levels are generally normal and are probably the best guide of thyroid status. Hyperthyroidism is not clearly associated with chronic renal disease, but has been reported to accelerate it.

Chronic renal disease is also responsible for deregulation of the gonadal axis, directly affecting gonadal function. There is loss of the appropriate pulsatile release of luteinising hormone from the pituitary gland, serum free and total testosterone levels are low, while serum levels of follicle-stimulating hormone may be increased as a result of peripheral resistance of the testes to follicle-stimulating hormone. A reduction in the renal clearance of prolactin can lead to elevated levels, with hyperprolactinaemia impairing gonadotropin release. Spermatogenesis is impaired, in part because of direct toxic effects on the testis. In women, serum oestradiol levels are usually low, the ovulatory cycle is disrupted, and amenorrhoea is not uncommon.

Impaired renal function is also associated with functional growth hormone resistance, particularly relevant to the growth retardation that is seen in children with chronic renal disease, but can be overcome with high doses of growth hormone. Growth hormone levels are normal or increased in patients with chronic renal disease as a result of reduced clearance; however, despite normal expression of the growth hormone receptor significant impairment of growth hormone signalling has been shown in patients with renal dysfunction (Schaefer et al, 2001). Circulating insulin-like growth factor-1 levels are either normal or low, but a greater proportion of insulin-like growth factor-1 is bound to insulin-like growth factor binding proteins which accumulate as a result of reduced renal clearance, thereby reducing the free (active) fraction of the hormone.

Insulin concentration is increased as a result of impaired metabolic clearance when estimated glomerular filtration rate falls below 40 ml/min/1.73m^2, resulting in fasting hyperinsulinaemia and accounts for decreased insulin requirement in diabetic patients with chronic renal disease. Clinical features of excess cortisol (osteopenia, proximal myopathy, hypertension and glucose intolerance) and cortisol deficiency (hypotension, weakness and hyperkalaemia) overlap with features of chronic renal disease. Assessment of the

Key points

- Acute illness can result in abnormal thyroid function tests. It is advised not to check thyroid function in acutely unwell adults unless a genuine thyroid disorder is clinically suspected.
- Hypogonadism diagnosed during acute illness need to be reassessed after recovery from the illness.
- It is important to rule out adrenal insufficiency before diagnosing syndrome of inappropriate antidiuretic hormone secretion.
- Patients with adrenal insufficiency (and those on long-term steroids) will need extra steroid doses if they going to have stressful procedure or surgery.
- Critical illness can cause a state of relative adrenal insufficiency. Consider corticosteroids in patients with sepsis unresponsive to fluid resuscitation and vasopressors.

hypothalamo–pituitary–adrenal axis in patients with chronic renal disease is challenging (Stroud et al, 2019). Conventional high dose (250µg) synacthen (adrenocorticotropic hormone) tests give normal cortisol responses. Uraemic patients may show suboptimal plasma cortisol suppression after oral dexamethasone. It is unknown if this is a result of poor intestinal absorption of dexamethasone or increased plasma clearance (Stroud et al, 2019).

Stress hormones

Many human hormone axes are activated during times of stress, including catecholamines, glucocorticoids, growth hormone and prolactin. As such measurement of levels of these hormones within inpatients who have been admitted with acute illness and the accompanying stress can lead to false diagnosis. Both basal hormone levels and suppression tests can give false positive results. It would be unusual to need to investigate abnormalities of these axes as an inpatient with the potential exception of suspicion of an acute phaeochromocytoma crisis leading to haemodynamic instability or end-organ dysfunction (Whitelaw et al, 2014).

Conclusions

Abnormalities of the endocrine system are frequently present in hospital inpatients. The accompanying stresses associated with acute illness, medications and comorbidities make interpretation of endocrine tests difficult. Where possible, endocrine testing should be performed in an outpatient setting and repeated to confirm or refute a diagnosis. Involvement of the local endocrine team is important where an abnormality is suspected, and they can help guide the appropriateness of tests in a given setting.

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References

Addison's Disease Self-Help Group. Surgical guidelines for Addison's disease and other forms of adrenal insufficiency. 2017. https://www.addisonsdisease.org.uk/Handlers/Download.ashx?IDMF=0c16e6d2-6de9-4b18-b200-7c489e731c59 (accessed 16 October 2020)

Annane D, Sébille V, Charpentier C et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA. 2002;288(7):862–871. https://doi.org/10.1001/jama.288.7.862

Annane D, Bellissant E, Bollaert PE et al. Corticosteroids for treating sepsis. Cochrane Database Syst Rev. 2015;(12):CD002243. https://doi.org/10.1002/14651858.CD002243.pub3

Annane D, Pastores SM, Rochwerg B et al. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. Intens Care Med. 2017;43(12):1751–1763. https://doi.org/10.1007/s00134-017-4919-5

Annane D, Renault A, Brun-Buisson C et al. Hydrocortisone plus fludrocortisone for adults with septic shock. N Engl J Med. 2018;378(9):809–818. https://doi.org/10.1056/NEJMoa1705716

Ball S, Barth J, Levy M. Society For Endocrinology Endocrine Emergency Guidance: emergency management of severe symptomatic hyponatraemia in adult patients. Endocr Connect. 2016;5(5):G4–G6. https://doi.org/10.1530/EC-16-0058

Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. Lancet Diabetes Endocrinol. 2015;3(3):216–226. https://doi.org/10.1016/S2213-8587(14)70142-1

Bhasin S, Brito JP, Cunningham GR et al. Testosterone therapy in men with hypogonadism: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2018;103(5):1715–1744. https://doi.org/10.1210/jc.2018-00229

Cuesta M, Garrahy A, Slattery D et al. The contribution of undiagnosed adrenal insufficiency to euvolaemic hyponatraemia: results of a large prospective single-centre study. Clin Endocrinol. 2016;85(6):836–844. https://doi.org/10.1111/cen.13128

DeGroot LJ. The non-thyroidal illness syndrome. In: Feingold KR, Anawalt B, Boyce A, Chrousos G (ed). Endotext. South Dartmouth (MA): MDText.com, Inc; 2015

Gariani K, Toso C, Philippe J, Orci LA. Effects of liver transplantation on endocrine function: a systematic review. Liver Int. 2016;36(10):1401–1411. https://doi.org/10.1111/liv.13158

Garrahy A, Dineen R, Hannon AM et al. Continuous versus bolus infusion of hypertonic saline in the treatment of symptomatic hyponatremia due to SIAD. J Clin Endocrinol Metab. 2019;104(9):3595–3602. https://doi.org/10.1210/jc.2019-00044

Gatta A, Verardo A, Di Pascoli M, Giannini S, Bolognesi M. Hepatic osteodystrophy. Clin Cases Miner Bone Metab. 2014;11(3):185–191

Grant P, Ayuk J, Bouloux P-M et al. The diagnosis and management of inpatient hyponatraemia and SIADH. Eur J Clin Invest. 2015;45(8):888–894. https://doi.org/10.1111/eci.12465

Holland-Bill L, Christiansen CF, Heide-Jørgensen U et al. Hyponatremia and mortality risk: a Danish cohort study of 279508 acutely hospitalized patients. Eur J Endocrinol. 2015;173(1):71–81. https://doi.org/10.1530/EJE-15-0111

Husebye ES, Allolio B, Arlt W et al. Consensus statement on the diagnosis, treatment and follow-up of patients with primary adrenal insufficiency. J Intern Med. 2014;275(2):104–115. https://doi.org/10.1111/joim.12162

Iglesias P, Prado F, Macías MC et al. Hypogonadism in aged hospitalized male patients: prevalence and clinical outcome. J Endocrinol Invest. 2014;37(2):135–141. https://doi.org/10.1007/s40618-013-0009-x

Kuczera P, Adamczak M, Wiecek A. Endocrine abnormalities in patients with chronic kidney disease. Pril (Makedon Akad Nauk Umet Odd Med Nauki). 2015;36(2):109–118. https://doi.org/10.1515/prilozi-2015-0059

Lamontagne F, Rochwerg B, Lytvyn L et al. Corticosteroid therapy for sepsis: a clinical practice guideline. BMJ. 2018;k3284. https://doi.org/10.1136/bmj.k3284

Lee S, Farwell AP. Euthyroid sick syndrome. In: Terjung R (ed). Comprehensive Physiology. 2016; Hoboken, NJ, USA: John Wiley: 1071–1080

Liu MM, Reidy AB, Saatee S, Collard CD. Perioperative steroid management approaches based on current evidence. Anesthesiology. 2017;127(1):166–172. https://doi.org/10.1097/ALN.0000000000001659

Misra M, Klibanski A. Endocrine consequences of anorexia nervosa. Lancet Diabetes Endocrinol. 2014;2(7):581–592. https://doi.org/10.1016/S2213-8587(13)70180-3

Mohamedali M, Reddy Maddika S, Vyas A, Iyer V, Cheriyath P. Thyroid disorders and chronic kidney disease. Int J Nephrol. 2014;2014:1–6. https://doi.org/10.1155/2014/520281

National Institute for Health and Care Excellence. Thyroid disease: assessment and management. NG145. 2019. https://www.nice.org.uk/guidance/ng145 (accessed 16 October 2020)

Peeters B, Meersseman P, Vander Perre S et al. Adrenocortical function during prolonged critical illness and beyond: a prospective observational study. Intensive Care Med. 2018;44(10):1720–1729. https://doi.org/10.1007/s00134-018-5366-7

Rhodes A, Evans LE, Alhazzani W et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock–2016. Intensive Care Med. 2017;43(3):304–377. https://doi.org/10.1007/s00134-017-4683-6

Rochwerg B, Oczkowski SJ, Siemieniuk RAC et al. Corticosteroids in sepsis: an updated systematic review and meta-analysis. Crit Care Med. 2018;46(9):1411–1420. https://doi.org/10.1097/CCM.0000000000003262

Salvatore D, Davies T, Schlumberger M-J, Hay I, Larsen PR. Thyroid physiology and diagnostic evaluation of patients with thyroid disorders. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM (eds). Williams Textbook of Endocrinology. 13th edn. 2016; Philadelphia, Elsevier

Schaefer F, Chen Y, Tsao T, Nouri P, Rabkin R. Impaired JAK-STAT signal transduction contributes to growth hormone resistance in chronic uremia. J Clin Invest. 2001;108(3):467–475. https://doi.org/10.1172/JCI11895

Schorr M, Miller KK. The endocrine manifestations of anorexia nervosa: mechanisms and management. Nat Rev Endocrinol. 2017;13(3):174–186. https://doi.org/10.1038/nrendo.2016.175

Spasovski G, Vanholder R, Allolio B et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Eur J Endocrinol. 2014;170(3):G1–G47. https://doi.org/10.1530/EJE-13-1020

Stroud A, Zhang J, McCormack A. Diagnosing Cushing's disease in the context of chronic kidney disease: a case report and literature review. Eur J Endocrinol. 2019;181(4):K29-K35. https://doi.org/10.1530/EJE-19-0326

Tajar A, Forti G, O'Neill TW et al. Characteristics of primary, secondary and compensated hypogonadism in ageing men: evidence from the European Male Ageing Study (EMAS). J Clin Endocrinol Metab. 2010;95(4):1810–1818. https://doi.org/10.1210/jc.2009-1796

Téblick A, Peeters B, Langouche L, Van den Berghe G. Adrenal function and dysfunction in critically ill patients. Nat Rev Endocrinol. 2019;15(7):417–427. https://doi.org/10.1038/s41574-019-0185-7

Vanderpump MP, Tunbridge WM, French JM et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol. 1995;43(1):55–68. https://doi.org/10.1111/j.1365-2265.1995.tb01894.x

Vries ED, Fliers E, Boelen A. The molecular basis of the non-thyroidal illness syndrome. J Endocrinol. 2015;225(3):R67–R81. https://doi.org/10.1530/JOE-15-0133

Wallace JD, Abbott-Johnson WJ, Crawford DHG et al. GH treatment in adults with chronic liver disease: a randomized, double-blind, placebo-controlled, cross-over study. J Clin Endocrinol Metab. 2002;87(6):2751–2759. https://doi.org/10.1210/jcem.87.6.8548

Whitelaw BC, Prague JK, Mustafa OG et al. Phaeochromocytoma crisis. Clin Endocrinol. 2014;80(1):13–22. https://doi.org/10.1111/cen.12324

Wu FC, Tajar A, Beynon JM et al. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med. 2010;363(2):123–135. https://doi.org/10.1056/NEJMoa0911101

Zacharias BT, Coelho JCU, Parolin MB et al. Hypothalamic-pituitary-gonadal function in men with liver cirrhosis before and after liver transplantation. Rev Col Bras Cir. 2014;41(6):421–425. https://doi.org/10.1590/0100-69912014006007