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Systemic illness

Marta Bondanelli · Maria Chiara Zatelli · Maria Rosaria Ambrosio · Ettore C. degli Uberti

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Abstract Systemic illnesses are associated with alterations in the hypothalamic–pituitary–peripheral hormone axes, which represent part of the adaptive response to stressful events and may be influenced by type and severity of illness and/or pharmacological therapy. The pituitary gland responds to an acute stressful event with two secretory patterns: adrenocorticotropin (ACTH), prolactin (PRL) and growth hormone (GH) levels increase, while luteinizing hormone (LH), follicle-stimulating hormone (FSH) and thyrotropin (TSH) levels may either decrease or remain unchanged, associated with a decreased activity of their target organ. In protracted critical illness, there is a uniformly reduced pulsatile secretion of ACTH, TSH, LH, PRL and GH, causing a reduction in serum levels of the respective target-hormones. These adaptations are initially protective; however, if inadequate or excessive they may be dangerous and may contribute to the high morbidity and mortality risk of these patients. There is no consensus regarding the type of approach, as well as the criteria to use to define pituitary axis function in critically ill patients. We here provide a critical approach to pituitary axis evaluation during systemic illness.

Keywords Pituitary function · Dynamic tests · Critical illness · System disease

M. Bondanelli · M. C. Zatelli · M. R. Ambrosio · E. C. degli Uberti (✉)
Section of Endocrinology, Department of Biomedical Sciences and Advanced Therapies, University of Ferrara, Via Savonarola, 9, Ferrara 44100, Italy
e-mail: ti8@unife.it

Introduction

Systemic illnesses may be associated with changes in hypothalamic–pituitary function, representing part of the adaptive response to stressful events. Pituitary function may be profoundly influenced by type and severity of illness and/or pharmacological therapy employed in the treatment of patients [1–3].

Among systemic diseases, critical illness is any condition requiring support for failing vital organ function, either mechanical aids (mechanical ventilation, hemodyalis of filtration, cardiac assistance devices) and/or with pharmacological agents (such as inotropes vasopressor), without which death would ensue. Critical illness is characterized by multiple and complex metabolic, immunological, and endocrine changes, primarily involving hypothalamo–pituitary peripheral hormone axes [1].

Pituitary plays a central role in the regulation of metabolic and immunologic homeostasis and is an important regulator of a variety of adaptive responses that allow survival during critical states of any type. The stress response is mediated mainly by the sympathoadrenal system (SAS), which includes the sympathetic nervous system (SNS) and the adrenal medulla, and by the hypothalamic–pituitary–adrenal (HPA) axis [2, 4]. During stressful conditions, growth, reproductive and thyroid axes are inhibited at many levels. Glucocorticoids suppress growth hormone (GH) and thyroid-stimulating hormone (TSH) secretion and exert an inhibitory effect on the pituitary gonadotrophs and the gonads [1, 5, 6]. These adaptations are initially protective for the human body; however, if inadequate or excessive they may be dangerous, causing endocrine, metabolic, autoimmune, and psychiatric disorders. Moreover, alterations within the hypothalamo–pituitary–peripheral hormone axes may contribute to the high

morbidity and mortality in patients with critical illness or systemic diseases [1–4]. And indeed, pituitary–peripheral hormone axes function can be profoundly altered during systemic diseases, such as chronic kidney disease, liver failure, malnutrition, psychiatric diseases, and infectious diseases [6–10].

The hypothalamic–pituitary–adrenal (HPA) axis

Activation of the HPA axis represents one of several important responses to stressful events and critical illnesses (surgery, trauma, burns, infection, or sepsis) in order to maintain homeostasis. It is well known that stress response is mainly mediated by the autonomic nervous system and the HPA axis. Moreover, during an inflammatory process, circulating cytokines (IL-1, IL-6, and TNFalfa) stimulate and maintain glucocorticoid production at high levels, both by peripheral and central actions [2, 4, 11]. The increase in cortisol production may reach levels greater than those observed in patients with Cushing's syndrome, being proportional to illness severity [12]. An impaired glucocorticoid clearance can contribute to the greatly increased serum cortisol concentrations, especially in patients with impaired liver and kidney function, or reduced thyroid function [13]. Besides the increased production of cortisol, abnormalities in cortisol secretion (abolition of the normal diurnal rhythm and inadequate suppression after dexamethasone) are present and may sometimes persist for many months after the event [1, 14, 15]. ACTH and cortisol responsiveness to exogenous CRF may be enhanced, whereas adrenal responsiveness to exogenous ACTH is normally maintained during acute illness [12].

Factors influencing HPA axis evaluation in critical illness

Despite a large number of published data, the definition of what represents 'normal' adrenal response to critical illness is unclear. A variety of biochemical criteria have been proposed to define the normal adrenal response, the concept of relative adrenal insufficiency, and, therefore, the use of glucocorticoids in critical illness setting. Depending on the criterion used, the prevalence of adrenal dysfunction in critically ill subjects ranges from 0 to more than 60%, and is significantly higher in patients with septic shock (40–65%) than in other Intensive Care Unit (ICU) patients (0–25%), including patients with coronary artery bypass graft surgery, ruptured abdominal aortic aneurysm, and a variety of other illnesses [11, 16].

The diagnosis of glucocorticoid deficiency is challenging during the acute phase of critical illness, due to the difficulty in selecting a reliable test for assessing cortisol secretion. Moreover, there are several confounding factors that hamper the interpretation of adrenal function tests in critical illness [11, 12, 17, 18] (Table 1). Most importantly, the commercially available assays for serum cortisol determine the total (free plus protein-bound fractions) hormone concentrations. In healthy individuals more than 90% of circulating cortisol is bound to corticosteroid-binding globulin (CBG), with less than 10% in the free,

Table 1 Factors influencing serum cortisol levels in critical illness

Factor	Mechanism	Changes in total cortisol levels	Changes in free cortisol levels
Drugs			
Estrogens	Increased CBG	Increased	No
Ketoconazole	Decreased cortisol synthesis	Reduced	Reduced
Etomidate			
Aminoglutathemide			
Megestrol acetate	HPA axis suppression	Reduced	Reduced
Rifampin	Increased cortisol metabolism	Reduced	Reduced
Phenytoin			
Illness type/severity			
Illness severity	Increased cortisol production	Increased	Increased
Septic shock	Glucocorticoid resistance	Increased	Increased
Liver disease	Increased CBG	Increased	No
Nephrotic syndrome	Reduced CBG and/or albumin	Reduced	No
Malnutrition			
Hemodilution			
Different assay methods	Sensitivity/specificity Heterophile antibodies	Variation in assay results	Variation in assay results

biologically active form [3, 11]. In critical illness, CBG levels fall by approximately 50%, with marked interindividual variations, leading to reduced basal and stimulated total cortisol levels. This may cause an overestimated number of critically ill patients classified as adrenocortical insufficient [11, 12, 17, 19]. Furthermore, as CBG binding sites become saturated, the percentage of free cortisol increases. Free cortisol levels may also increase at sites of inflammation, owing to CBG inactivation by neutrophil elastase, an effect that liberates cortisol [12]. Therefore, in critically ill patients total cortisol levels may not reflect the biologically free (unbound) cortisol. In addition, cytokines can increase tissue cortisol levels through changes in peripheral cortisol metabolism. In particular, cytokines can increase glucocorticoid receptors' affinity for cortisol in inflammatory conditions. By contrast, in severe sepsis and septic shock excessive cytokine production leads to a decreased glucocorticoid receptor number and affinity, thereby causing glucocorticoid resistance [20].

Type, severity and phase of illness may influence interpretation of HPA axis function parameters. In general, HPA axis displays a biphasic pattern during the course of critical illness [1, 4]. During the initial acute phase (varying from hours to a few days) of illness, HPA axis is primarily activated by CRF secretion and cytokine production, whereby both plasma ACTH and serum cortisol levels are increased. Thereafter, in the post-acute phase, plasma ACTH concentrations rapidly fall to normal levels, whereas serum cortisol concentrations decline slowly, reaching high normal values 48–72 h after a stressful event, such as major surgical procedure. During the acute phase, increased circulating cortisol levels seem to reflect a more severe illness, since a direct relationship has been found between total cortisol levels and mortality rate [1]. On the other hand, severity of acute stress may also be predictive of mortality associated with adrenal insufficiency [4].

In protracted critical illness (lasting many days or weeks) the secretory activity of HPA axis starts to diminish and plasma ACTH declines gradually to normal levels. However, serum cortisol levels may continue to be elevated, indicating an alternative activation of cortisol secretion (e.g. cytochines, AVP, ANF, and endothelin) [21–23]. The persistence of hypercortisolism may be beneficial by providing energy, maintaining plasma volume, and reducing inflammation, but it may also contribute to the development of longer-term complications (hyperglycemia, myopathy, poor wound healing, and psychiatric alterations) [4, 23, 24].

Many other factors can impair the normal corticosteroid response to stress during severe illness, which could directly impair HPA function (brain injury, drugs, inflammation). CRF and ACTH secretion can be impaired by brain injury, central nervous system depressants, or pituitary infarction [15, 25, 26]. Cortisol synthesis can be directly impaired by drugs, such as the anesthetic agent etomidate and the antifungal agent ketoconazole, and/or by high levels of inflammatory cytokines in patients with sepsis. Moreover, hepatic metabolism of cortisol may be enhanced by drugs, such as rifampin or phenytoin. In addition, adrenal insufficiency can be caused by adrenal haemorrhage (especially in patients with septicemia and coagulopathy), tumors or infections causing extensive destruction of the adrenal gland. Exogenous corticosteroid therapy, as well as medroxyprogesterone and megestrol acetate treatment, suppresses HPA axis and can induce adrenal atrophy that may persist for months after treatment cessation. Care is also required in the interpretation of cortisol levels in women taking oral contraceptives, since synthetic estrogens increase CBG circulating levels [11, 12].

Evaluation of HPA axis function in critical illness

Basal serum total cortisol

The proposed lower thresholds for stress-induced basal cortisol concentrations vary widely in the literature (Table 2). They range from 276 nmol/l (10 μg/l) to 935 nmol/l (34 μg/dl), depending on the degree and chronicity of the critical illness [14, 16, 23–26] and surgical stress [16, 21, 23, 24, 27, 28]. However, most Authors believe that the 15 μg/dl threshold level best identifies critically ill patients with adrenal insufficiency or those who would benefit from corticosteroid replacement [11]. This might be true in patients with normal binding protein

Table 2 Serum cortisol levels identifying critically ill patients with adrenal insufficiency

Variable	Most used criteria μg/dl (nmol/l)	Range in different studies μg/dl (nmol/l)
Total cortisol		
Albumin > 2.5 g/dl		
Basal	15 (416)	10–34 (276–935)
After ACTH test		
Peak	20–25 (552–693)	
Δ-Cortisol	9 (250)	7–9 (195–250)
Albumin ≤ 2.5 g/dl		
Basal	10 (276)	
After ACTH test		
Peak	15.5 (428)	15–20 (416–552)
Δ-Cortisol		
Free cortisol		
Basal	1.8 (50)	1.8–2.0 (50–55)
After ACTH test	3.1 (86)	

Cortisol units: 1 μg/dl = 27.6 nmol/l

levels. In fact, an albumin concentration of 2.5 g/dl or less indicates a reduction in binding proteins, that significantly influences total cortisol levels. Therefore, in hypoalbuminemic patients a corresponding threshold level of 10 μg/dl total cortisol has been identified [11, 17, 18]. In addition, specificity, sensitivity, and performance of the commercially available assays are not uniform, further complicating interpretation of serum cortisol level [29]. It is speculated that assay variability might be even more significant in critically ill patients, especially those with septic shock, due to the presence of interfering heterophile antibodies [30]. Mass spectrometry provides reliable results, but is not commonly available [18].

Basal serum free cortisol

Measurement of serum free cortisol could be the most appropriate approach for assessing glucocorticoid secretion in critical illness, especially in hypoproteinemic patients [11, 17, 18, 31–34]. A serum free cortisol level of 1.8–2.0 μg/dl has been considered the threshold to identify patients at risk for adrenal insufficiency during critical illness, regardless of serum protein concentrations. This value corresponds to the minimum ACTH-stimulated levels in normal, unstressed subjects. At present, serum free cortisol determination is performed only by specialized laboratories, and the results are not immediately available to clinicians. An alternative approach could be the use of a calculated free cortisol index, defined as the ratio of serum cortisol over that of serum CBG concentrations [19, 35], but CBG measurement is not always available.

Other measures

Salivary cortisol concentrations correlate with serum free cortisol levels and have been proposed as a surrogate marker for serum free cortisol levels [36]. This assay is relatively easy to perform, but is not currently available in all laboratories. In critically ill patients, salivary cortisol concentrations could be more useful than measurement of serum total cortisol levels, particularly in hypoproteinemic patients. However, data on salivary cortisol in critical illness are limited and no cut-off levels have been proposed in order to diagnose adrenal insufficiency in these settings [11].

Dehydroepiandrosterone (DHEA) and its sulphate (DHEAS) are the most abundant steroids secreted by the adrenal cortex. DHEA blood concentration oscillates in parallel with cortisol, in response to ACTH, but without feedback control at hypothalamic–pituitary level. Serum DHEA(S) concentration are low in patients with primary adrenal insufficiency, but limited data are available on DHEA(S) levels in critically ill patients. Extremely low DHEAS levels have been detected in septic shock and in multiple trauma patients, frequently showing adrenal insufficiency, suggesting DHEAS as prognostic marker and sign of exhausted adrenal reserve in critical illness [37]. On the other hand, more recently, it has been reported that serum DHEA levels tend to be elevated [38]. More severe disease and higher mortality were associated with an increased cortisol to DHEA ratio, which may represent a novel prognostic marker in septic shock [39].

Dynamic tests

There is no consensus regarding the approach, as well as the criteria to use to define normal HPA axis function in critically ill patients. Some Authors have suggested that adrenal insufficiency appears to be unlikely when a random serum cortisol measurement is greater than 34 μg/dl. Conversely, adrenal insufficiency is likely when serum cortisol level is below 15 μg/dl during an acute severe illness. Patients with cortisol levels between these two values should perform an ACTH test, in order to evaluate the possibility of adrenal insufficiency and to indicate an adequate corticosteroid supplementation [12].

In critically ill patients in whom adrenal insufficiency is suspected, if ACTH test cannot be performed immediately, dexamethasone can be administered and the test performed within the next 12 h. Dexamethasone does not significantly cross-react with cortisol and can be administered to patients pending adrenal testing [17]. Clinical characteristics suggesting adrenal insufficiency in critically ill patients are depicted in Table 3.

The high-dose ACTH stimulation test has been largely performed in critically ill patients [intravenous administration of 250 μg of cosyntropin (a synthetic peptide consisting of the first 24 amino acids of ACTH), with plasma cortisol levels measured 0, 30, and 60 min after administration]. An increment (delta) of 9 μg/dl or more from baseline to the highest cortisol level (measured at 30 or 60 min) and/or a peak response of 20–25 μg/dl have been advocated as a criterion for normality. Keeping in

Table 3 Clinical characteristics suggesting adrenal insufficiency in critically ill patients

Hypotension
Unresponsiveness to catecholamine infusion
Ventilator dependence
Abdominal or flak pain
High fever with negative cultures and unresponsive to antibiotic therapy
Unexplained mental changes (i.e. apathy, depression)
Electrolyte abnormalities (hyponatremia, hyperkaliemia)
Hypoglycemia
Neutropenia, eosinophilia

mind that alterations in the binding proteins may affect the stimulated total cortisol concentration, in hypoalbuminemic patients (albumin <2.5 g/dl) the peak ACTH-stimulated serum cortisol would be expected to be more than 15–20 μg/dl [11, 17, 18]. Alternatively, ACTH-stimulated serum free cortisol concentrations of 3.1 μg/dl or more have been identified as excluding adrenal insufficiency in critically ill patients [32] (Table 2). However, additional data, involving larger patient numbers, are necessary in order to validate this criterion.

The cortisol response to high-dose ACTH test may have prognostic implications, since an inadequate rise <9 μg/dl (250 nmol/l) may be associated with an increased risk of death [40, 41].

The reproducibility of the high-dose ACTH test has been investigated in critically ill patients. Recent studies indicated reproducible results after repeated ACTH test in patients without sepsis, but discordance between two consecutive testing results in patients with septic shock. The reason for this discordance is not clear [42, 43].

Recent data indicate that the use of the ACTH-stimulated increment in serum total cortisol (commonly taken as 9 μg/dl) as a diagnostic criterion in critically ill patients can be misleading. Widmer et al. found that about 40% of patients did not achieve the delta cortisol cut-off >9 μg/dl, nevertheless they recovered from their illness without glucocorticoid therapy. These patients would have been misdiagnosed with "*relative adrenal insufficiency*" [16]. The term of relative adrenal insufficiency has been proposed especially for hypotensive septic critically ill patients who show hemodynamic improvement upon corticosteroid administration. In these patients, cortisol levels, despite their being in the normal range or elevated, are still considered inadequate for the severity of stress, and the patients may be unable to respond to any additional or protracted stress [4, 33]. A relative adrenal insufficiency has been defined by basal cortisol level <34 μg/dl (935 nmol/l) combined with an increase (delta) <9 μg/dl (250 nmol/l) after high dose ACTH stimulation. This condition has been associated with a high mortality rate (80%) [41].

The high-dose ACTH test has been widely accepted as a valuable substitute for the insulin-induced hypoglycemia (ITT) in routine practice. However, it is important to remember that in case of ACTH deficiency the test results only reflect the presence or absence of adrenal cortex atrophy. Administration of 250 μg of synthetic ACTH test induces supraphysiological ACTH concentrations (10,000–60,000 pg/ml) which exceed several times the levels achieved during major surgery and may evoke false-normal cortisol responses. It has been reported that the high-dose ACTH test can be used to diagnose adrenal insufficiency if performed at least 4 weeks after onset of ACTH deficiency [44, 45].

Therefore, the *low-dose* (1 μg) *ACTH test* (inducing ACTH levels of 100–300 pg/ml) has been suggested to be more sensitive to diagnose adrenal insufficiency, but limited data are available on the use of low-dose ACTH test in critical illness [4]. Recently, a subgroup of septic shock patients was described to respond adequately to the high-dose ACTH test, yet inadequately to the low-dose test. A delta cortisol >9 μg/dl was considered adequate for both tests [46]. The Authors speculated that the low-dose test might identify an additional group of septic shock patients who can benefit from therapy with corticosteroids. Moreover, the low-dose ACTH test has been proposed in the suspicion of an ACTH deficiency during the acute or post-acute phase of TBI or stroke, when the time elapsed from injury may be insufficient for the development of adrenal cortex atrophy [3, 15, 47, 48]. However, at present only the high-dose ACTH test has been demonstrated as capable of detecting patients who are likely to receive a mortality benefit from corticosteroid replacement therapy [49]. Moreover, in the settings of severe illness and stress, the use of the low-dose ACTH stimulation test may increase the number of overdiagnosed patients [4].

Other tests assessing HPA axis function include ITT, metyrapone, glucagone and CRF testing. The ITT assesses the integrity of the whole HPA axis and should be considered the gold standard, but it is regarded as potentially dangerous in critically ill patients [44, 45]. Metyrapone is difficult to obtain, unsafe and the results are difficult to interpret [45].

Recently, Agha et al. proposed the glucagon stimulation test as a reliable alternative to the ITT in the early acute phase after TBI [50]. They considered a peak cortisol response >16 μg/dl as a criterion for normality, identifying a subnormal cortisol response in 16% (n. 8) of patients. After 6 months, 4 out of 8 patients had recovered and 5 new deficiencies were detected. Further studies are needed to define the role of glucagon test for HPA evaluation in critically ill patients.

CRF (100 μg as a bolus) stimulation test also assesses ACTH production from the pituitary, but few data are available in critical illness and they often demonstrate an enhanced responsiveness to CRF administration. Therefore, data concerning the sensitivity and specificity of the test for detecting adrenal insufficiency in critical illnesses are not available [17]. Besides, CRF testing is expensive and has not been generally considered more predictive of adrenal function than morning cortisol concentration assessment [45].

HPA in specific systemic diseases

Chronic liver diseases (CLD)

Impairment of cortisol metabolism, evidence of endogenous hypercorticism and sensitivity to oral corticosteroids

are known to occur in patients with chronic liver disease [51, 52]. CLD patients, who are not critically ill have reduced CBG by 13–30%. When CBG decreases, free cortisol concentration increases [53]. The presence of impaired metabolism and reduced CBG in patients with hepatic disease, may explain the features of endogenous hypercorticism, as well as the increased sensitivity to corticosteroid therapy seen in such patients. On the other hand, it has recently been reported that adrenal insufficiency may be frequently associated with liver disease in critically ill patients, and may carry prognostic value [8]. However, at present non clear recommendation can be made on the use of adrenal function testing in liver failure.

Chronic kidney disease (CKD)

In the past, divergent findings on the HPA axis function has been reported in patients with chronic renal failure. More recently, it has been shown that adrenal response to ACTH is unaffected, both in patients treated with hemodialysis or continuous ambulatory peritoneal dialysis. Moreover, circadian rhythm of cortisol is preserved in patients with CKD [54]. In chronic renal failure, 11beta-hydroxysteroid dehydrogenase type (11b-HSD2) activity is reduced, causing diminished cortisol inactivation which is thought to contribute to arterial hypertension in CKD [55]. Plasma and urinary cortisol/cortisone ratios are elevated, and it has been demonstrated they do not return to normal in children after renal allograft transplantation [56]. This suggests that renal transplantation does not normalize 11b-HSD2 activity. The ratio of the urinary metabolites (tetrahydrocortisol/tetrahydrocortisone, THF/THE) is also increased in CKD patients, especially in hypertensive CKD patients [57]. In saliva, an increase in cortisone and a low cortisol/cortisone ratio have been found, suggesting stimulation of parotid 11b-HSD-2 in response to the impaired renal 11b-HSD-2 activity [58].

Human immunodeficiency virus (HIV) Infection

Patients infected with HIV usually have higher basal serum cortisol levels, that may be associated with subnormal cortisol response to ACTH stimulation test [9]. These patients may also show lower levels of ACTH, DHEA and adrenal androgen [59, 60]. It has been suggested that the pattern of high cortisol and low DHEA levels could indicate a worsening in immune status, by shifting the cytochine production from the so-called TH1 (cellular) to TH2 (humoral) immunologic response, a hallmark of disease progression [61]. An altered circadian rhythm of ACTH and cortisol has also been reported, whereas normal cortisol suppression by dexamethasone is described. Nevertheless, adrenal reserve may be marginal (as suggested by a subnormal cortisol response to ACTH test in many cases), clinical adrenal insufficiency is rare [62]. In fact, it occurs in less than 5% of patients, usually involving those in advanced disease stages or under treatment with drugs (ketoconazole, rifamin, megestrol acetate) which interfere with cortisol metabolism [9]. In most cases, these patients have primary adrenal insufficiency due to infection with cytomegalovirus or mycobacteria, or sometimes with HIV itself, or due to adrenal metastases or haemorrhage. Rarely, they have secondary adrenal insufficiency due to hypothalamic or pituitary involvement by the same infectious agents or infiltration by an associated lymphoma or Kaposi's sarcoma [9]. On the other hand, some patients have symptoms of cortisol insufficiency, with normal or increased basal serum cortisol levels. These patients may have a syndrome of peripheral glucocorticoid resistance, due to acquired abnormalities of the glucocorticoid receptors [9, 62].

Anorexia nervosa

Patients with anorexia nervosa show endocrine changes that suggest pituitary or hypothalamic involvement. They develop amenorrhea, temperature dysregulation, and abnormal GH secretion [6]. They also have biochemical evidence of hypercortisolism, associated with normal ACTH secretion. The CRF stimulation test shows decreased ACTH response, suggesting increased CRF secretion (caused by central activation of the stress axis) with dowregulation of pituitary ACTH receptors. In addition, there is abnormal cortisol suppressibility with dexamethasone, indicating a decreased feedback sensitivity [63]. The coexistence of elevated serum cortisol and normal ACTH levels suggests an enhanced sensitivity of the adrenal cortex, which has been confirmed by a greater cortisol response to ACTH test [6].

Hypothalamo–pituitary–thyroid (HPT) axis

Abnormalities in thyroid homeostasis occur in a variety of non thyroid illnesses (NTI), such as chronic malnutrition, starvation, sepsis, surgery, myocardial infarction, coronary artery bypass graft surgery, bone marrow transplantation, TBI, and probably any severe illness [5, 64–66]. The prevalence of one or more abnormalities of thyroid function tests in patients with NTI has been reported from 40% to 70% [65, 67]. The most prominent alterations are low serum triiodothyronine (T3) and elevated reverse T3 (rT3) levels, leading to the general term low T3 syndrome (or euthyroid sick syndrome). TSH, thyroxine (T4), free T4, and free T4 index (FTI) are also affected at variable degrees, based on NTI severity and duration [64–68].

The early response of the thyroid axis to a severe physical stress consists of a rapid decline in circulating T3

Table 4 Changes in thyroid function tests during non thyroidal illness (NTI)

	Free T4 or T4	Free T3 or T3	Reverse T3	TSH
Mild illness	⇔	⇓	⇑	⇔
Moderate illness	⇑/⇔	⇓⇓	⇑⇑	⇔
Severe or chronic illness	⇓	⇓⇓⇓	⇑/⇔	⇓

⇑ increased; ⇓ Reduced; ⇔ normal

and a rise in rT3 levels, predominantly as a consequence of altered peripheral conversion of T4. This phenomenon is due to inhibition of 5′-monodeidination, which decreases whenever caloric intake is low and during any NTI, even when mild. TSH and T4 levels rise for a short time (about 2 h), but subsequently normalize, and in those who are more severely ill, T4 levels may also decrease. Although TSH levels measured in a single day time sample are normal in acute critical illness, the TSH profile is affected, as the normal nocturnal TSH surge is absent [65–67].

In chronic patients, these changes occur in addition to a loss of TSH pulsatile secretion and a fall in T4 and T3 levels; serum free T4 levels may also be reduced. The fall in T4 levels may be associated with very low (almost undetectable) serum T3, whereas serum rT3 levels may return to normal [64, 65]. The changes are consistent with an acquired transient central hypothyroidism. In critically ill patients recovering from NTI, a rise in TSH concentration (which transiently reach supranormal values) may precede T4 normalization. Despite the described abnormalities, treatment of these patients with thyroid hormone, while controversial, appears to be of little benefit, and may even be harmful. It is possible that these changes during severe illness are protective in that they prevent excessive tissue catabolism [64, 69].

Therefore, thyroid function should not be assessed in seriously ill patients unless there is a strong suspicion of thyroid dysfunction. When thyroid dysfunction is suspected in critically ill patients, measurement of serum TSH alone is not adequate for the evaluation of thyroid function. In this case, the diagnosis requires measurement of a full thyroid panel including TSH, T3, total T4, and free T4 levels [70] (Table 4).

Evaluation of HPT axis function in non thyroid illnesses (NTI)

Serum T3 and free T3 levels

Most hospitalized patients have low serum T3 concentrations, as do some outpatients who are ill. A reduced activity of the peripheral 5′-monodeiodinase (type 1 deiodinase, D1) can explain the low serum T3 concentrations, and may be due to several mechanisms: (a) high endogenous serum cortisol concentration and exogenous glucocorticoid therapy; (b) circulating inhibitors of deiodinase activity, such as free (non-esterified) fatty acids; (c) treatment with drugs that inhibit 5′-monodeiodinase activity, such as amiodarone and high doses of propranolol; (d) cytokines (such as tumor necrosis factor, interferon-alfa, NF-kB, and interleukin-6) [64, 71–73]. Loss of type 2 deiodinase (D2) activity during critical illness has also been proposed as contributing to low T3 levels [65].

Serum T3 or free T3 levels are rarely considered as a screening test for thyroid function. It is, however, useful to measure serum T3 or free T3 in hospitalized patients who have a low serum TSH concentration, in whom the differential diagnosis is hyperthyroidism versus low T3 syndrome. Serum T3 and free T3 values should be high (or high-normal) in hyperthyroidism, but low (or low-normal) in NTI. Rarely, a very sick patient with hyperthyroidism will have a low serum T3 concentration [63].

Although isolated low T3 levels usually represent the mildest form of NTI, the magnitude of the drop in T3 level reflects the severity of illness. A very low serum T3 level has been associated with an increased mortality rate in patients with hepatic cirrhosis, congestive heart failure, and other systemic diseases [64–66].

Serum rT3 levels

Serum rT3 concentrations are high in patients with NTI, except in those with renal failure [74] and some with Acquired Immunodeficiency Syndrome (AIDS) [75]. Reverse T3 is the product of 5-monodeiodination of T4 (type III deiodinase, D3), which is induced in these conditions. Moreover, rT3 clearance to diiodothyronine (T2) is reduced because of D1 activity inhibition [76]. Measurement of serum rT3 may help to distinguish between low T3 syndrome and central hypothyroidism, where both these values are reduced due to low substrate production (T4). In patients with mild hypothyroidism, however, serum rT3 concentrations may be normal or even slightly high, limiting its usefulness [77]. Measurement of rT3 during the acute phase of critical illness may have prognostic value, since high rT3 and low T3/rT3 ratio on the first day in an ICU correlates with increased mortality [78, 79].

Serum T4 and free T4

Serum total T4 levels can be decreased (low T4 syndrome) typically in patients with chronic and severe systemic illness [77]. From 15% to 20% of hospitalized patients and up to 50% of patients in ICU have low T4 syndrome. In critically ill patients, a marked decrease in serum T4 is

associated with a high probability of death [79]. Low serum T4 concentrations are due to a decrease in circulating binding proteins, especially thyroxine-binding globulin (TBG), and a reduced TBG affinity [80]. Serum free T4 may be either normal or slightly decreased, and occasionally elevated. This variability in free T4 levels reflects both the assay method used and the underlying illness [64]. A possible contributing factor for decreased T4 and free T4 levels is an increased concentration of serum free fatty acids (FFA), which inhibit T4 binding to serum proteins. Decreased T4 binding to TBG may also be induced by drugs such as salicylates, furosemide, and heparin (via FFAs) [81]. On the other hand, T4 clearance is increased by phenytoin, carbamazepine, rifampin, or phenobarbital treatment. By contrast, high serum total T4 is seen in situations where TBG is elevated (acute intermittent porphyria, chronic hepatitis, and primary biliary cirrhosis) [82] (Table 5).

Serum TSH

TSH levels might be considered as a sensitive marker of thyroid hormone levels [83, 84]. In NTI, however, despite the decrease in serum T3 (and T4 in severe cases), TSH concentrations typically remain within low to normal range. Patients with severe and prolonged NTI may have an acquired transient central hypothyroidism. In addition, the TSH-suppressive effects of therapeutic agents (e.g. dopamine, dobutamine, glucocorticoids) on the central thyroid axis should be considered in these patients [66, 85]. Moreover, true central hypothyroidism occurs in 10–15% of patients following TBI, but it should be confirmed later during convalescence [3, 15, 86]. It may be caused by functional or anatomical damage at the hypotalamus and/or pituitary level. In critically ill patients, changes in TSH levels should be assessed using a sensitive third generation assay with a detection limit of 0.01 mU/l. A normal TSH level most likely excludes primary hyperthyroidism or hypothyroidism [87, 88]. In particular, almost all patients who have a TSH concentration >0.05 mU/l and <0.3 mU/l will be euthyroid when reassessed after recovery from critical illness. By contrast, approximately 75% of patients with undetectable serum TSH concentrations (<0.01 mU/l) have hyperthyroidism [89]. Transient elevations in serum TSH concentrations may be observed during the recovery phase of NTI. Elevated TSH concentration associated with reduced free T4 can be confusing, because it meets the laboratory criteria for primary hypothyroidism. However, in NTI, TSH values rarely exceed 10 mIU/ml and only few patients with TSH levels <20 mU/l have hypothyroidism when reevaluated after recovery from the disease. By contrast, patients with serum TSH >20 mU/l usually have permanent hypothyroidism [5, 68, 80, 89]. Thyroid autoantibodies may support a diagnosis of primary hypothyroidism [5].

Dynamic testing is generally not necessary for the diagnosis of central hypothyroidism, because it does not add diagnostic reliability [45]. It may add information on the pathophysiology of NTI. For example, prolonged critically ill patients show diminished TSH pulsatility,

Table 5 Medications affecting thyroid function or thyroid function tests

	Mechanism
Drugs causing abnormal thyroid function tests with normal thyroid function	
Androgens, danazol, glucocorticoids, nicotinic acid, l-asparaginase	Low serum TBG
Estrogens, tamoxifen, raloxifene, methadone, 5-fluouracil, clofibrate, heroin, mitotane	High serum TBG
Salicylates, furosemide, heparin	Decreased T4 binding to TBG
Phenytoin, carbamazepine, rifampin, phenobarbital	Increased T4 clearance
Amiodarone, glucocorticoids, contrast agents for oral cholecystography (e.g., iopanoic acid), propylthiouracil, beta-blockers (propanolol, nadol)	Impaired conversion of T4 to T3
Dopamine, dobutamine, glucocorticoids, octreotide	Suppression of TSH secretion
Drugs causing hypothyroidism	
Thionamides, lithium, perchlorate, aminoglutethimide, thalidomide, and iodine and iodine-containing drugs	Inhibition of thyroid hormone synthesis and/or release
Cholestyramine, colestipol, aluminum hydroxide, calcium carbonate, sucralfate, ferrous sulfate, raloxifene, omeprazole	Decreased absorption of T4
Interferon-alfa, interleukin-2	Immune alterations
Sunitinib	Possible destructive thyroiditis
Drugs causing hyperthyroidism	
Iodine, amiodarone	Stimulation of thyroid hormone synthesis and/or release
Interferon-alfa, interleukin-2, denileukin diftitox	Immune alterations

characterized by an absent nocturnal TSH surge and decreased TSH pulse amplitude. Moreover, the observations of a blunted TSH response to TRH, and of a significant increase in serum TSH, T4 and T3 concentrations after continuous infusion of TRH are consistent with central pathogenesis [5, 90].

HPT axis in specific systemic diseases

Chronic kidney disease (CKD)

The kidney normally plays an important role in metabolism, degradation, and excretion of thyroid hormones. As a result, abnormalities in thyroid function tests are frequently encountered in uremia [74]. Moreover, the symptom overlap between uremic syndrome and hypothyroidism requires a cautious interpretation of these tests. Most patients with end stage renal disease have decreased plasma free T3 levels, which reflect diminished peripheral conversion of T4 to T3 [74, 91]. This abnormality is not associated with increased conversion of T4 to the metabolically inactive rT3. Low levels total T3 may be observed due to metabolic acidosis and reduced protein binding. Although circulating TBG and albumin levels are typically normal in uremia (in the absence of the nephrotic syndrome), retained substances in renal failure may inhibit hormone binding to these proteins. As a consequence, serum T4 levels may also be reduced [74, 91, 92]. TSH plasma concentration is usually normal in CKD [74]. However, TSH response to exogenous TRH is often blunted and delayed, with a prolonged time required to return to baseline [93]. Therefore, uremic patients are considered to be euthyroid as evidenced by normal TSH and free T4 plasma concentrations.

HIV infection

Thyroid function is normal in most patients with HIV infection, at least until serious illness and the hormonal changes of the NTI appear [94]. Multiple abnormalities have been described: normal or increased T4 (due to TBG increase), normal free T4, decreased rT3, and normal T3 even in the setting of severe illness. Serum TSH concentrations are usually normal [94–97]. Primary hypothyroidism can occur in patients with HIV infection but is rare. Pneumocystis carinii can cause thyroiditis that can result in either hypothyroidism or hyperthyroidism [98].

Psychiatric diseases

Acute psychosis, particularly schizophrenia, may be associated with transient elevations in serum T4 concentrations with or without low serum TSH concentrations [99, 100]. Patients with bipolar disorder may have slight elevation in TSH and reduction in free T4 levels [65]. Severe depression may show changes similar to those of patients with glucocorticoid excess [101]. The etiologic mechanism of these minor abnormalities is not clear.

Anorexia nervosa

Malnutrition secondary to anorexia nervosa has been associated with changes in HPT axis function that may be difficult to distinguish from the euthyroid sick syndrome [6, 102]. Patients with anorexia have serum total and free T4, total and free T3, TSH, TBG values lower than normal subjects. In contrast, rT3 is higher. Only 10% of the patients have a normal response to TRH, the remaining being either hyporesponsive or showing a delayed response. Therefore, anoretic patients with mild secondary hypothyroidism are difficult to diagnose because the hormonal profile may be identical in the two conditions. Calculation of the free T4 to free T3 ratio may be helpful, because in hypothyroidism the ratio decreases, whereas in anorexia free T3 decreases more than free T4 [6].

Glucocorticoid excess and deficiency

Acute administration of glucocorticoid eliminates pulsatile TSH secretion presumably by reducing TRH release. After continuous administration, escape from suppression develops. Pharmacological glucocorticoid doses decrease serum T3 concentrations and increase rT3 production, indicating an increased D3 activity. The decrease in binding protein has only modest effects on T4 concentrations. On the other hand, primary adrenal insufficiency may be associated with reduced serum T4 and elevated TSH levels, simulating a primary hypothyroidism [66, 103, 104].

Hypothalamo–pituitary–gonadal (HPG) axis

In acute stress or illness, gonadal function is harmed indirectly via gonadotrophin suppression and directly by cytokine action on ovaries and testes [1, 105]. Hypogonadism that accompanies most chronic systemic diseases is primary, but in many cases the derangement is located at both central and peripheral levels. For example, in chronic renal failure, apart from the testicular and ovarian effects, the elevated LH levels are due to insufficient renal excretion [106], while concurrently there is a reduction in the amplitude and frequency of the pulsatile LH waves [105]. It is interesting that both types of gonadal dysfunction appear to be reversible, since studies performed in patients after kidney or liver transplantation have shown full recovery of gonadal function [107, 108]. The type of

hypogonadism may vary during illness course; moreover, primary and secondary hypogonadism may alternate or may be superimposed. For example, a suppression of previously high gonadotrophin levels occurs during the terminal stages of cirrhosis with the onset of hepatic coma [109]. Severe starvation leads to low LH/FSH levels, which may rise during refeeding, causing a transient excess of estrogen production and gynecomastia in males [105].

Critical illness

Conditions of acute stress, such as surgery or myocardial infarction, cause an immediate fall in serum testosterone levels, even though LH levels are elevated, suggesting an immediate stress-induced Leydig-cell suppression [1]. Prolactin (PRL) is among the first hormones that increase in response to acute stress, a rise that may be mediated by VIP, oxytocin, dopaminergic pathways activation and cytokines. PRL variations may be related to changes in immune function during the course of critical illness, but this remains speculative [1, 110, 111].

In the prolonged phase of critical illness, circulating levels of testosterone become very low and are associated with decreased gonadotrophin concentrations and reduced pulsatile LH release. This phenomenon might be due to suppression of LH-releasing hormone (LHRH) synthesis following prolonged brain exposure to IL-1 [112]. On the other hand, estradiol concentrations may increase in both genders, because of increased aromatization of adrenal androgens [113]. Serum PRL levels are no longer as high as in the acute phase, since there is a reduction pulsatile fraction. It is unclear whether the blunted PRL secretion contributes to immune suppression or increased susceptibility to infections associated with prolonged critical illness [1, 111].

A high incidence of sex-steroid deficiency has been reported in the immediate post-TBI period. In this phase, testosterone concentration has been shown to correlate negatively with injury severity [113]. Testosterone levels in men and estrogen levels in women significantly fall within 24 h following brain injury and remain lowered for 7–10 days. Testosterone levels may return to normal after 3–6 months or remain low [114, 115]. Gonadotrophin levels may also decrease, but their response to gonadotrophin releasing hormone (GnRH) administration may be normal [116] or increased [114], indicating a hypothalamic mechanism. Central hypogonadism has been detected in up to 80% of patients in the early acute phase of moderate-to-severe TBI [3, 86]. After the recovery phase, a regression of LH/FSH deficiency has sometimes been observed in TBI patients. However, later occurrence of pituitary hormone deficiency may be observed after months or years following TBI [15, 117].

Hyperprolactinemia is found in more than 50% of patients in the early acute phase post-TBI and may persist in 31% of cases during rehabilitation [15, 118, 119]. The demonstration of a negative correlation between PRL concentrations and severity of TBI may suggest a good prognostic role for PRL responses during the acute phase of critical illness [15].

Evaluation of HPG axis function in critical illness

Gonadotrophin secretion in males is tested by measuring the morning serum total testosterone concentration on two or more occasions. A low testosterone in the absence of elevated LH levels indicates secondary hypogonadism [45, 120]. In elderly men, it is a clinical dilemma whether low testosterone levels in the presence of normal gonadotrophin need further evaluation for underlying diseases of the hypothalamic–pituitary axis [121]. In fact, low-normal testosterone levels and symptoms suggestive of hypogonadism in the absence of chronic illness and environmental factors are increasingly diagnosed as partial androgen deficiency of the aging male. Therefore, hypogonadism may be diagnosed in aging men if early morning serum total testosterone concentration is consistently and unequivocally subnormal [<200 ng/dl (6.9 nmol/l)] [121].

Gonadotrophin secretion in premenopausal females with amenorrhea is tested by measuring estradiol concentrations. A low estradiol level in the absence of elevated FSH indicates secondary hypogonadism. During or after menopause, absence of typical rise in LH and FSH shows central hypogonadism [45, 120].

Before diagnosis of LH and FSH deficiency, PRL excess should always be excluded, which might be due to functional disturbance in hypothalamic regulation of PRL secretion, hypothalamic/pituitary stalk lesions or drug interference [122, 123] (Table 6).

In critically ill patients and other systemic diseases, basal plasma sex steroid and gonadotrophin levels, together with an appropriate clinical context, are sufficient for diagnosis of central hypogonadism, which is disclosed in 1–80% of cases [1, 105].

The measurement of the sex hormone binding globulin (SHBG) may be helpful in the diagnosis of hypogonadism in systemic diseases. Of the circulating testosterone in adult men, approximately 45% is bound with high affinity to SHBG, 50% is bound to albumin and less than 4% is free. Many factors may decrease or increase plasma SHBG levels (Table 7), therefore affecting sex hormone levels and the relationship between estrogen and androgen [105].

Table 6 Causes of hyperprolactinaemia

Physiologic	Pharmacologic
Stress	*Typical antipsychotics*
Sleep	Phenothiazine drugs (e.g., chlorpromazine, clomipramine, fluphenazine, prochlorperazine, thioridazine)
Pregnancy	Haloperidol
Lactation	Pimozide
Sexual activity	*Atypical antipsychotics*
Pathologic	Risperidone
Lesions of hypothalamus or pituitary stalk	Molindone
Tumors	Olanzapine
Inflammatory o granulomatous diseases	*Antidepressant agents*
Other expanding lesions	Clomipramine
Irradiation	Desipramine
Traumatic brain injury	*Antidopaminergic gastrointestinal drugs*
Pituitary lesions	Metoclopramide, domperidone, cisapride
Prolactinoma	*Histamine H2 receptor antagonists*
GH-PRL secreting adenoma	Cimetidine, Ranitidine
Non-functioning adenoma	*Antihypertensive drugs*
Empty sella	Methyldopa
Lymphocytic hypophysitis	Reserpine
Neurogenic	Verapamil
Chest wall lesion	*Hormones*
Nipple stimulation	Estrogens (e.g. oral contraceptives)
Spinal lesion	Protirelin (TRH)
Other	*Miscellaneous*
Hypothyroidism	Amphetamine
Chronic renal failure	Opiates (e.g. codeine, morphine)
Liver cirrhosis/severe liver disease	
Adrenal insufficiency	
Polycystic ovary syndrome	
Macroprolactinaemia	
Idiopathic	

Table 7 Causes of altered circulating SHBG levels

Increased	Decreased
Aging	Prepubertal development
Growth hormone deficiency	Growth hormone excess
Estrogens	Obesity
Testosterone deficiency	Hyperinsulinemia
Hyperthyroidism	Progestins
Chronic liver disease	Androgens
Porphyria	Glucocorticoids
	Hypothyroidism
	Familial

GnRH stimulation test has been used in the diagnosis of hypothalamic hypogonadism, but this test lacks both sensitivity and specificity, and rarely adds helpful additional information to basal endocrine evaluation [120]. However, GnRH stimulation test may be useful to identify patients with normal sex steroid hormone levels and reduced LH/FSH response, who may be at risk of future hypogonadism and therefore need close follow-up [123].

The study of LH pulsatility may add helpful information on the site of HPG axis suppression, since it is frequently disturbed in systemic illness. The pulsatile release of GnRH is the first step in the cascade of neuroendocrine events that enables sexual differentiation and reproduction, and is modulated by many factors, including those influenced by stress. The presence of a stressor stimulates CRF and PRL, which in turn suppress GnRH. GnRH secretion reduction may also be related to low leptin levels, found in nutritional deficit states [1, 124].

HPG axis in specific systemic diseases

Chronic liver diseases (CLD)

Normal HPG axis function is affected in liver diseases [105, 125]. LH pulsatile secretion and response to GnRH and clomiphene are reduced. Clinical signs of hypogonadism are more pronounced in alcoholic patients due to the direct effect of ethanol upon testis and ovary [126]. In male cirrhotic patients, the estrogen/androgen ratio is usually increased. Testosterone and dihydroepiandrosterone levels are reduced, while estradiol levels are normal or slightly elevated. Several other factors may contribute to these hormonal changes in cirrhosis, including hepatic overproduction of SHBG, production of different SHBG isoforms, elevated PRL levels, direct suppression of Leydig cell function by estrogens, increased estrogen receptors in the liver and cyclic variations in the severity of liver illness [105].

Chronic kidney disease (CKD)

Chronic renal failure causes major effects on the reproductive system, notably impairment of fertility and sexual function, through effects at all levels of the HPG axis [127]. Disturbances of the axis can be detected with only moderate reductions in the glomerular filtration rate and progressively worsen as the renal failure progresses. In males, plasma LH, FSH and inhibin-a levels are slightly elevated along with reduced circulating total and free testosterone levels and normal SHBG levels. Although these changes are consistent with a primary defect in testicular function, there is also strong evidence for defective neuroendocrine regulation causing reduced LH pulsatility [127, 128]. Moreover, the increase in gonadotrophins is largely explained by the significant reduction in renal filtration. Administration of GnRH increases LH levels to the same degree as in healthy subjects; however, the peak value and return to baseline may be delayed [129]. The human Chorionic Gonadotropin (hCG) test with a single injection is abnormal, but the long-term administration of hCG may restore testosterone levels, proving that testes retain their reserve secretion [128, 129]. In uremic patients, hyperprolactinemia is frequent, due to a functional hypothalamic disturbance, which appears to be autonomous [130]. ITT or TRH infusion elicits no response or a blunted PRL response. On the other hand, dopamine infusion or L-dopa administration fails to reduce PRL levels. However, only a small percentage of uremic patients have PRL levels >100 ng/ml. In these cases, imaging studies should be performed to exclude the presence of a pituitary adenoma [105].

The hormonal profile of uremic women includes elevated PRL levels, normal FSH and modestly elevated LH levels, along with an increased LH/FSH ratio and relatively low estradiol, estrone, progesterone and testosterone levels [131]. The normal pulsatile release of gonadotrophins is disturbed, but the response to GnRH is preserved and may be excessive and prolonged. Clomiphene administration to patients with chronic renal failure induces an appropriate rise in both LH and FSH levels, suggesting that the negative feedback control of testosterone/estrogen on the hypothalamus is intact and that pituitary gonadotrophins release is normal [127].

Psychiatric diseases

In depressed women, the incidence of amenorrhea is quite high and hormonal tests reveal low to normal gonadotrophin levels with normal responses to GnRH, prolonged suppression of gonadotrophins in response to estradiol and failure of positive feedback response to estradiol [10, 105]. In patients with depression, the disturbance of hypothalamic–pituitary–ovarian axis is similar to hypothalamic amenorrhea caused by exercise or disordered eating [124, 132].

Anorexia nervosa and malnutrition

Anorexia nervosa is associated with low and apulsatile gonadotrophins, low plasma leptin levels, altered menstrual function and amenorrhea [132]. In men, anorexia nervosa rarely occurs, but severe under-nutrition presents the same hormonal changes as expected in women, namely low serum LH and FSH levels and a poor response to GnRH administration. These disturbances are normalized with attainment of normal weight [133]. Starvation has a profound suppressive effect on gonadotrophin secretion and ovarian or testicular function, regardless of its etiology. The main mechanism of gonadotrophin suppression is inhibition of GnRH secretion, as is apparent from LH secretion suppression [105]. Much evidence indicates that leptin, as a signal for starvation, mediates the under-nutrition induced alterations in the reproductive axis [134].

Severe obesity

Circulating testosterone levels are reduced in massively obese men primarily due to reduced SHBG levels. Moreover, free and non-SHBG-bound testosterone levels are reduced in massive obesity [135]. As Leydig cell function is normal in obese subjects, these effects are mainly due to reduced LH levels and pulse amplitude. The reduced LH pulse amplitude in obesity may result from increased estrogen production, because of an increased testosterone conversion to estradiol by aromatase [136].

HIV infection

In men with HIV infection, there is a high prevalence of low testosterone levels, resulting from defects at all HPG axis levels. Both hypogonadotrophic and hypergonadotrophic hypogonadism have been described, the former being more prevalent. Early in the disease, serum testosterone concentrations are usually normal [137]. Later, however, many men have low serum testosterone, but normal serum gonadotrophin concentrations [137]. Because these changes can occur in men with any severe illness, it is unclear whether HIV infection or general debility are responsible for this clinical picture.

In women, pituitary–ovarian function and menses are usually unaffected [138, 139]. However, 50–95% of HIV-infected women have serum total and free testosterone concentrations below the median for normal premenopausal women. Serum free testosterone concentrations correlate inversely with HIV copy number, and directly with muscle mass [140].

Hemochromatosis in its primary form is a genetic disease, causing excessive iron accumulation and toxicity in the pituitary and gonad. Hypogonadotrophic hypogonadism is frequent, due to the unresponsiveness of LH to GnRH. Secondary hypogonadism results from iron deposits in the pituitary and gonadotrophin secretion is selectively impaired [105]. Patients with thalassemia major and repeated transfusions develop similar disturbances of HPG axis, frequently showing delayed puberty, hypogonadotrophic hypogonadism or gonadal failure [141].

GH–IGF-I axis

During the acute phase of critical illness (first hours to days after an acute insult), GH profile shows remarkable changes. Elevated GH levels may be detected, due to increased pulse amplitude and frequency, as well as interpulse concentration. By contrast, serum IGF-I, IGF-BP3 and acid labile subunit (ALS) levels decrease, indicating a state of peripheral GH resistance. A decrease in circulating GH-binding protein, which presumably reflects the functional GH status, may also be observed. The reduced expression of GH receptors and, therefore, low circulating IGF-I have been suggested as the primary event driving increased GH secretion. This could enhance the direct lipolytic and insulin-antagonist effects resulting in elevated FFA and glucose levels, whereas the IGF-I mediated anabolic effects are attenuated. Teleologically, this GH axis response to acute injury seems to be appropriate for survival [142–145].

During the prolonged phase of critical illness, the non-pulsatile GH release remains elevated, but the pulsatile GH release is suppressed causing a reduction in serum concentrations of IGF-I, IGF-BP3 and ALS [142, 146].

During the course of critical illness men display a greater GH pulsatility reduction (despite an indistinguishable total GH output) and lower IGF-I levels than women, in keeping with the higher risk of an adverse outcome associated with male gender [113]. In the chronic phase of critical illness, the administration of GH secretagogues causes an important GH release, followed by an increase in circulating IGF-I and IGFBPs levels. The response to GHRP2 injection is more pronounced than that observed after GHRH administration, indicating a hypothalamic defect [147].

In the last years, pituitary function, in particular GH axis, has been investigated in patients with acquired cerebral injury (TBI, stroke, subarachnoid hemorrhage) at different times from acute event. Early after TBI, low, normal or high basal circulating GH levels associated with low IGF-I concentrations have been reported [3, 15]. In this phase, the entity of GH response to stimulation tests has been proposed as an index of prognosis or clinical outcome, but the conflicting results obtained so far do not allow reliable conclusions. For example, a blunted GH response to GHRH or arginine (ARG) stimulation test has been found in patients with severe TBI and very poor outcome [148]. By contrast, a normal GH response to GHRH has been reported in severely head-injured patients, with a progressive increase in such response from day 2 to day 15 after injury in the patients with poor outcome [149]. The adequacy of GH reserve has also been investigated by dynamic testing both in acute and chronic phase of TBI. A reduced GH response to glucagone (1 mg intramuscularly), suggestive of GHD, has been demonstrated in 9/50 (18%) patients during the early phase (7–20 days) following TBI, regardless of patient age, body mass index (BMI) or injury severity. At 6 and 12 months, new hypothalamic–pituitary deficit was evidenced, while some patients completely recovered [86]. Indeed, GHD discovered during the acute or post-acute phase of TBI may be temporary or may persist after the end of critical illness. In the long term, GHD has been observed in 8–21% of patients with TBI and 9–28% of patients with subarachnoid hemorrhage [15, 150, 151].

Evaluation of GH axis

The diagnosis of GHD must be performed by clinical and biochemical criteria. The current consensus is that patients with appropriate clinical history should have the diagnosis of GHD confirmed by a provocative test of GH secretion [152, 153]. Patients who should be tested for GHD are those who show evidence of hypothalamic–pituitary disease, and in whom there is an intention to treat, including those with TBI or subarachnoid hemorrhage. As the GH axis may recover after TBI, the 2007 consensus [152]

suggests that testing for GHD should be undertaken no earlier than 12 months after the injury. This implies that, during the acute phase of critical illnesses, GH provocative tests could have speculative and/or prognostic values, since they may be helpful to define patient follow-up, but they do not define GHD and eventually select for treatment.

Dynamic tests

Among the provocative tests, ITT is widely considered as the gold standard for diagnosis of adult GHD. To select the patients with severe GHD, the arbitrary cut-off has been established as <3 μg/l [153]. However, ITT is contraindicated in patients with ischemic heart disease or seizures, and in the elderly. ITT is potentially dangerous in patients with critical illness or TBI who are at high risk of developing post-traumatic seizures.

The combined GHRH plus ARG infusion provides an excellent alternative test to assess somatotroph function, with well-defined cut off levels [152, 153]. In the past years, a GH response peak >16.5 μg/l was considered normal; a response <9 μg/l was considered as diagnostic for severe GHD; a response between 16.5 and 9 μg/l indicative of partial GHD. This test demonstrated good intra-individual reproducibility, good sensitivity and high specificity for the diagnosis of GHD, and has no contraindications. Since GH axis is altered in the obese state, recent studies defined BMI-dependent cut-offs, that account for the reduced GH response to GHRH plus ARG with increasing BMI. The values suggested for lean (BMI <25), overweight (BMI ≥25 to <30), and obese (BMI ≥30) patients are 11.5, 8.0, and 4.2 μg/l, respectively [154]. However, since the combined test stimulates both hypothalamus and pituitary, GHD due to hypothalamic disease may be missed. Moreover, in patients with acquired cerebral lesions (TBI, irradiation) as well as those with inflammatory and infiltrative lesions, GHD may develop many years after the initial insult. Therefore, this group should be followed in the long term with repeat testing, as clinically indicated [153].

Glucagon test may also be used, since it shows 100% sensitivity and specificity at GH peak of 3 μg/l [155]. However, results depend on age and BMI and the test is more time-consuming than other stimulation tests [45].

Another alternative may be GHRH plus GH-releasing peptide 6 test, that displays a cut-off of 15 μg/l as the best balance of sensitivity and specificity [156]. However, 100% specificity was achieved for a cut-off of 10 μg/l, and a further limitation for this test is the relative lack of validated normative data based on age, gender, and BMI. Moreover, it seems to be of limited sensitivity for hypothalamic disease [45].

Clonidine, L-DOPA, and ARG are not useful tests in adults. The ARG test alone is used in the transition period, but the response is very dependent on BMI; therefore the ARG test should be limited to non-obese adolescents [153].

IGF-I levels

Low IGF-I levels have been suggested as diagnostic of GHD when other multiple pituitary deficits are present [157]. Patients with three or more pituitary hormone deficiencies and an IGF-I level below the reference range have 97% chance of being GHD, and therefore do not need a GH stimulation test. On the other hand, IGF-I level has low diagnostic sensitivity and is not applicable to patients with acquired cerebral lesions, who frequently display isolated pituitary defects. In fact, IGF-I levels in TBI patients with GHD may be either lower or similar to those of patients without GHD [15, 158].

Currently, IGF-I is the only valuable marker of GH action. IGF-I may be a good screening test for GHD in younger lean patients (<40 years, BMI <25 kg/m^2) with evidence of hypopituitarism. However, a normal IGF-I does not rule out GHD at any age, because IGF-I levels depend on many factors other than GH status [159]. In clinical practice, other causes of low serum IGF-I such as malnutrition, diabetes, hypothyroidism, liver disease, etc., should be excluded before applying these diagnostic criteria [156, 159] (Table 8). Severe medical conditions (i.e., multiple trauma, surgical trauma, TBI, and systemic illness) also have an important influence [3, 15, 48, 160, 161].

Optimal serum IGF-I levels require adequate caloric intake and nutritional elements. Serum IGF-I levels are increased by dietary protein and fat and are decreased by high-carbohydrate diets and caloric restriction. Decreased IGF-I levels are reported in anorexia nervosa, as well as in celiac disease and inflammatory bowel diseases, probably due to malnutrition and/or inflammation [157, 162]. In adult obesity, serum IGF-I levels negatively correlate with BMI and usually remain in the lower half of the normal range or may be low in subjects with visceral obesity. Although serum total IGF-I concentrations may be reduced

Table 8 Causes of altered circulating IGF-I levels

Reduced IGF-I levels	Increased IGF-I levels
Malnutrition	Critical illnesses
Chronic Liver Diseases	Sepsis
Diabetes	Systemic inflammatory diseases
Hypothyroidism	Multiple and/or brain injuries (acute phase)
Wasting syndrome	Chronic renal failure

in obesity, serum free IGF-I levels are increased, most likely due to hyperinsulinemia. By contrast, normal as well as increased IGF-I levels are reported in obese children [159].

Since the liver is the primary IGF-I production site, patients with hepatic cirrhosis have low IGF-I levels. In addition to the chronic fibrotic changes in the liver, alcohol abuse itself decreases IGF-I levels, which increase after alcohol withdrawal [159]. Also patients with poorly controlled diabetes mellitus have low circulating IGF-I levels due to decreased hepatic production [163]. In patients with chronic renal failure, the bioavailability of IGF-I is low, despite normal or elevated serum total IGF-I concentrations [164].

Acute administration of supraphysiological doses of glucocorticoids may increase serum total IGF-I concentrations, but IGF-I bioactivity decreases [159]. However, chronic treatment with oral or inhaled glucocorticoids do not seem to alter IGF-I levels in children with asthma [165]. Although GH secretion is suppressed in patients with Cushing's syndrome, IGF-I levels are reported to be normal (or low-normal) [159].

Activation of the immune system causes suppression of IGF-I levels (e.g., sepsis, systemic inflammatory disease, multiple injuries, TBI) [3, 15, 160, 161]. Critically ill patients are reported to have low IGF-I levels, which normalize in those who recover from their illness after a few days, but fail to normalize in non-survivors [1, 142]. In protracted critical illnesses (more than 21 days duration) a gender dissociation within the GH/IGF-I axis has been reported, men having lower serum IGF-I levels compared to women [113]. In the post-acute phase of injury low IGF-I levels may reflect a persistent GH resistance status [1, 142]. Therefore, IGF-I level has low diagnostic sensitivity and is not applicable to patients with critical illness or systemic diseases.

GH axis in other specific systemic diseases

Chronic liver diseases (CLD)

The GH/IGF-I axis is deranged in patients with CLD [166, 167]. Endogenous GH secretion rates in patients with CLD are twice those of normal control subjects, characterized by augmented pulsatile secretion and increased basal concentrations [166]. Worsening hepatocellular function is paralleled by decreased serum IGF-I concentrations. Because the liver is the main source of circulating IGF-I, increased endogenous GH secretion most likely reflects diminished IGF-I-mediated feedback inhibition. Therefore, a state of hepatic GH resistance exists in CLD.

Chronic kidney disease (CKD)

CKD in children is associated with dramatic changes in GH–IGF-I axis, resulting in growth retardation [168]. Renal failure is a state of GH resistance and not GHD. In fact, GH concentration is commonly elevated in CKD, primarily due to decreased renal clearance. Enhanced GH secretion may also contribute to the rise in plasma levels. Children with end-stage renal disease have an increased number of GH secretory bursts when compared to children with normal renal function [169]. The cause of this phenomenon is not clear, but protein-caloric malnutrition and stress may play a role. Plasma GH levels fall to low-normal values after the institution of maintenance dialysis or administration of recombinant human erythropoietin [170]. Since hypothalamic–pituitary regulation of GH is perturbed in CKD, abnormal responses to dynamic tests are observed. A paradoxical GH response to glucose load has been observed in advanced renal failure, by contrast GH response to ITT is reduced in uremic patients [171, 172]. Moreover, TRH stimulates GH release in uremic patients, but has little or no effect in normal individuals/subjects [172].

Anorexia nervosa

Patients with anorexia nervosa show GH hypersecretion and low IGF-I levels. It is unclear whether these changes are due to peripheral GH resistance and reduced IGF-I feedback or to a primary hypothalamic dysfunction. The neuroendocrine alterations include an enhanced GH response to GHRH, and impaired GH response to cholinergic stimuli. Moreover, paradoxical GH responses to glucose load, TRH and LHRH have been reported [162, 173, 174].

Conclusions

Critical illnesses and systemic diseases are associated with alterations in the hypothalamic–pituitary–peripheral hormone axes, which represent part of the adaptive response to the stressful event and may be influenced by type and severity of illness and/or pharmacological therapy. There is no consensus regarding the type of approach, as well as the criteria to use to define pituitary axis function. Therefore, each patient should be accurately evaluated and the several factors that may influence pituitary axis function in these settings should also be taken into consideration. In particular, criteria for evaluating normal corticotroph axis response to systemic illness are different from those accepted for the general population. Concerning the other pituitary axes, interpretation of test results is similar to that of the general population, even if a more accurate

evaluation is frequently required. As a consequence, the patient should be evaluated from the endocrine point of view in each phase of the systemic disease and accurately followed-up for possible permanent endocrine axis disruption.

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