

# Glucose Homeostasis and Neuroendocrine Regulation in Critical Illness

Alper Gürlek

Selçuk Dağdelen

Ayşegül Atmaca

Bülent O. Yıldız

Olca Gedik

*Hacettepe University School of Medicine, Department of Internal Medicine, Division of Endocrinology, Ankara*

Glucose metabolism and homeostasis change considerably during the course of critical illness. The hyperglycemic response to stress is thought to be an adaptive change to restore the glucose supply of poorly perfused tissues. Endogenous glucose production is severely impaired in sepsis, and the resultant hypoglycemia is a significant cause of death in many cases. The neuroendocrine changes during the acute and chronic phases of severe illness are differentially regulated. The initial changes consist primarily of activated anterior pituitary function, the peripheral anabolic pathways being inactivated. In prolonged critical illness, however, there is a uniform reduction in the pulsatile secretion of pituitary hormones. In this phase, the pulsatility may be reestablished by the administration of relevant combinations of releasing factors. In the existence of partial adrenocortical insufficiency, treatment with high doses of glucocorticoids remains controversial, but physiological doses might be beneficial. Similarly, there is no adequate data concerning the beneficial effect of treatment of thyroid hormone abnormalities, the so-called euthyroid sick syndrome. In the acute phase of critical illness, high dose growth hormone administration is not recommended due to increased mortality and morbidity. It remains plausible that growth hormone/insulin-like growth factor-I provided in conjunction with appropriate nutritional support would be of benefit in appropriately selected groups particularly in the chronic phase of critical illness.

**Key words:** Glucose metabolism, critical illness, growth hormone, insulin-like growth factor-I, hypothalamic-pituitary axis

## Introduction

By definition, critical illness is any condition requiring support for failing vital functions, either with mechanical aids or with pharmacological agents (1). Concept of the modern critical care firstly appeared during the poliomyelitis epidemic of 1952 in Denmark. The increasing hospital admissions of patients with respiratory failure brought about the need for a distinct medical staff and department specifically managing these critically ill patients. Beyond that epidemic, critical care was accepted and

practiced as a way of giving advanced life support only through the cardiopulmonary therapeutic modalities. In view of that limited medical approach, survival rates of these critically ill patients were unsatisfactory, having a mortality rate of 20% among patients hospitalized at critical care units for more than 5 days, reaching a mortality of 54% in case of nosocomial infections associated with higher APACHE scores. Recently, much of modern critical care practice is based on restoring not only cardiac and/or pulmonary abnormalities, but also manipulating the cellular and metabolic responses to critical illness including energy expenditure, changes in substrate utilization and negative nitrogen balance. The novel critical care approach seems to vindicate the 19<sup>th</sup>-century theories of Claude Bernard, who has proposed that "systems respond to pathogens by maintaining cellular homeostasis".

## Correspondence address:

Alper Gürlek  
29. Sokak 36/3  
06490 Bahçelievler, Ankara  
Fax : (0312) 3101773  
E-mail: agurlek@hacettepe.edu.tr

The organism responds to critical illness by three major regulatory systems: the endocrine system, the nervous system and the immune system (2). The stress response is divided into three overlapping stages: the acute stage (the first hours to days), the chronic stage (from 7 to 10 days onwards) and the stage of exhaustion/recovery (1). With an intensive care stay of more than 21 days, mortality may reach up to 24% in adults (3). During stress, the hypothalamus-pituitary axis must be kept intact for metabolic and immunological homeostasis.

In this review, after summarizing the changes in glucose homeostasis, the hypothalamic-pituitary responses to critical illness will be emphasized. The treatment strategies taking into account these neuroendocrine responses will be discussed in light of the available clinical trials. The spectrum of the endocrine responses and their variability during the acute and chronic phases of the critical illness will be stated where appropriate.

### Changes in glucose homeostasis in critically ill patient

While analysing the metabolic responses to critical illness, two principle issues of metabolism must be considered: Firstly, there are important distinctions between quantitative events and the physiological significance of these. For example, the large negative nitrogen balance observed during the first few days of starvation is easily tolerated, and is of little physiological significance. In contrast, the small negative nitrogen balance observed in protein-depleted critically ill patients is poorly tolerated and may result in death if not interrupted. Secondly, the quantity of a fuel consumed, or produced, assumes more relevance when it is integrated with the quantities of other fuels produced or consumed. For example, the quantity of glucose consumed or produced assumes more relevance when it is integrated with the quantities of free fatty acids, keton bodies, and amino acids metabolized (4).

Metabolic profile of critically ill patients (burn, trauma, post-operative period, geriatric patients, AIDS, renal failure) could be described in view of two overlapping stages of starvation and stress. The metabolic fuels available in a healthy 70 kg man at the beginning of a fast are composed of 15 kg of fat (equals 135 000 kcal), 6 kg of protein (24

000 kcal), 0.2 kg of glycogen (800 kcal). Despite the enormous caloric stores available, the body can not utilize them conveniently. For example, only one third of the body's protein could be used for energy production without compromising vital functions. From the non-protein respiratory quotient (RQ), the quantities of carbohydrate and lipids catabolised can be estimated, and thus, the ratio of carbohydrate to lipid catabolized can be calculated. Humans in the resting, overnight fasting state have an average non-protein RQ of about 0.86, implying that carbohydrate and lipid each supplies energy of one-half equally. After few days of fasting (2-3 days), the non-protein RQ decreases to about 0.73, indicating that more than 85% of fuel is derived from lipids. During prolonged starvation (longer than 2 weeks) the non-protein RQ is about 0.68. When fatty acid utilization is at maximum, the non-protein RQ should be theoretically at a minimum of 0.70. The reason for this low RQ in case of prolonged starvation is the loss of some energy sources as keton bodies *via* urinary excretion (4).

During starvation, liver first uses glycogen degradation and then gluconeogenesis to maintain blood glucose levels stable. For the first days of starvation, the brain exclusively continues to use glucose as a fuel, whereas in prolonged starvation keton bodies are used as a fuel by the brain, reducing the need for protein catabolism for gluconeogenesis. While the organism as a whole tries to overwhelm hypoglycemic complication of starvation through these adaptive changes, critical illness also induces a stress hormone response including decreased insulin/glucagon ratio. Apart from an energy depleted state of starvation, endocrine and metabolic response to stress inclines a hyperglycemic trend by increasing resistance to insulin and growth hormone as well. This hyperglycemic response to stress is suggested to be an adaptive change to restore the glucose supply of poorly perfused tissues through the concentration gradient at earlier stages. However, in advanced stages, it could be transformed into a maladaptive state creating its own complications. On the other hand, when the hyperglycemic stress condition is associated with hypoglycemic starvation, the status of glycemia seems to depend on the underlying comorbidity.

Sepsis and related syndromes are the main causes of multiple-organ failure and death in critically ill

patients. Thirty to 60% of these patients die eventually (5). Sepsis is associated with catabolism of lean body mass (particularly muscle wasting) despite adequate nutritional support (6). Substrate metabolism is dramatically altered in septic patients. The normal suppressive effect of exogenous glucose on glucose production is decreased. In the post-absorptive state, glucose clearance is generally increased potentially causing hypoglycemia. Paradoxically, the ability of insulin to stimulate glucose uptake is diminished, so that hyperglycemia is often evident during nutritional support (7).

Septic rats seem to have metabolically distinct phases: an initial hyperglycemic phase, followed by a hypoglycemic phase (8). Cytosolic protein kinase C (PKC) is inactivated in rat liver during late hypoglycemic phase of sepsis. Since PKC-mediated phosphorylation plays an important role in regulating hepatic glucose metabolism, an inactivation of cytosolic PKC activity may contribute to the development of hypoglycemia during late phase of sepsis (9).

Tang et al. (10) have shown that beta-adrenergic receptors are progressively internalised from surface membranes to the intracellular sites and, furthermore, they are underexpressed in the rat liver during the progression of sepsis. Since hepatic glucose metabolism is regulated by catecholamines, in part, through beta-adrenergic receptors, the authors have proposed that an internalisation/under expression of hepatic beta-adrenergic receptors may play a role in the altered glucose homeostasis during sepsis, particularly in the late hypo-metabolic phase of sepsis (10).

Rattarasarn et al. (11) have determined the risk factors and clinical characteristics of hypoglycemia in 52 patients with sepsis in a case-control study. One third of patients was found having hypoglycemia since the time of arrival at the hospital. Mortality rate was reported to be 90%, and 80% of the patients have died within 48 hours of the first hypoglycemic attack. Starvation and liver disease were independent risk factors for mortality (11).

Contribution of the kidney to glucose homeostasis during starvation is negligible within the first 24 hours, but increases significantly with prolonged fasting. By the fourth week, the kidney is responsible for one-half of the total glucose appearing in the circulation. Haviv et al. (12) have documented the

clinical presentation of hypoglycemia in patients with renal failure. Of a total of 1545 admissions of end stage renal failure, 56 (3.6%) were admitted during a ten-year period with hypoglycemia. The most common etiology reported was drug-induced hypoglycemia in 26 (46%) of patients. In 22 (39%) cases, sepsis was the contributing cause of hypoglycemia. Severe malnutrition caused 7% of hypoglycemic episodes. Of the patients, 18 (32%) with end stage renal failure eventually died, and none of them were from the drug-induced group. However, mortality rate in the sepsis-induced hypoglycemia group was 66%, while the malnutrition group had 17% of the deaths. The authors concluded that hypoglycemia is frequent in end stage renal failure patients, and is fatal if associated with either sepsis or malnutrition (12).

Shilo et al. (13) have investigated hypoglycemic episodes occurring among non-diabetic hospitalised geriatric patients. Symptoms and signs of hypoglycemia were noted in only two-fifths of the patients. Albumin less than 3.0 g/dl, liver disease, renal insufficiency, malignancy, congestive heart failure, and sepsis were statistically significant predictors of developing hypoglycemia. The overall mortality rate was significantly higher among the hypoglycemic patients, and was independent of glucose levels. They estimated that odds of mortality in an older patient with hypoglycemia were 3.67 times higher than in those without hypoglycemia (13).

Since patients with AIDS would often develop malnutrition, hepatic/renal failure and sepsis, AIDS also is assumed as a predisposing factor for hypoglycemia. Besides, pentamidine, a frequently used antibiotic for pneumocystis carinii among patients with AIDS, may cause betacell lysis and may complicate either hyper- or hypoglycemia.

Apart from increased protein turnover and negative nitrogen balance, hypoglycemia is also a catastrophe for critically ill patient even in case of adequate nutritional supports. In order for its prevention and for early management strategies, further clinical evidences and reports are required.

### **The hypothalamic-pituitary-adrenal response to critical illness**

More than a century ago, Claude Bernard speculated that the 'milieu interne' must be maintained to

preserve life. Walter B. Cannon later extended Bernard's concepts by showing that the maintenance of a stable internal environment depends mainly on an intact sympathoadrenal system. Later on, Hans Selye stated that any stimuli that disturbed the physical integrity of the organism resulted in a general adaptation syndrome (2).

The pituitary-adrenal axis responds differently in acute and chronic stages of critical illness.

*A. Acute stage.* In this stage, hypercortisolism induced by stress, trauma or sepsis is associated with increased adrenocorticotrophic hormone (ACTH) levels, which, in turn, is stimulated by corticotropin-releasing hormone (CRH), cytokines and noradrenergic system (1,2). In contrast to high cortisol levels, adrenal androgens such as dehydroepiandrosterone sulphate (DHEAS), a marker of clinical well being and which has stimulatory effects on Th1-helper cells, are low during critical illness (1,2).

The pharmacokinetics of cortisol is also changed during stress. The rate of hepatic cortisol extraction from the blood is decreased and the plasma half-life of cortisol is increased (2). Cortisol binding globulin (CBG) concentration and consequently, CBG binding affinity for cortisol are decreased, so that free and biologically active cortisol concentrations are increased (2). Glucocorticoid receptors, in turn, exert an enhanced sensitivity to cortisol in acute stage (2).

In acute stage, there is a shift of pregnenolone metabolism away from mineralocorticoid and adrenal androgen pathways toward the glucocorticoid pathway. Hypercortisolism acutely shifts carbohydrate, fat and protein metabolism, so that the anabolism is delayed and energy is shifted to vital organs such as brain (1). There is intravascular fluid retention and increased vasopressor and inotropic response to angiotensin II and catecholamines, respectively. The organism itself, *via* hypercortisolism, dampens down its own inflammatory responses, thus protecting itself against overresponses. As a result, hyperactive state of the biological effects of cortisol during acute stress seems to protect the body against a life-threatening event and is a beneficial adaptational response (1,2).

*B. Chronic stage.* The development of critical care medicine changed the natural course of an otherwise lethal condition to a prolonged illness. This catabolic

stage is characterised by inappropriate hormonal responses, such as reduced pulsatile secretion of pituitary hormones, and decreased activity of target organs.

During this prolonged stage of critical illness, the plasma ACTH level is low, but the total serum cortisol concentration is still elevated indicating that cortisol release at this stage may be driven through an alternative, non-ACTH mediated pathway such as endothelin (2). Why ACTH levels are low and cortisol levels are high in chronic stage is unclear; a role for enkephalins, neuropeptide Y, substance P, vasopressin, atrial natriuretic hormone and pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1 and IL-6 has been suggested. It has recently been shown that IL-6 directly stimulates the release of glucocorticoids from adrenocortical cells. Together with the fact that IL-1 and TNF-stimulate IL-6 production, IL-6 plays a central role in the non-ACTH-mediated activation of adrenal cortex. On the other hand, glucocorticoids can inhibit IL-6 production. Thus, it is difficult to explain high IL-6 levels during critical illness in the presence of high cortisol levels. Recently, physiological counter regulatory hormone for glucocorticoid action, macrophage migration inhibitory factor (MIF), has been discovered. MIF is thought to inhibit immunosuppressive effects of glucocorticoids or cytokine production (2,14).

During chronic stage, DHEAS levels remain low and there is dissociation between low aldosterone and high renin levels. Low DHEAS levels indicate that the disease is reaching the stage of exhaustion. The CBG concentration begins to rise, resulting in free cortisol levels not significantly higher than those in control subjects (14,15).

Whether hypercortisolism in the chronic stage of critical illness is beneficial for the organism remains uncertain. Recently, Barquist et al. (15) have stated that adrenal failure is 20 fold higher in critically ill patients over the age of 50 who are being treated in intensive care unit for more than 14 days. High levels of glucocorticoids seem to be essential for hemodynamic stability. On the other hand, high glucocorticoid levels together with low DHEAS levels evoke an imbalance between immunosuppressive and immunostimulatory pathways, creating a susceptibility to complications such as infection, impaired wound healing and myopathy.

It is difficult to speculate whether hypercortisolism in the chronic stage of critical illness is beneficial or not.

*C. Stage of exhaustion/recovery.* The chronic stage ideally ends with recovery stage, or in the worse case, the stage of exhaustion. In the stage of exhaustion, homeostatic balance shifts in the direction of catabolic events. Pathophysiological changes such as endothelial dysfunction and failure of microcirculation lead to misdistribution of blood flow and ischemia. With inappropriate immunomodulatory and endocrine responses, these changes lead to apoptosis induced by hypercortisolism (14).

The chronic stage more often leads to recovery stage in which homeostatic balance is shifted to the direction of anabolism. In this stage, there is normalisation of pituitary hormone secretion and peripheral feedback regulation (14).

### **Relative adrenal failure in critical illness**

Many reports state that absolute adrenal failure (AF) is rare in critically illness, occurring in 2 to 3% of patients (16). However, the concept of occult or relative AF has been proposed. In relative AF, the cortisol level despite being normal or high, is inadequate for the increasing demands of the organism, and the patient is unable to respond to any physiological or pathological stress (17). Pre-existing conditions, acute alterations in hypothalamo-pituitary-adrenal axis, and drugs may also be the cause of relative AF (Table 1). Symptoms and signs that might raise the suspicion of relative AF are shown in Table 2. In relative AF, clear symptoms and signs are usually absent. The clinical clue to diagnosis may be the unexplained hypotension, resistance to high doses of inotropic agents and vasoactive drugs, and improvement in clinical condition with glucocorticoid therapy.

Relative AF lacks clear-cut diagnostic criteria. In which patients should basal cortisol levels be measured, and which values should be considered as normal? Should ACTH-stimulated cortisol levels be measured? What are the other diagnostic tests for relative AF? Should all patients who were considered as having relative AF receive high dose glucocorticoids? All these questions remain to be answered.

**Table 1.** Contributory factors or causes of hypoadrenalism in critically ill patients

• Previously undiagnosed primary adrenal failure
Autoimmune adrenalitis
Metastatic disease
Granulomatous diseases
• Previously undiagnosed secondary adrenal failure
• Suppression of adrenocortical reserve as a result of prolonged stress
• Inhibition of cortisol and ACTH production by circulating inflammatory mediators
• Critical illness
Haemorrhage (disseminated intravascular coagulation, thrombocytopenia)
Surgery (adrenalectomy, suprarenal vascular surgery)
Disseminated bacterial, viral or fungal infection
• Drugs
Previous unknown use of glucocorticoids
Decreased synthesis of glucocorticoids (ketoconazole, etomidate)
Increased metabolism of glucocorticoids (rifampicin, phenytoin, phenobarbital)

**Table 2.** Symptoms and signs that raise the suspicion of relative adrenal failure

• General	Fever without a cause, not responding to antibiotics
• Mental	Weakness, fatigue, lethargy, agitation, apathy, depression, delirium, coma
• Gastrointestinal	Anorexia, nausea, vomiting, diarrhoea, abdominal or flank pain
• Haemodynamic	Unexplained circulatory instability Hypovolemic shock Hyperdynamic shock
• Laboratory	Hypoglycemia, hyponatremia, hyperkalemia, hypercalcemia, neutropenia, eosinophilia, hyperprolactinemia, hypothyroidism

In acute illness, basal cortisol levels tend to raise 20 times above the normal. Many authors believe that the lowest normal level of cortisol in critically ill patients should be 10 to 20 µg per deciliter (18). The values are higher in patients with highest illness-severity scores, and the highest values are reached shortly before death (30 to 260 µg per deciliter) (16). Adrenal function in critically ill patients are often evaluated with standard ACTH stimulation test in which cortisol is measured at baseline and after 30 to 60 minutes after the intravenous administration of 250 µg of cosyntropin. There are no agreed criteria for evaluating the changes in cortisol levels after ACTH administration. In most patients, serum cortisol levels increase above 18 µg per deciliter after ACTH, but if patients have high

baseline cortisol levels, subsequent increments may be small (16,18). This may be due to the fact that hypothalamo-pituitary-adrenal axis is already maximally stimulated, or it may be a result of interference with the capacity of adrenal cortex to produce glucocorticoids and a lack of cortisol reserve. Nevertheless, high basal cortisol levels and inadequate increments in cortisol after ACTH administration indicate to the presence of relative AF and are associated with higher mortality. Another disadvantage of standard ACTH test is the dose to be used and the timing of cortisol measurement. The standard 250 µg ACTH may overstimulate the adrenal cortex. Normally, plasma ACTH levels of 100-300 pg per milliliter produce maximum cortisol response. After 250 µg of ACTH, plasma levels of ACTH are greater than 10 000 pg per milliliter. Thus, 250 µg ACTH is a supraphysiological dose. A 1 µg ACTH test, in which cortisol response after 30 minutes of ACTH administration is measured, produces an ACTH level of about 300 pg per milliliter (17). Hence, low dose ACTH test is considered to be more physiological and sensitive, and correlates well with insulin tolerance test (17). Relative eosinophilia is a promising diagnostic tool, but lacks proper diagnostic criteria (17).

The relative AF occurs more frequently during sepsis and septic shock than after trauma and surgery. Barquist and Kirton have reported that 11% of patients older than 55 years and with an intensive care unit stay of 14 days or longer were found to have AF (15). As the criteria for relative AF diverge, the incidence has been reported from zero to 75% (17). It also probably occurs more frequently than observed in the past because of a more prolonged hospital stay.

Several mechanisms in the pathogenesis of relative AF in septic shock have been proposed. Necrosis, haematomas, microthrombi and platelet aggregation have been shown throughout the adrenal cortex in varying degrees of severity, but contribution of these changes to the pathogenesis of relative AF is controversial. Mediators released during septic shock such as TNF- (suppressing cortisol production), corticostatin (blocking the ACTH receptors), MIF (causing glucocorticoid resistance) and other cytokines (decreasing the number of glucocorticoid receptors and the affinity glucocorticoids for their receptors)

are thought to be responsible for the development of relative AF (17).

### *Treatment of relative AF*

The use of high dose glucocorticoid in critically ill patients still remains controversial. Most clinical studies have been carried out in patients with sepsis and septic shock. In two meta-analyses of effect of glucocorticoids in sepsis and septic shock, it has been emphasized that high dose glucocorticoids have no beneficial effect on survival (19,20). Lower doses of glucocorticoids, i.e. a maximum of 300 mg hydrocortisone daily, have a beneficial effect on hemodynamic parameters and outcome in critically ill patients (17). In randomised trials glucocorticoids have been shown to be beneficial in patients with gram-negative sepsis, bacterial meningitis, typhoid fever, acute spinal cord injury, pneumocystis carinii pneumonia, and the adult respiratory distress syndrome (16).

The effects of glucocorticoid treatment require further confirmatory trials to answer the following: Which patients derive the most benefit? When should glucocorticoids be started-early or late? What is the minimal effective dose and the route of administration-bolus or continuous infusion? How long should the glucocorticoids be given?

In summary, conflicting advice about routine screening of adrenocortical function in critically ill patients has been given. In general, routine screening is warranted in patients who are 55 years or older, and in patients with a long hospital stay. The basal cortisol level less than 20µg per deciliter is strongly associated with AF. If the basal cortisol level is more than 20 µg per deciliter, ACTH test is often required to elucidate whether the adrenal response is suppressed or not. If the clinical picture is strongly suggestive of AF and the treatment is urgent, dexamethasone 4 mg (not detected by the plasma cortisol assay) may be given until the interpretation of the test results. When the results are positive, there is an immediate need for glucocorticoid replacement. However, negative test results should not always prohibit a trial of glucocorticoid replacement, particularly in patients with a high basal cortisol level, an inadequate response to ACTH and a strong suspicion for relative AF. A rapid response to glucocorticoids may be the best clue for the diagnosis of relative AF.

## Hypothalamic-pituitary-thyroid axis in the critically ill patient

During critical illness, profound changes may occur in the hypothalamic-pituitary-thyroid (HPT) axis. Thyroid function studies in critically ill patients are often abnormal. The most consistent change is a decrease in serum tri-iodothyronine (T3) level, but in severe illness, serum thyroxine (T4) may also decrease. The persistence of a normal or even decreased serum level of thyrotropin (TSH) in the face of decreased serum thyroid hormone concentrations implies a major change in HPT axis setpoint regulation. Since these abnormalities do not appear to be associated with thyroid disease, and thyroid function tests return to normal once the underlying illness is resolved, they have been known as the "euthyroid sick syndrome" (ESS). It remains unclear whether ESS is a part of the neuroendocrine adaptation to illness, with lower levels of thyroid hormone leading to reduced metabolic demand during illness, or whether ESS represents a maladaptive response requiring endocrine intervention. Recent observations suggest that both may be true, depending on the time course and severity of illness (21,22).

### Thyroid physiology: an overview

Thyrotropin is released from the anterior pituitary gland and stimulates the thyroid gland. T4 is released into circulation by the thyroid; about 80% of circulating T3 is produced in peripheral tissues while the thyroid itself secretes the remainder. Ninety-nine percent of T4 is bound to thyroxine-binding globulin, albumin, and thyroxine-binding pre-albumin. The remaining 1% is physiologically active. This amount is converted into the more active form, T3, in the peripheral tissues through deiodination of the outer ring by 5' deiodinase. An alternative pathway is deiodination of the inner ring by 5 deiodinase, which results in an inactive compound, reverse T3 (rT3). The same enzyme, 5' deiodinase, responsible for the production of T3, accomplishes the clearance of rT3. Both T4 and T3 provide negative feedback on TSH secreted by the pituitary, and thyrotropin-releasing hormone (TRH) secreted by the hypothalamus (23).

### Alterations in thyroid function tests

In general, three patterns are seen; low T3, low T3 and T4, and low TSH. These reflect different phases on a continuum and severity of illness. A fourth

form of ESS has been described in psychiatric inpatient settings; elevated T4.

**Low T3 syndrome.** The most rapid and consistent change in serum concentrations of thyroid hormones in the setting of illness is a fall in T3 and an increase in rT3 level. This may occur within hours of the onset of a surgical procedure and can also be observed in a wide variety of illnesses including severe infection, trauma, myocardial infarction, malignancy and burns (22).

Mild to moderate illness results in impaired 5' deiodinase activity, resulting in decreased T4 to T3 conversion and decreased clearance of rT3. The most common thyroid profile seen is a low T3, high rT3, normal T4, and normal TSH. In a study by Gardner et al (24), after normal subjects were fasted for 36 hours, T3 concentrations began to fall and, after 48 hours, urinary nitrogen increased, reflecting proteolysis to fuel gluconeogenesis. The administration of T3 led to a further increase in urinary nitrogen excretion. This increase indicates that a low level of T3 may be protective, preventing the breakdown of skeletal muscle for protein in the stressed state. Other studies have shown low T3 levels in critically ill patients to be a predictor of mortality (23). It has been suggested that there exists an inhibitor of extra-thyroidal conversion of T4 to T3, resulting in decreased T3. The exact nature of this inhibitor is unclear, although free fatty acids have been proposed (23).

**Low T3 and T4 syndrome** In about 20% of critically ill patients, a low T3 level is accompanied by a low T4 (25). TSH levels, however, are usually normal. This occurs more commonly in severely ill patients with more protracted illnesses. Free T4 (fT4) levels can be high, normal or low. These variations in fT4 levels may be attributable to different assay techniques, variations in the underlying causes of ESS in different clinical settings, or both. Low T4 level is correlated with overall mortality rate (21).

**Low TSH syndrome** Thyrotropin levels can be found outside the lower reference range in up to 15% of hospitalised patients (26). However, it is unusual to find serum TSH levels below 0.01 mU/L, a level associated with clinically overt thyrotoxicosis. In low TSH syndrome, TSH levels are low or inappropriately normal for the decreased T3 and T4. Whether the mechanism is pituitary or hypothalamic in origin is unclear, although low or

normal TSH levels in the face of low T3 and T4 levels suggest a diminished pituitary responsiveness to circulating thyroid hormone. TSH secretion, pulsatility and TSH response to TRH is blunted in critically ill patients. Again, low TSH is correlated with severity of illness and mortality (21-23).

The low TSH syndrome is easily confused with thyrotoxicosis unless T4 and T3 levels are also checked. In thyrotoxicosis, elevated levels of thyroid hormones accompany low TSH levels. The low TSH syndrome can also be confused with hypothyroidism secondary to hypothalamic or pituitary lesions. These forms of hypothyroidism are extremely rare without a prior history of pituitary or hypothalamic dysfunction.

*Elevated T4 syndrome.* Elevation of total T4, and fT4 levels is common in patients hospitalised with acute psychiatric illness. Typically, these abnormalities occur with normal T3 and normal or elevated TSH levels. Such laboratory abnormalities are usually transient and resolve within a few weeks (27).

## ***Effects of environmental factors on thyroid function tests***

Frequently used pharmacological agents in critically ill patients may contribute to confusion in the assessment of thyroid function tests (28). Dopamine infusion suppresses both basal TSH level and blunts the TSH response to TRH. Glucocorticoid administration suppresses both basal and TRH stimulated TSH release, decreases thyroid hormone binding to its proteins, and inhibits peripheral 5' deiodinase activity. These changes result in low T3, high rT3, normal fT3 and fT4 levels.

Iodinated contrast agents decrease hepatic conversion of T4 to T3, resulting in a low T3, and high rT3. Amiodarone can cause a low T3 syndrome similar to that seen with the iodinated contrast agents. Amiodarone may cause hypothyroidism if iodine intake is sufficient, or alternatively, may cause hyperthyroidism if iodine intake is insufficient. Diphenylhydantoin is commonly used for seizure disorders and may result in decreases in serum T4 levels.

## ***The controversy of the treatment of ESS in critically ill patient***

Studies aimed at normalization of the serum concentration of thyroid hormones in critically ill

patient with ESS are scarce. Limited data available from trials involving the administration of T4 or T3 have not convincingly shown a beneficial effect. It is unclear whether treating these patients with thyroid hormone is beneficial or hazardous. Multiple studies have addressed this issue in patients with cardiac disease, sepsis, pulmonary disease or severe infection, or with burns and trauma. There are currently no conclusive studies indicating long-term benefits, in terms of improving morbidity or mortality, of the administration of thyroid hormone to the critically ill patients (22).

There is no indication for the use of thyroid hormone supplementation in critically ill patients whose thyroid hormone abnormalities are consistent with ESS (22,29). Recent clinical studies involving the administration of hypothalamic peptides such as TRH and growth hormone secretagogues to critically ill patients have shown partial thyroid axis reactivation, from TSH secretion to increases in T3 and T4 (30). The outcome benefit of TRH infusion alone or in combination with growth hormone secretagogues in prolonged critical illness has yet to be defined. At the present time, there is no evidence-based approach to the treatment of ESS, and more research in this area is clearly needed.

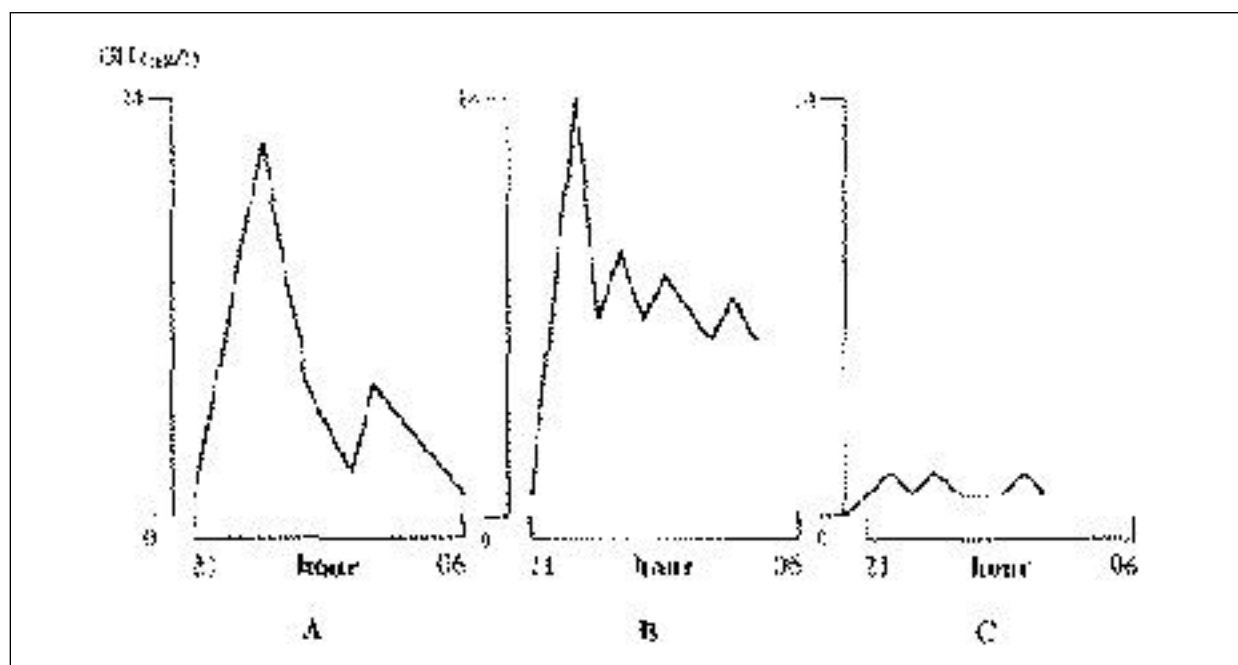
## **Growth hormone/insulin-like growth factor-1 axis in critically ill patients**

### ***Changes in growth hormone/insulin-like growth factor-1 axis during acute and chronic phases of critical illness***

Growth hormone (GH) is released from the somatotropes in a pulsatile fashion (Figure 1A), under the interactive control of the stimulatory hypothalamic growth hormone-releasing hormone (GHRH) and the inhibitory somatostatin (31). GH has anabolic, immunomodulatory and lipolytic properties. Its action is partly mediated *via* insulin-like growth factor-1 (IGF-1), which is synthesized in the liver as well as the kidneys, cartilage, and pituitary gland.

The importance of an intact hypothalamo-pituitary axis for metabolic and immunological homeostasis during stress is well recognized. During the first hours or days after an acute insult, the following changes occur: the peak GH levels and the inter-pulse concentrations are high, and the GH pulse frequency is increased (Figure 1B) (31). A more





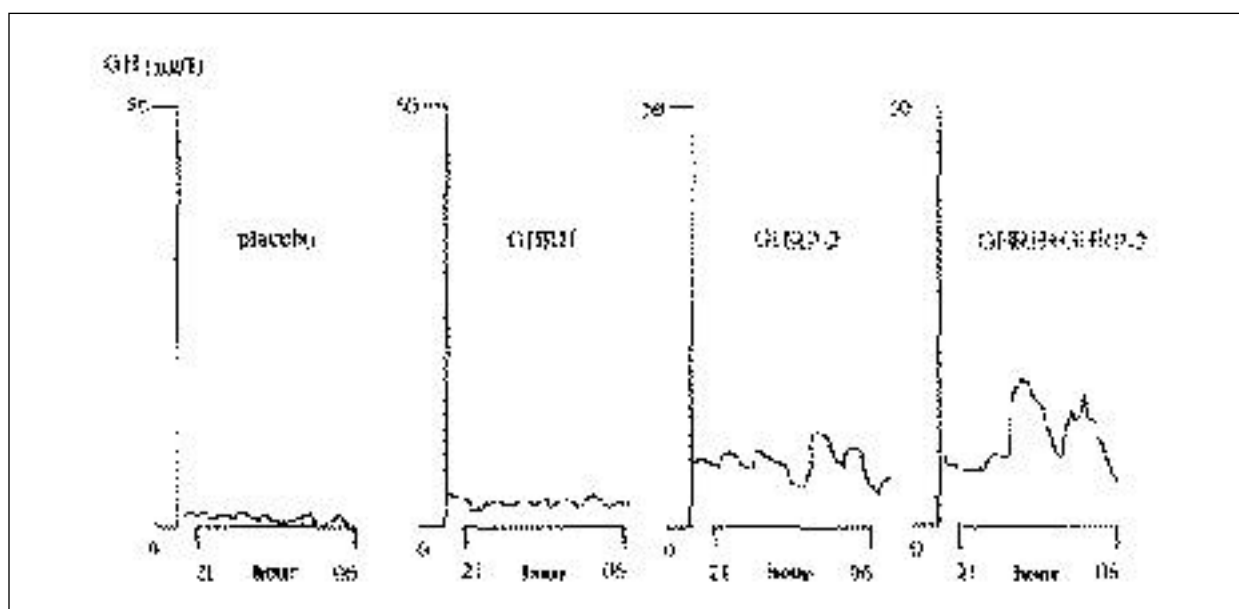
**Figure 1.** Nocturnal serum growth hormone (GH) profiles in health (A), acute phase (B) and chronic phase (C) of critical illness. (Adapted from reference 31)

frequent withdrawal of somatostatin and/or an increased availability of growth hormone-releasing factors might be implicated in these changes in GH profile. Serum insulin-like growth factor-I (IGF-I) and IGF-binding protein-3 (IGFBP-3) levels decrease in the acutely ill patients (30). This picture is interpreted as being acquired peripheral resistance to GH, probably brought about by cytokines (30). It has been suggested that reduced GH receptor expression, and therefore a low circulating IGF-I level derives the substantial release of GH during the course of acute stress (30). The excess GH exerts direct lipolytic, insulin-antagonizing and immune stimulatory actions, whereas the indirect IGF-I mediated somatotrophic effects are attenuated. This explanation is plausible in that such changes would prioritise essential substrates such as glucose, free fatty acids and amino acids (glutamine) for survival rather than anabolism, and can thus be viewed as being adaptive and beneficial.

In prolonged critical illness, the changes observed in the GH/IGF-I axis are different. The pattern of GH becomes very chaotic, the amount of GH released in pulses being much reduced compared with that seen in the acute phase (Figure 1C) (31). Moreover, although the concentration of the non-pulsatile fraction is still somewhat elevated and the number of very small pulses is still high, the mean nocturnal GH levels are hardly elevated compared

with that of healthy, non-stressed condition, and is substantially lower than the levels seen in the acute period (31). The pulsatile component of GH secretion is specifically and positively correlated with the circulating levels of IGF-I (32). In other words, the more the pulsatile GH secretion is suppressed, the lower the levels of IGF-I become. These findings suggest that a relative hypsomatotropism and a lack of pulsatile GH secretion participates in the pathogenesis of "wasting syndrome" distinctive to the chronic period of critical illness. It has been shown that men appear to lose more with respect to GH pulsatility than women and therefore, have much lower IGF-I levels compared with their female counterparts (3).

The GH response to GH-releasing peptide-2 is amplified in chronic intensive care unit patients, and this response is several-fold higher than that seen after GH-releasing hormone administration (Figure 2)(31). Co-administration of GH-releasing hormone and GH-releasing peptide-2 substantially amplifies the pulsatile GH secretion, even more than seen after GH-releasing peptide-2 alone (Figure 2) (31). The high GH response to secretagogues excludes a lack of pituitary capacity to synthesise. It has been suggested that reduced somatostatin availability and endogenous GH-releasing peptide like ligands might explain the increased frequency



**Figure 2.** Nocturnal serum growth hormone (GH) profiles in the chronic phase of critical illness, illustrating the effects of a continuous infusion of placebo, GHRH, GHRP-2 and combined GHRH+GHRP-2. (Adapted from reference 31)

GHRH: growth hormone releasing hormone; GHRP-2: growth hormone releasing peptide-2.

of spontaneous GH secretory burst with diminished amplitudes (30).

### *Studies investigating the effects of GH and IGF-1 in critical illness*

A large number of studies have addressed the effect of GH administration on protein metabolism in a variety of clinical states (33-38). The controlled studies are summarized in Table 3. As seen in Table 3, GH has improved nitrogen balance and increased protein synthesis in most instances, particularly when used in conjunction with nutritional support. Similarly, IGF-1 treatment has improved nitrogen balance in AIDS patients, although the improvement was confined to the first 10 days of administration. The major drawback in the studies cited above was, however, that the number of the subjects included was quite small. Moreover, the administration of GH therapy has not always begun in the acute period of the insult, and none of these studies has addressed the impact of GH administration on mortality as an end-point.

Recently, a multi-center European study which has addressed the morbidity and mortality in critically ill patients in intensive care unit (ICU) was published (39). In this study, there were two separate arms: 1) The Finnish trial and 2) international multi-center trial. Both of the study arms

were conducted with virtually identical protocols. A total of 532 ICU patients were included. Four diagnostic categories were eligible, including trauma, respiratory failure, post-cardiac surgery or abdominal surgery. Entry criteria included an initial residence in ICU of 5-7 days and an anticipated further ICU stay of at least 10 days. The patients were randomized to receive either 16-24 U daily GH or placebo beginning at the acute phase of the insult. Treatment was maintained up to a maximum of 21 days. In both arms, it has been observed that GH treatment was associated with a significant increase in death rate (relative risks 1.9 and 2.4 in the Finnish and international groups, respectively). In addition, morbidity was increased, a longer duration of ICU stay and a greater dependency on mechanical ventilation being recorded in the GH groups. The excess mortality was mainly associated with multi-organ dysfunction. Furthermore, GH treatment caused increased requirements for insulin dosage in patients who developed hyperglycemia. The excess mortality was independent from the severity of the underlying illness, patient demography and illness category.

The exact mechanisms underlying the increased mortality are ill-defined. Based on the known effects of GH administration, some explanations may be introduced (40). One of the candidates is that GH administration might have worsened sepsis

**Table 3.** Summary of controlled clinical trials about the effects of growth hormone administration on protein metabolism in critically ill patients.

Patient category	Effect	P value (versus placebo)	Reference
Major gastrointestinal surgery	Increased nitrogen balance, increased fat oxidation	<0.01	33
Severe burns	Increased nitrogen balance/increased whole body protein synthesis	<0.03	34
Trauma	Increased nitrogen balance/increased whole body protein synthesis	<0.001	35
AIDS	Increased LBM (unsustained)	NS	36
Postsurgical sepsis	Increased nitrogen retention	<0.001	37
Septic shock (+TPN)	Increased nitrogen balance	<0.05	38

LBM: lean body mass; NS: Not significant; TPN: total parenteral nutrition

or systemic immune response syndrome due to induction of pro-inflammatory cytokines. Secondly, prevention of the mobilization of aminoacids might have resulted in a lower availability of substrate for wound healing and the maintenance of gut mucosal integrity, leading to bacterial translocation and consequent multi-organ dysfunction. A deterioration in acid-base balance related to increased lipolysis with ketone body production and cardio-respiratory compromise as a result of volume overload related to the anti-natriuretic effect of GH might also have a causal role. However, more work is required to elucidate which of these mechanisms are really operative in this condition.

Taking into account the data presented in the aforementioned studies, the Growth Hormone Research Society has recently recommended that pharmacological GH treatment should not be initiated during the acute phase of critical illness and that the cessation of GH treatment should be considered in critically ill subjects (41). It remains unclear, however, that subgroups of ill patients may benefit from lower doses of GH, and equally how nutritional support as an adjunct to anabolic treatments would be best provided. In a number of studies, glutamine has been provided in this regard. This aminoacid has been shown to have independent benefits on protein metabolism and to be influenced by GH treatment. It remains plausible that anabolic therapy provided in conjunction with appropriate nutritional support would be of benefit in appropriately selected groups particularly in the chronic phase of critical illness.

## References

1. Van den Berghe G. Novel insights into the neuro-endocrinology of critical illness. *Eur J Endocrinol* **143**: 1-13, 2000.
2. Vermes I and Beishuizen A. The hypothalamic-pituitary-adrenal response to critical illness. *Best Pract Res Clin Endocrinol Metab* **15**: 495-511, 2001.
3. Van den Berghe G, Baxter RC, Weekers F, Wouters P, Bowers CY and Veldhuis JD. A paradoxical gender dissociation within the growth hormone/insulin-like growth factor I axis during protracted critical illness. *J Clin Endocrinol Metab* **85**: 183-192, 2000.
4. Owen OE. Metabolism during catabolic states of starvation, diabetes and trauma in humans. Diabetes mellitus and obesity. 1st edition, (editors: Brodoff B. Bleicher S), Baltimore, 172-183, 1982.
5. Ewans T. Hemodynamic and metabolic therapy in critically ill patients, editorial. *N Engl J Med* **345**: 1417-1418, 2001.
6. Deutschman CS, Andrejko KM, Haber BA, Bellin L, Elenko E, Harrison R, Taub R. Sepsis-induced depression of rat glucose-6-phosphatase gene expression and activity *Am J Physiol* **273**: 1709-1718, 1999.
7. Wolfe RR. Substrate utilization/insulin resistance in sepsis/trauma. *Baillieres Clin Endocrinol Metab* **11**: 645-657, 1997.
8. Yang J, Dong LW, Tang C, Liu MS. Transcriptional and posttranscriptional regulation of beta(2)-adrenergic receptor gene in rat liver during sepsis. *Am J Physiol* **277**: R132-139, 1999.
9. Hsu C, Jao HC, Yang SL, Hsu HK, Liu MS. Inactivation of protein kinase C in rat liver during late hypoglycemic phase of sepsis. *Mol Cell Biochem* **181**: 181-189, 1998.
10. Tang C, Yang J, Liu MS. Progressive internalization of beta-adrenoceptors in the rat liver during different phases of sepsis. *Biochim Biophys Acta* **30**: 225-233, 1998.
11. Rattarasarn C. Hypoglycemia in sepsis: risk factors and clinical characteristics. *J Med Assoc Tha* **80**: 760-766, 1997.
12. Haviv YS, Sharkia M, Safadi R. Hypoglycemia in patients with renal failure. *Ren Fail* **22**: 219-223, 2000.
13. Shilo S, Berezovsky S, Friedlander Y, Sonnenblick M. Hypoglycemia in hospitalized nondiabetic older patients. *J Am Geriatr Soc* **46**: 978-982, 1998.
14. Beishuizen A, Thijs LG, Haanen C and Vermes I. Macrophage migration inhibitory factor and hypothalamo-pituitary-adrenal function during critical illness. *J Clin Endocrinol Metab* **86**: 2811-2816, 2001.

15. Barquist E and Kirton O. Adrenal insufficiency in the surgical intensive care unit patient. *J Trauma* **42**: 27-31, 1997.
16. Lamberts SWJ, Bruining HA and de Jong FH. Corticosteroid therapy in severe illness. *N Engl J Med* **337**: 1285-1292, 1997.
17. Beishuizen A and Thijs LG. Relative adrenal failure in intensive care: an identifiable problem requiring treatment? *Best Pract Res Clin Endocrinol Metab* **15**: 513-531, 2001.
18. Shenker Y and Skatrud JB. Adrenal insufficiency in critically ill patients. *Am J Resp Crit Care Med* **163**: 1520-1523, 2001.
19. Lefering R and Neugebauer EAM. Steroid controversy in sepsis and septic shock: a meta-analysis. *Crit Care Med* **23**: 1294-1303, 1995.
20. Cronin L, Cook DJ, Carlet J. Corticosteroid treatment for sepsis: a critical appraisal and meta-analysis of the literature. *Crit Care Med* **23**: 1430-1439, 1995.
21. Martinez FJ, Lash WL. Endocrinologic and metabolic complications in the intensive care unit. *Clin Chest Med* **20**: 401-421, 1999.
22. Fliers E, Alkemade A, Wiersinga WM. The hypothalamic-pituitary-thyroid axis in critical illness. *Best Pract Res Clin Endocrinol Metab* **15**: 453-464, 2001.
23. Vasa FR, Molitch ME. Endocrine problems in the chronically critically ill patient. *Clin Chest Med* **22**: 193-208, 2001.
24. Gardner DF, Kaplan MM, Stanley CA. Effect of tri-iodothyronine replacement on the metabolic and pituitary responses to starvation. *N Engl J Med* **300**: 579-584, 1979.
25. Rolih CA, Ober PK. The endocrine response to critical illness. *Med Clin North Am* **79**: 211-224, 1995.
26. Spencer C, Eigen A, Shen D, Duda M, Qualls S, Weiss S, Nicoloff J. Specificity of sensitive assays of thyrotropin (TSH) used to screen for thyroid disease in hospitalized patients. *Clin Chem* **33**: 1391-1396, 1987.
27. Cohen KL, Swigar ME. Thyroid function screening in psychiatric patients. *JAMA* **242**: 254-257, 1979.
28. Burman KD, Wartofsky L. Thyroid function in the intensive care unit setting. *Crit Care Clin* **17**: 43-58, 2001.
29. Ligtenberg JJM, Girbes ARJ, Beentjes JAM, Tulleken JE, van der Werf TS, Zijlstra JG. Hormones in the critically ill patient: to intervene or not to intervene? *Intensive Care Med* **27**: 1567-1577, 2001.
30. Van Den Berghe G. The neuroendocrine response to stress is a dynamic process. *Best Pract Res Clin Endocrinol Metab* **15**: 405-419, 2001.
31. Van den Berghe G, de Zegher F, Bouillon R. Acute and prolonged critical illness as different neuroendocrine paradigms. *J Clin Endocrinol Metab* **83**: 1827-1834, 1998.
32. Van den Berghe G, Wouters P, Weekers F, Mohan S, Baxter RC, Veldhuis JD, Bowers CY, Bouillon R. Reactivation of pituitary hormone release and metabolic improvement by infusion of growth hormone releasing peptide and thyrotropin releasing hormone in patients with protracted critical illness. *J Clin Endocrinol Metab* **84**: 1311-1323, 1999.
33. Ward HC, Halliday D, Sim AJW. Protein and energy metabolism with biosynthetic human growth hormone after gastrointestinal surgery. *Ann Surg* **206**: 56-61, 1987.
34. Gore DC, Honeycutt D, Jahoor F, Wolfe RR, Herndon DN. Effect of exogenous growth hormone on whole body and isolated limb protein kinetics in burned patients. *Arch Surg* **126**: 38-43, 1991.
35. Jeevanandam M, Ali MR, Holaday NJ, Petersen SR. Adjuvant recombinant human growth hormone normalises plasma aminoacids in parenterally fed trauma patients. *J Parenter Enteral Nutr* **19**: 137-144, 1995.
36. Ellis KJ, Lee PD, Pivarnik JM, Bukar JG, Gesundheit N. Changes in body composition of human immunodeficiency virus-infected males receiving insulin-like growth factor I and growth hormone. *J Clin Endocrinol Metab* **81**: 3033-3038, 1996.
37. Koea JB, Brier BH, Douglas RG, Gluckman PP, Shaw JH. Anabolic and cardiovascular effects of human growth hormone in surgical patients with sepsis. *Br J Surg* **83**: 196-202, 1996.
38. Voerman HJ, van Schijndel RJ, Groeneveld AB, de Boer H, Nauta JP, van der Veen EA, Thijs LG. Effects of human recombinant growth hormone in patients with severe sepsis. *Ann Surg* **216**: 648-655, 1992.
39. Takala J, Ruokonen E, Webster NR, Nielsen MS, Zandstra DF, Vundelimckx G, Hinds CJ. Increased mortality associated with growth hormone treatment in critically ill adults. *N Engl J Med* **341**: 785-792, 1999.
40. Carroll PV. Treatment with growth hormone and insulin-like growth factor-I in critical illness. *Best Pract Res Clin Endocrinol Metab* **15**: 435-451, 2001.
41. Critical evaluation of the safety of recombinant human growth hormone administration: statement from the Growth Hormone Research Society. *J Clin Endocrinol Metab* **86**: 1868-1870, 2001.