13 Common Endocrine Abnormalities in ICU

Abstract: With sophisticated mechanical devices and monitoring systems, mortality and morbidity in the critically ill patients in the intensive care units (ICU) has been improving steadily. Critical illness is characterized by dysregulation of the endocrine glands resulting in metabolic arrhythmias, which must be recognized by the intensivist. It is particularly important to differentiate the probably adaptive endocrine profiles seen during the initial phase of critical illness, from those in the prolonged phase of critical illness, which can result in prolonged convalescence. In the acute phase of critical illness, growth hormone (GH) levels are high with elevated peaks and pulses; in contrast, in the prolonged phase, these are low: this low GH level can result in wasting. A low T3 can occur in acute phase in association with normal or low T4 and TSH. On the other hand, in prolonged phase, all these levels are low owing to low TRH surge from pituitary. In the acute phase of critical illness there may be increased cortisol levels with increased CRH and ACTH drive. In the prolonged phase of critical illness also, there is elevation of cortisol, but from the non-ACTH pathway. With regard to the gonadal axis, low testosterone levels associated with slightly elevated LH is the usual pattern observed initially. But during the prolonged phase both testosterone and LH are low. Hyperglycemia seen in critically ill patients is associated with poor outcome, even if it is of a moderate degree only. During the acute phase of critical illness, endocrine adaptations are directed towards reducing energy and substrate consumption and directing the substrate for vital tissues. As such these alterations are beneficial and need not be pharmacologically interfered with. In the prolonged phase of critical illness there is sustained catabolism with delay in healing and there may be a case for judicious therapy.

INTRODUCTION

One of the major advances in medical therapeutics during the last two decades has been the establishment of high tech ICU to manage the critically ill patients with sophisticated mechanical devices, monitoring systems and newer drugs. This has saved the lives of many critically ill patients, with most of the patients being discharged from ICUs within a few days, but also created a state of prolonged critical illness, with altered metabolic profile. At least 30% of the patients, however, enter a chronic phase of critical illness during which they remain dependent on vital organ support and face a more than 20% risk for death. This high mortality usually is ascribed to nonresolving failure of multiple organ systems and vulnerability to infectious complications, rather than determined by the type or severity of the initial disease for which they were admitted to an ICU. Critical illness is characterized by a uniform dysregulation of all hypothalamic– anterior pituitary axis, long known to contribute to the high risk for morbidity and mortality. The endocrine response to critical illness vary in two phases of critical illness. In the acute phase the pituitary is secreting actively, but the target organs are resistant and most of the peripheral hormones are low.[1] These adaptations may be beneficial in the struggle for short term survival. In the prolonged phase there is uniform suppression of neuroendocrine axis which may be responsible for low target hormones. These may not be beneficial as they may contribute to the wasting syndrome of prolonged critical illness.

CHANGES IN GH/IGF-1 AXIS

During the first few hours to days after an acute insult, the GH profile changes dramatically and a state of peripheral GH resistance develops, triggered by cytokines like TNFα and Interleukin 6.The amount of circulating GH increases, with high peaks, more pulses frequency and elevated interpulse concentrations, but serum IGF-1, IGFBP-3 and ALS decrease.[2] When recovery does not occur in a few days, different GH secretion pattern sets in. The GH pulses become suppressed,

the nonpulsatile fraction becomes mildly elevated, levels of IGF-I, IGFBP-3, and ALS are even lower in prolonged critically ill patients, due to the absence of GH pulses. GH resistance of acute illness - reversed at least partially in the chronic disease of critical illness. The GH deficiency from lack of GH pulses contributes to the "Wasting Syndrome" associated with prolonged critical illness.

CHANGES IN THYROID AXIS

The acute phase of the critical illness is characterized by low T3 levels and elevated rT3, because of the altered peripheral conversion of T4. T4 may be normal or briefly elevated, but subsequently normalize, but in those who are severely ill it is always low. TSH may be elevated briefly, or within normal range in acute illness, if the thyrotropin profile is studied, the nocturnal TSH surge is absent.[3] The low T3 level persists even after normalization of TSH levels and this state may be referred as " the low T3 syndrome". The cytokines may be responsible for the low T3 syndrome as they are capable of mimicking the acute stress response of the thyroid axis. The other causes of low T3 syndrome may be due to the low levels of thyroid hormone binding proteins and the inhibition of hormone binding, transport and metabolism by the elevated levels of free fatty acids and bilirubin associated with critical illness. Low T4 and T3 level implies a poor prognosis during the initial 24 hrs.

In the chronic phase of critical illness, there is absent nocturnal thyrotropin surge, with reduced pulsatile thyrotropin secretion, resulting in low T4 and T3 levels. The decline in serum T3 correlates positively with the diminished pulsatile release of thyrotropin. The reduced synthesis and release of thyrotropin may be due to reduced TRH induced stimulation of TSH and elevated somatostatin tone. Reduced TRH gene expression in the hypothalamus has been documented in chronically ill patients who have died, which confirms the central origin of the suppressed thyroid axis. Reduced levels of endogenous GH secretagogues may also be involved in the low pulsatility of thyrotropin secretion, as the infusion of TRH with GHRP normalizes the thyrotropin pulsatility.

In the chronic phase of illness there is low T3 levels due to the disturbance of peripheral metabolism of thyroid hormones. There is reduced activity of type 1 deiodinase, the enzyme mediating peripheral conversion of T4 to T3, and there is activation of type 3 deiodinase enzyme, responsible for the conversion of T4 to inactive rT3.[4] Experimental studies have shown that the activity of type 1 deiodinase is under thyroid axis whereas type 3 deiodinase activity is under the joint control of the somatotrope and thyroid axis. There is also evidence that the activity of thyroid hormone receptors are also altered in critical illness, possible upregulated sensitivity to low circulating levels of T3.

CHANGES IN ADRENAL AXIS

In normal healthy humans, cortisol is secreted according to a diurnal pattern and exerts a negative feedback control on hypothalamic corticotropin releasing hormone (CRH) and pituitary corticotropin (ACTH). More than 90% of circulating cortisol is in the bound state, the predominant binding protein is corticosteroid binding globulin (CBG). In acute phase of critical illness, cortisol level is increased due to elevated CRH and ACTH secretion, and the diurnal variation in cortisol secretion is lost.[5] It may be attributed to the resistance or inhibition of negative feedback by cortisol. The CBG levels are decreased, in part due to the elastase induced cleavage, so more free cortisol is available to the tissues. The elevated cytokines also increase the production of cortisol and alter the receptor affinity and number. Elevated cortisol response is essential for survival because hypercortisolism helps to provide energy by shifting carbohydrate, protein and fat metabolism. It suppresses the excessive inflammatory response and improves hemodynamic status by fluid retention and sensitizing vasopressor response to catecholamines. Both high and low levels of cortisol are associated with high mortality. High cortisol levels reflect

more severe illness and low levels points to an inability to respond to stress substantially, usually labeled as "relative adrenal insufficiency". Cortisol levels are elevated in chronic phase of critical illness from non-corticotropin mediated pathways and the ACTH levels are decreased in prolonged phase. Cortisol levels slowly decrease, reaching normal levels only in the recovery phase. CBG levels also start recovering during this time. Whether the elevated cortisol levels in the chronic phase of critical illness are beneficial or not, is still uncertain.

CHANGES IN GONADAL AND LACTOTROPIC AXIS

In early sepsis, dehydroepiandrosterones (DHEAS) levels are low. Nonsurvivors have lower DHEAS levels as compared with survivors due to exhausted adrenal reserve.

Levels decline further with late sepsis in survivors and nonsurvivors despite preservation of cortisol secretion. In contrast, the non sulfated androgen precursor, DHEA, increases with early sepsis and normalizes in late sepsis only in survivors. Acute physical stress, such as surgery or myocardial infarction, brings along an immediate fall in the serum levels of testosterone, even though leutinising hormone (LH) levels are elevated.[6] This suggests an immediate suppression of androgen production Leydig's cells, which may be viewed, at least in the short term, as an attempt to reduce energy consumption and conserve substrates for more vital functions. Prolactin (PRL) levels rise in response to acute physical or psychological stress. More dramatic changes develop within the male gonadal axis with prolongation of the disease, and hypogonadotropism ensues. The circulating levels of testosterone becomes, extremely low and often even are undetectable, in the presence of suppressed mean LH concentrations and pulsatile LH release. Total estradiol levels also are relatively low but the level of bioavailable estradiol probably is maintained in view of the simultaneous decrease in sex-hormone–binding globulin. The pulsatile fraction of PRL release becomes suppressed in patients in the prolonged phase of critical illness. It is unclear whether or not the blunted PRL secretion contributes to the immune suppression or increased susceptibility to infection associated with prolonged critical illness.

HYPERGLYCEMIA IN CRITICALLY ILL

Even a modest degree of hyperglycemia was associated with a substantial increase in the hospital mortality. Hyperglycemia was associated with a high risk of death after stroke and myocardial infarction, and poor functional recovery in those who survived. Stress hyperglycemia is caused by cytokine influences, oxidative stress, stress signaling pathways, defective insulin signaling, insulin resistance, enhanced glycogenolysis and increased hepatic gluconeogenesis. In critically ill patient, the exercise induced uptake of glucose to the skeletal muscle is totally absent and the insulin dependant glucose transport by GLUT-4 is reduced. But the action of insulin nondependant glucose transporters are increased, in fact GLUT-1, 2 and 3 are over expressed in critically ill by the various cytokines, produced by inflammatory process.[7] This results in glucose overload in CNS, hepatocytes, renal cells, immune cells and produces mitochondrial dysfunction and associated bioenergic failure. Intensive insulin therapy prevents these by maintaining normoglycemia, and protecting the mitochondria. Intensive Insulin therapy prevents hyper triglyceridemia, raises HDL and reduces FFA levels. Insulin attenuates the catabolic syndrome of prolonged illness, stimulate muscle protein synthesis and attenuates protein break down.[8] Insulin lowered serum CRP and mannose-binding leptin levels. Insulin lowers pro-inflammatory cytokines and stimulates anti-inflammatory cascade. Insulin improves myocardial function. Insulin prevents endothelial dysfunction and hypercoagulation state in critically ill.

The effect of tightly, controlled hyperglycemia associated with critical illness in reducing mortality , in ICU settings was shown by the landmark study of Van den Burg et al in 2001. This study has convinced the medical fraternity that the hyperglycemia seen in critical illness in the modern ICU era requires aggressive treatment with insulin infusion. Maintenance of

normoglycemia with a simple metabolic intervention by insulin infusion, prevents morbidity and improves the survival in critically ill patients.[9]

DYSLIPIDEMIA IN CRITICAL ILLNESS

Hypocholesterolemia has been reported in patients with sepsis and in critically ill and injured patients. In patients who have severe sepsis, total and HDL cholesterol levels fall rapidly and reach 50% of the recovery levels by day 3, followed by a slow increase over the next 28 days. The degree of hypocholestrolemia correlates with severity, morbidity and mortality. Low serum cholesterol levels on admission to a surgical ICU were associated with higher APACHE III, longer length of stay, and higher mortality.

BODY WATER HOMEOSTASIS IN CRITICAL ILLNESS

Disorders of body water homeostasis is commonly seen in ICU settings, and this can be classified as hypoosmolar disorders, in which there is an excess body water relative to body solutes and hyperosmolar disorders in which there is deficit of body water relatives to solutes. Both these disorders, as well as over enthusiastic correction of them, can lead to considerable morbidity and mortality. Prompt identification and appropriate treatment requires a good basic knowledge of the physiology. Sodium metabolism is predominately regulated by renin-angiotensin-aldosterone system (RAAS), while water metabolism is controlled by arginine vasopressin (AVP). Dysregulated AVP secretion is often the cause of impaired water regulation in critical illness, where so many different factors affect AVP secretion, like norepinephrine, dopamine, histamine etc.[10] Hyponatremia is the commonest electrolyte abnormality seen in ICU settings and in most instances it is associated with hypotonicity, although isotonic and hypertonic hyponatremia are also seen.

THERAPEUTIC IMPLICATIONS

During the acute phase of critical illness, the endocrine adaptations are directed towards reducing energy and substrate consumptions, driving the release of substrates for vital tissues, postponing costly anabolism and modulating immune responses for improved survival. These changes are beneficial for the host and, as such, there is no supportive evidence to intervene. In the chronic phase of the critical illness there is sustained catabolism, despite feeding, results in substantial loss of lean body mass, and often with fatty infiltration of vital organs with delay in recovery. Therefore, therapeutic interventions to correct these abnormalities, may be helpful to improve survival. Intensive insulin therapy, for correcting the stress hyperglycemia of the critically ill patient, is one well accepted therapeutic intervention.

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MULTIPLE CHOICE QUESTIONS

1. **Regarding the prolonged phase of critical illness, which is correct ?**
   A. About 50% of patients admitted to the ICUs go into prolonged phase
   B. There is uniform suppression of neuro endocrine axis
   C. The endocrine changes occurring are beneficial for the survival
   D. Growth hormone resistance is responsible for the wasting syndrome of prolonged illness
   E. All of the above statements are correct

2. **Thyroid hormone changes in critical illness include:**
   A. Low T3, low T4 and elevated TSH is the common pattern
   B. The nocturnal TSH surge is normal or elevated
   C. The thyroid hormone binding proteins are elevated in acute phase
   D. The cytokines and elevated FFAs are responsible for low T3 syndrome
   E. Low T3 and T4 levels implies a good prognosis

3. **Thyroid axis in the prolonged phase of critical illness is characterized by:**
   A. Elevated T4 with low T3 and normal TSH levels
   B. The action of Type-3 deiodinase is reduced .
   C. There is reduced TRH gene expression in hypothalamus
   D. Decreased somatostatin tone may be contributing to low TSH
   E. There is decrease in circulating rT3 in the prolonged phase

4. **Regarding the Adrenal axis in critically ill patients which is correct?**
   A. The diurnal variation of cortisol secretion is maintained
   B. In the acute phase there is elevation of cortisol with decrease in ACTH
   C. The level of CBG is increased due to elastase induced cleavage
   D. There is elevation of both cortisol and ACTH in the prolonged phase of critical illness
   E. Both high and low levels of cortisol are associated with high mortality

5. **Regarding Gonadal axis in critical illness which is correct?**
   A. Nonsurvivors of critical illness have higher DHEAs
   B. Serum testosterone and LH are elevated in acute phase
   C. Prolactin levels rise in response to stress in acute phase
   D. During the prolonged phase there is elevation of testosterone with feedback decrease in LH
   E. There is increase in pulsatile secretion of prolactin in prolonged phase

6. **Regarding stress induced hyperglycemia which statement is correct?**
   A. Moderate hyperglycemia in critically ill patient is a protective phenomenon
   B. Stress hyperglycemia is always due to insulin resistance
   C. GLUT-1, 2 and 3 activity is reduced in critically ill patients
   D. Intensive insulin therapy prevents hypertriglyceridemia, reduces FFA level and lowers CRP levels
   E. Tight blood sugars to less than 110 mg%, has shown to increase mortality in ICU patients

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1. B 2. D 3. C 4. E 5. C 6. D