Endocrine and Metabolic Changes During Sepsis: An Update

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KEYWORDS

- Hyperglycemia • Adrenal insufficiency • Thyroid dysfunction • Glucocorticoids
- Insulin • Hypoglycemia

KEY POINTS

- Strict glycemic control need not be stringent.
- Mineralocorticoid use does not modify outcome.
- Thyroid dysfunction does not require treatment.
- Fluid and electrolyte abnormalities must be corrected.
- Aggressive management of sepsis with appropriate and judicious use of antibiotics remains a top priority.
- Use of glucocorticoids in persistently hypotensive and vasopressin-dependent patients appears to be beneficial.

INTRODUCTION

Stress of critical illness/sepsis brings about several and serious changes in hormonal concentrations and metabolism that become difficult to interpret and manage. Some of the changes are adaptive to accommodate stress and protect tissues from catabolic breakdown. Others are the consequence of the impact of factors such as toxins and cytokines released during stress related to infection/sepsis. Alternatively, changes may be the consequence of treatments such as antifungal therapy, particularly in immunocompromised patients.

Sepsis is one of the most stressful situations encountered by humans and animals alike. Sepsis-related stress is not only acute in onset but also is sustained until the incriminating source has been eliminated. Stress-related endocrine/metabolic changes reflect this temporal profile. Ordinarily responses may be choreographed based on degree of stress, and if the stress remains unabated a metabolic chaos

may set in, placing a patient in harm's way. Stress comprises a set of complex biological perturbations imposed by aggression on the body's defense systems. Two systems, the endocrine and autonomic nervous systems, provide mechanisms to provide rapid adaptation thus maintaining homeostasis. This concept has been further expanded by the introduction of the term allostasis by Sterling and Eyer[1] in 1988. In attempting to explain how the cardiovascular system adjusts to the changing state of body, this paradigm can be easily applied to other concurrent systems undergoing resetting such as the hypothalamo-pituitary-adrenal (HPA) axis and the hypothalamo-pituitary-thyroid (HPT) axis. Humans try to cope with stress through modulation of the autonomic nervous system, neuroendocrine axis, and the metabolic and immune systems. When stress abates rapidly, these systems come into quick equilibration with the prestress state. However, unrelenting stress leads to decompensation and breakdown of these systems, with development of a pathologic illness. When there is repeated stress, a certain degree of wear and tear is to be expected. This phenomenon is now referred to as allostatic load, resulting from repeated cycles of allostasis.

In situations such as sepsis, the rapidity with which an organism must respond depends on genetic, developmental, and experiential factors. This aspect would explain some of the differences often reported in cohorts of people for whom such factors may not have been considered. However, in general most patients exhibit a predictable response during acute stress of sepsis. It must be noted that activation of neuroendocrine and autonomic nervous system responses is an energy-consuming process, and the robustness of a response is determined by energy stores and availability of energy (nutrients) to tissues facing the brunt of stress. Thus in patients in a dysglycemic state, such as diabetes mellitus, tissues may still be starving in the face of concurrent insulinopenia or insulin resistance even though there might be surfeit of energy (glucose) in circulation.

Specific Neuroendocrine and Metabolic Perturbations
1. Activation and depression of HPA axis
2. Biphasic vasopressin secretory response
3. Hyperglycemia/dysglycemia
4. Depression of pituitary-thyroid
5. Depression of gonadotropins and hypogonadism
6. Disorders of Na/K balance, hypophosphatemia, hypocalcaemia, and hypomagnesaemia.

PITUITARY-ADRENAL AXIS IN SEPSIS

During infection several factors collude together; for example, viral and bacterial products such as bacterial lipopolysaccharides (LPS) cause release of cytokines from immune cells that then travel to the brain. In addition, LPS may induce cytokines such as interleukin (IL)-1 within the neurons in the brain. Cytokines can freely diffuse into pituitary because of the absence of the blood-brain barrier. Several cytokines are produced by glial cells as well as IL-1, IL-2, and IL-6.[2] There is evidence for expression of anti-inflammatory mediators such as IL-1 receptor antagonist, IL-10, and IL-13 in pituitary and pineal glands. These cytokines possibly antagonize the effects of proinflammatory mediators on neurohormones.[3] IL-2, by stimulation of cholinergic neurons, leads to activation of nitric oxide (NO) synthase and release of NO. NO diffuses into corticotropin-releasing hormone (CRH)-secreting neurons, and releases CRH.[4] Cytokines are capable of directly acting on the pituitary to stimulate synthesis and release of corticotropin (formerly adrenocorticotropic hormone).[5] The neural axis

independently also participates in the activation of CRH release via interaction with cholinergic interneurons in the parvocellular nucleus.[6] In general, the magnitude of HPA-axis activation is proportional to the severity of stress. Rising cortisol levels have a significant impact on immunomodulation and preservation of vascular reactivity to circulating catecholamines. Cortisol is important in maintaining vascular reactivity to norepinephrine, and is important in preserving perfusion to vital organs. As the stress of sepsis progresses there is blunting of HPA activation, leading to transient or permanent adrenal insufficiency in critically ill subjects.[7]

During critical illnesses such as sepsis, adrenal hypofunction can result from overwhelming destruction of adrenal glands themselves (bleeding/ischemic necrosis or Waterhouse-Friderichsen syndrome). Often the presenting signs are hemodynamic instability and persistent hypotension, and a petechial/purpuric rash. This syndrome is complicated by hypoglycemia, hyponatremia, and hyperkalemia. It is a medical emergency and needs to be treated urgently with antibiotics and hydrocortisone.

In less severe forms of HPA-axis infection pattern, activation followed by hypocortisolemia may be seen. In all patients with sepsis-persistent hypotension, hypoglycemia, hyponatremia, and hyperkalemia should be treated as adrenal insufficiency unless proved otherwise.

Much controversy surrounds what constitutes biochemical hypoadrenalism. This debate has also brought attention to the so-called relative or functional hypoadrenalism of critical illness, usually unaccompanied by any structural insult to the HPA axis. Theoretically it is possible that circulating cytokines and other inflammatory products may lead to suppression of corticotropin production/release and consequent hypocortisolemia. Alternatively, some mediators may lead to a state of peripheral glucocorticoid resistance.[7]

Ordinarily, stress imposed by sepsis itself should serve the function of a dynamic test to assess adrenal response. However, objections have been raised based on total cortisol measurement being less reliable than measurement of free cortisol.[8] In a later study it was found that even though free cortisol could be used to diagnose adrenal insufficiency in sepsis, free cortisol was not superior to total cortisol levels despite theoretical advantages.[9] The argument put forth to use free plasma cortisol is based on observed reductions in plasma albumin and cortisol-binding globulin (CBG) during critical illness (these normally bind 20% and 70% of cortisol, respectively). Another difficulty with diagnosing adrenal insufficiency arises from the lack of uniform diagnostic cutoffs for plasma cortisol levels.

Interest in using glucocorticoids in infections in not new, actually dating back to 1940 when Perla and Marmorston[10] demonstrated beneficial effects of such therapy in infections such as malaria and pneumonia. The use of steroids has seen ups and downs. In a review of glucocorticoid use at supraphysiologic doses in unselected patients with sepsis, no favorable effect on morbidity and mortality was seen.[11] More recently, however, using the cosyntropin stimulation test (CST) in patients with septic shock, relative adrenal insufficiency has been better defined as lack of incremental increase in plasma cortisol of less than 9 μg/dL following standard high-dose CST.[12] In a study of 300 patients with septic shock, use of hydrocortisone (50 mg intravenously every 6 hours) plus fludrocortisones (50 μg by mouth daily) for 7 days, a significant reduction in mortality and duration of vasopressin therapy was demonstrated.[13] The best evidence from which to draw definitive conclusions is still elusive. In a more recent randomized trial in adult patients with septic shock, addition of fludrocortisone did not result in statistically significant improvement in in-hospital mortality. Furthermore, use of hydrocortisone at a dose of 50 mg every 6 hours was associated with higher basal blood glucose levels.[14] It can, however, be inferred

that corticosteroid therapy will most likely benefit patients in severe septic shock (blood pressure <90 mm Hg, no response to fluid resuscitation, and vasopressin administration). It should preferably be started within 8 hours of the onset of shock. Impact of drugs often used in seriously ill patients (etomidate, ketoconazole and phenytoin) must lead one to interpret dynamic testing with caution because of the impact of such drugs on glucocorticoid synthesis. Commonly used laboratory tests may be unreliable because of cross-reactivity with other steroids.

Finally, adrenal dysfunction in septic shock may represent a sick euadrenal state rather than true adrenocortical insufficiency, and should be treated as such.[15] It is quite possible that end-organ sensitivity to corticotropin and glucocorticoids itself may be altered to protect against tissue wasting under catabolic states. This position is supported by the evidence of the glucocorticoid receptor being a target for toxins related to bacterial infection.[16]

IMPACT OF INFECTION/SEPSIS ON OTHER PITUITARY HORMONES

- The key impact of sepsis is on blocking release of luteinizing hormone–releasing hormone, thereby affecting release of luteinizing hormone; this may in part be accomplished by stimulation of γ-aminobutyric acid neurons and β-endorphins.[17–19]
- Growth hormone levels are initially elevated, with concurrent peripheral resistance leading to low levels of insulin-like growth factor 1. However, this state transitions then to a state of low growth hormone, depending on the duration of critical illness.[20,21]
- Initially the prolactin levels are increased, and these drop off as stress enters the chronic phase.[22]
- Vasopressin levels are almost always increased at the initial stage of septic shock, and decline thereafter.[23]

Implications of these findings for possible targets for therapy need to be carefully considered. When growth hormone therapy was instituted in critically ill adult patients to decrease catabolism, increased mortality was seen.[24] Despite observed low levels of vasopressin, no cases of sepsis-related diabetes insipidus are reported in adults. Rarely cases of diabetes insipidus (central) have been reported in neonates with sepsis.[25]

SEPSIS AND GLUCOSE METABOLISM

During infection and critical illness hyperglycemia is a common occurrence, and it has generated much heated debate. Hyperglycemia is seen even in those not previously diagnosed to have diabetes. Hyperglycemia is indeed one of the most striking metabolic derangements seen with sepsis, and has been independently associated with increased mortality in patients with undiagnosed diabetes.[26] Critically ill patients with known diabetes fare better than those who present with hyperglycemia without known diabetes. This phenomenon, referred to as the diabetes paradox, remains of heightened interest.[27] Given the understanding that sepsis is associated with activation of overwhelming production of both proinflammatory and anti-inflammatory mediators, a serious impact on glucose stability is not unexpected.[28] Hyperglycemia is largely a consequence of lipolysis and muscle glycolysis associated temporally with hepatic glycogenolysis and neoglucogenesis. In the state of shock this is further augmented by muscle lactate released into circulation being used by the liver to produce glucose (the Cori cycle).[29] Furthermore, all of this is happening in the setting

of insulin resistance mediated through actions of counterregulatory hormones (catecholamines, cortisol, growth hormone, and so forth), and numerous cytokines affecting actions of insulin through mechanisms involving insulin receptor and postreceptor signaling. Hyperglycemia is a marker of severity of illness and is a predictor of poor outcome.[30] Hyperglycemia impairs the host's ability to combat infection through an adverse impact on innate immunity, leading to reduced chemotaxis and phagocytosis, formation of reactive oxygen species, increased concentration of proinflammatory cytokines IL-1, IL-6, and tumor necrosis factor (TNF)-α, and impairment in the generation of endothelial NO.[31,32] Severe sepsis remains a major cause of mortality in critically sick patients.[33] The Surviving Sepsis Campaign Guidelines recommend a glycemic target of below150 mg/dL.[34] Undoubtedly, attention needs to be paid simultaneously to managing infections/sepsis through emergent, judicious, effective use of antibiotics (and drainage of abscesses/debridement of necrotic tissue where possible), and effective glucose control.

The rigor and extent of glycemic control has been a matter of great interest and study. In a ground-breaking article published in 2001 by Van den Bergh and colleagues[35] in the setting of the surgical intensive care unit (ICU), marked improvements in survival, length of hospital stay, bloodstream infections, acute renal failure requiring dialysis or hemofiltration, number of red blood cell transfusions, and critical illness neuropathy were reported when intensive insulin therapy was used to maintain blood glucose at or below 110 mg/dL. In another study by the same authors in the medical ICU setting, mortality with intensive insulin therapy was increased if the patient spent less than 3 days in the ICU.[36] In those who stayed for more than 3 days, improvements in morbidity were noted. While Van den Bergh and associates continued to promote the advantages of tight glycemic control (glucose level <110 mg/dL), several other subsequent studies have concluded that tight glycemic control as defined by Van den Bergh's group does not reduce the hospital mortality significantly, and is associated with a significant risk of hypoglycemia. The German Multicenter Efficacy of Volume Substitutions and Insulin Therapy in Severe Sepsis (VISEP) Study of Intensive Insulin Therapy (IIT) for septic patients in multidisciplinary ICUs was stopped prematurely because of a higher risk of hypoglycemia (17.0% vs 4.1% in intensified treatment group).[37] A much larger and long awaited study, the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation) trial, showed that intensive glucose control increased mortality in adults in the ICU.[38] This study further concluded that a blood glucose target of 180 mg/dL or less resulted in lower mortality than seen with a target of 81 to 108 mg/dL. The mean difference of blood glucose levels for 2 treatment groups was 29 mg/dL. Furthermore, severe hypoglycemia was noted more frequently in the intensified insulin-treated groups. No difference was seen between groups in terms of corticosteroid therapy, length of stay in the ICU, length of stay in hospital, need for renal replacement therapy, or duration of mechanical ventilation.

The meta-analysis by Wiener and colleagues[39] concluded that tight glycemic control does not lead to reduced hospital mortality, but rather results in a significantly increased risk of hypoglycemia. A subsequent meta-analysis of 29 randomized trials came to similar conclusions.[40] These developments lead to revised recommendations in 2009 by the Surviving Sepsis Campaign Guidelines Committee Subgroup for glucose control. It was recommended that teams seeking to implement glucose control should consider initiating insulin therapy when blood glucose levels exceed 180 mg/dL with a goal blood glucose approximating 150 mg/dL, as was observed in the beneficial arm of NICE-SUGAR trial (posted on the Surviving Sepsis Campaign Web site and list server 6/12/2009).

Patients who are critically ill remain at high risk for hypoglycemia, and these patients also remain at greater risk of death.[41] Hypoglycemia remains a strong limitation in intensified insulin treatment strategies. A carbohydrate-restrictive strategy with the aim of maintaining blood glucose levels less than 180 mg/dL, ideally less than 150 mg/dL, receiving regular insulin subcutaneously 4 times daily, when compared with intensified insulin treatment with insulin infusion targeting glucose between 80 and 120 mg/dL, revealed a 5-fold reduction in the incidence of hypoglycemia. No difference in mortality and morbidity was reported.[42] However, this finding remains to be verified in larger trials. For now, intensified insulin therapy implies a formidable risk for hypoglycemia. Sepsis further enhances the risk for hypoglycemia and glycemic variability.[43] Krinsley and Grover[44] indicated that even a single episode of hypoglycemia increased the risk of mortality. Several factors predisposing to hypoglycemia have been reported.[44,45]

1. Sepsis
2. Insulin use
3. Continuous renal replacement therapy with bicarbonate based substitution fluid
4. Diabetes
5. Nutritional decrease without adjustment for insulin use
6. Inotropic support

At present, evidence supports a glycemic target between 140 and 180 mg/dL for most of the patients admitted to ICUs without a prior history of diabetes mellitus.[46] To avoid hypoglycemia and also to achieve the recommended target, frequent bedside glucose monitoring becomes essential. Several factors may confound results in a critically sick patient, and these must be taken into account:

1. Source of sample (capillary, venous blood, whole blood)
2. State of peripheral perfusion (vasoconstriction/vasospasticity)
3. Speed of sample processing
4. Amount of blood sample (when using strips)
5. Substances interfering with glucose measurement (L-dopa, aspirin, mannitol, acetaminophen, maltose, icodextrin, ascorbic acid); the effects vary with the methodology used in bedside glucose monitoring[47,48]

Mechanisms of beneficial effects of glycemic control in sepsis remain of considerable interest, and include the direct anti-inflammatory role of insulin, the inhibitory effect of insulin on glycogen synthase kinase 3β, and reductions in inflammatory response mediated through advanced glycation end-product and receptor for advanced glycation end-product.[49] Interesting new directions are being pursued to facilitate glucose control in sepsis, including use of a cytokine-absorbing hemofilter (made from polymethylmethacrylate [PMMA]) for continuous hemodiafiltration (CHDF). In patients with hypercytokinemia (IL-6 blood level >10,000 pg/mL), blood glucose management became easier once the level of cytokines was lowered with PMMA-CHDF.[50] Modulation of glucose use and gluconeogenesis in sepsis with adrenergic β-receptor blockade has been proposed.[51]

HYPOTHALAMO-PITUITARY-THYROID AXIS IN SEPSIS/STRESS

Critical illness such as sepsis is often associated with alterations in thyroid hormone concentrations. A vast body of literature has evolved, but its clinical significance remains elusive. This state of abnormalities in thyroid function tests is often referred to as low T3 syndrome, euthyroid sick syndrome, or nonthyroidal illness syndrome

(NTIS). It has been debated whether changes in the HPT axis reflect an adaptive response or a pathologic state that requires hormone replacement.

The initial and most commonly observed abnormality is a decrease in total triiodo-thyronine (total T3) concentration secondary to a block in the action of type 1 deiodi-nase (5′-monodeiodinase) that catalyzes conversion of thyroxin (T4) in the periphery to T3 (type 1 deiodinase is located in the kidney, liver, and muscle). Several factors have been proposed as possible candidates involved in reducing 5′-deiodinase activity (hypocaloric state, endogenous or exogenous glucocorticoids, high-dose propranolol, free fatty acids, iodinated contrasts, amiodarone, and cytokines such as TNF, IL-6, interferon-α, and nuclear factor κB).[52,53] While total T3 levels are reduced, thyroxin conversion to reverse T3 (rT3) still occurs. However, because 5′-deiodinase is a down-stream enzyme for degradation of rT3, reduction in its activity leads to a significant accumulation of rT3.

The typical progression of abnormalities is an initial low total T3 followed by a drop in total T4 (caused by a decrease in thyroxin-binding globulin [TBG]) as well as a reduc-tion in its binding affinity; or inhibition of binding caused by other mediators such as circulating cytokines, or drugs such as salicylates, phenytoin furosemide, and carba-mazepine. Some drugs accelerate clearance of T4, thereby effectively reducing its circulating levels (antiseizure medications, rifampin). Despite reductions in total T3 and T4 levels, free hormone levels remain normal initially. These levels should be inter-preted with caution, because of the impact of binding protein abnormalities that may result in both overestimation and underestimation of free hormone levels, owing to changes in binding protein concentrations.[54] Even though free T4 measurement by equilibrium dialysis is the most touted and trusted, this technique is also prone to spurious results. An interesting in vitro phenomenon, the heparin effect, may lead to spurious increases in free T4. Heparin induces lipase activity in the blood, leading to the generation of free fatty acids that then displace T4 from binding sites on the TBG.[55]

Parallel with decreases in serum T4 concentrations, there is a decline in pituitary secretion of thyrotropin. Again, this can be multifactorial (magnitude of illness, suppression from glucocorticoids, caloric deprivation [importantly carbohydrates], use of medications such as dopamine, cytokines, and compromise of the biological activity of the TSH molecule due to glycosylation).[56–60]

Recently, the mechanisms behind hormonal changes seen in the NTIS have become somewhat clearer. Defects can be traced to effects of malnutrition and reduced leptin, leading to decreased thyrotropin-releasing hormone (TRH) and enhanced D2 deiodi-nase (tancyte) activity because of sepsis/inflammation causing local generation of more T3, leading to reductions in TRH secretions at the level of the hypothalamus. Cytokines elaborated during sepsis also directly suppresses TSH release. Defects in thyroid hormone binding proteins occur due to changes in quantity, affinity, and binding inhibition, as discussed earlier. Defects in tissue transport activity and changes in intracellular deiodination exist as well. Furthermore, alterations (depres-sion) in nuclear thyroid hormone receptors and coactivators have been suggested. A recent review discusses these mechanisms in detail.[61]

Unless there is strong suspicion of primary thyroid disease (preexisting conditions and strong clinical evidence such as hypothermia, bradycardia, dry skin, and effusion in serosal spaces), treatment is not warranted.[62]

HYPOGONADISM OF SYSTEMIC ILLNESS

Hypogonadism has been associated with systemic acute and chronic illness. Acute systemic stress as seen in sepsis is indeed associated with marked and sharp

reductions.[63] Acute central hypogonadism occurs with acute illness in both genders, and is evident within 24 to 48 hours.[64]

Suppression of the hypothalamo-pituitary gonadal axis is proportional to the severity of illness in critically ill patients. There is no established role for the treatment of critically ill patients with sex steroids.[65] Gonadotropin suppression is consequent to reduction in pulsatility of the gonadotropin-releasing hormone (GnRH) pulse generator. This process may be due to an increase in glucocorticoids/administration of glucocorticoids, hyperprolactinemia (stress or drug related), use of opioids, or possible inflammation-related reduction in kisspeptin and decreased responsiveness to it.[66] Exact implication of acute hypogonadism is far from clear. Restoration of the axis can be seen following administration of GnRH, verifying the hypothalamus as the dominant site for the downregulated axis.

ELECTROLYTE DISTURBANCES IN CRITICALLY ILL PATIENTS

Fluid and electrolyte disturbances in acutely ill patients with sepsis are common. Volume resuscitation in a volume-depleted septic patient is of paramount importance. Changes seen in electrolytes may be a consequence of sepsis/disease itself or result from use of medication such as antibiotics, antifungal agents, vasopressors, or a host of other medications used in septic sick patients. Practically any abnormality may be seen:

1. Hyponatremia/hypernatremia
2. Hypocalcemia/hypercalcemia
3. Hyperkalemia/hypokalemia
4. Hypophosphatemia/hyperphosphatemia
5. Hypomagnesaemia/hypomagnesaemia (less common).[67–69]

SUMMARY

The authors have reviewed the most recent and relevant literature from which reasonable conclusions may be drawn. This article highlights important endocrine and metabolic changes, and provides possible explanations for observed perturbations. Obviously infectious disease specialists are not charged with the primary responsibility of addressing these issues, which have largely remained the domain of endocrinologists and intensivists. However, infectious disease specialists use a variety of drugs that can contribute to these abnormalities. Therefore, a constant dialogue between specialists would enhance the quality of care and also contribute immensely to favorable outcomes.

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