Review Article

Endocrine dysfunction during sepsis—are changes in hormone levels a physiological adaptation or a therapeutic target?

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Abstract: During the acute phase of sepsis, defined as a life-threatening organ-dysfunction caused by a dysregulated host response to an infection, patients often show severe changes in hormones and metabolic markers. These include downregulation of hormones such as TSH, T3, testosterone and estrogen, and an upregulation of other hormones such as cortisol, vasopressin, insulin-like growth factor I (IGF-I) and insulin. Whether these endocrine changes during sepsis are part of a physiological response and have beneficial effects on clinical outcomes, or in contrast, further worsen the clinical course and need therapeutic modulation has important therapeutic implications. The objective of this review is to discuss the current pathophysiological concepts underlying hormonal changes that frequently occur in patients with sepsis and important modulation factors (e.g., acute *vs.* chronic illness, pre-existing illness among others).

Keywords: Sepsis; thyroid hormones; growth hormones (GH); glucose metabolism; malnutrition; procalcitonin (PCT)

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Introduction

Sepsis is defined as a life-threatening organ-dysfunction caused by a dysregulated host response to infection (1). Sepsis is the most common reason for intensive care unit admission and mortality remains higher than 30%. Septic shock is the most common cause of death in intensive care unit (2). Some of the components of the innate immune response can, under special circumstances like sepsis, lead to cell and tissue damage resulting in multiple organ failure (3). Sepsis is associated with a high production of pro- and anti-inflammatory cytokines. An excessive release of anti-inflammatory cytokines is likely associated with the dysregulation of the immune system in sepsis (4). Cytokines are produced by multiple cells and have local effects. Hormones are produced in endocrine cells and act systemically. The term "hormokine" has been used to describe proteins that follow a classical hormonal expression or, with inflammatory stimulation, show a more cytokine-like behaviour (5).

When looking at the neuroendocrine response to critical illness (i.e., sepsis), there is a strong activation of parts of the anterior pituitary function and an inactivation of the peripheral anabolic pathways. This reaction helps to provide metabolic substrates to support host defense mechanisms, similar to the "fight or flight" reaction. These initial adaptations seem to be adaptive and beneficial. If the acute phase of critical illness changes to chronic disease, mostly a reduced stimulation of the pituitary function can be observed impairing the function of target organs and leading to wasting syndrome and intensive care dependency (6). From an evolutionary point

of view, the human species has developed natural defense mechanisms to face illness. Most of these mechanisms are accompanied by temporary starvation, without having to rely upon external support. Consequently, the initial response to illness results in an increased availability of glucose, amino acids and free fatty acids. These substrates are directed toward vital organs such as the brain and the immune system. This acute metabolic response is thought to be at least partly evoked by endocrine changes, including an activated hypothalamic-pituitary-adrenocortical axis, hypersecretion of growth hormone (GH) in the presence of low circulating insulin-like growth factor I (IGF-I), and a low activity state of the thyroid axis. Importantly, these changes can be adaptive and beneficial for the clinical course, as they may reduce and redirect energy consumption, postpone anabolism and activate the immune response. Yet, it remains unclear to which extent some of these defense mechanisms may be harmful, particularly if the changes are severe and remain for a prolonged time period. However, one may argue that these hormonal changes are the result of a selection process by nature over time and there is at present little argument for therapeutic modulation during the first hours or days of illness. This may be different for prolonged or chronic diseases. For this reason, acute and prolonged critical illness may have different effects on the neuroendocrine paradigms and thus need a different therapeutic approach (7).

The objective of this review is to discuss the current pathophysiological concepts underlying hormonal changes that frequently occur in patients with sepsis including thyroid hormones, GH, insulin among others.

Thyroid hormones and sepsis

During illness, the body reduces thyroid hormone levels by different central (i.e., on the level of the pituitary and hypothalamus) and peripheral (i.e., reduced conversion) mechanisms. As a consequence, patients with mild illness often show a decrease in serum levels of triiodothyronine (T3) and a mild increase in thyroxine (T4) levels, while TSH is also lowered. This condition is called the euthyroid sick syndrome—or the low T3 syndrome. This name is based on the current understanding that patients with this constellation of thyroid hormones are not hypothyroid despite the low hormone levels in blood, but that this decrease in thyroid hormones may be an adaptive response of the body. Patients with this syndrome do not show clinical signs of hypothyroidism and there are no adverse physiological effects or increased mortality associated with this syndrome (8). Yet, the extent of hormonal changes of the euthyroid sick syndrome correlate with disease severity and are thus predictors of poor outcome in sepsis and critical illness. In critically ill patients non-survivors had lower T3 on the day of death compared with survivors (9). A decrease in fT4 levels in the course of disease may also point to adverse outcome (10).

The regulation of thyroid hormones also depends on the time course of disease. During the initial phase of an infection, changes in the peripheral metabolism and receptor binding of thyroid hormones have been found. In the chronic phase of an illness a smaller activity of the hypothalamic-pituitary-axis is found. In the chronic phase of the euthyroid sick syndrome there is less secretion of TSH (10). The depression of the thyroid axis seems to play an important role in the explanation of the protein wasting state in chronically ill patients, because a normal level of T3 is needed for protein synthesis, lipolysis and fuel utilization by muscle (9). Because of these observations the question appears if replacement of thyroid hormones could possibly be beneficial in these patients and could increase their chance of survival (8). Klemperer *et al.* showed that patients who have undergone cardiopulmonary bypass also have low serum T3. The decrease in serum T3 concentrations in patients undergoing cardiac surgery is likely associated with the activation of inflammatory-response mediators. The substitution with T3 improved postoperative cardiovascular performance but there was no decrease in the need for inotropic support (11). There are not many studies relating to the effect of a substitution of thyroid hormones in patients with sepsis. Inan *et al.* showed in an experimental study that thyroid hormone supplementation resulted in lower mortality in septic rats (12) and Coskun *et al.* showed that the therapeutic effect of substitution of T3 could be promising in septic rats (13). Similar studies in humans, however, are currently lacking.

Based on the current understanding of thyroid hormone changes during illness, there is little evidence that hormone replacement would be beneficial and the “euthyroid sick” constellation observed in illness is rather a physiological adaptation (9). More studies are needed to clarify if there could be a benefit with substitution of thyroid hormones, especially in chronically ill patients.

GHs and sepsis

In sepsis there is an activation of the hypothalamic-pituitary

axis that leads to an increase in circulating levels of GHs in the early phase of illness. Yet in the peripheral tissues, there is an acquired peripheral GH resistance with a down regulation of IGF-1 leading to protein catabolism. GH showed to be an independent predictor for mortality, which means that GH levels correlated with the severity of disease (14). What could explain the poor prognosis of patients with high GH concentrations? On the one hand, GH increases with the individual stress level of patients. On the other hand, the GH resistance and the resulting increase of GH concentrations induce catabolism and may be therefore harmful for these critically ill patients (14).

Because of this knowledge it was assumed that the administration of GH could attenuate the catabolic response to sepsis. For this reasons Dr. Takala *et al.* performed a large trial in 1999 to study the effects of high doses GH administration on the outcome of critically ill adults. The authors found no benefit of GH therapy, but conversely an increase in mortality associated with GH was found. Furthermore, the duration of mechanical ventilation, intensive care and hospitalization was prolonged by GH treatment in the patients who survived. Although the precise mechanisms for the increase in morbidity and mortality remains unclear, a modulation of immune function could be involved (15).

Glucose metabolism, insulin resistance and glucose lowering treatment

There are several preclinical studies finding that hyperglycemia interacts with different components of the innate immune system in vitro. Hyperglycemia and diabetes have also direct inhibitory effects on the adaptive immune system (i.e., on the function of T lymphocytes, immunoglobulins and complement). In line with these findings, clinical studies find a higher susceptibility for diabetic patients to acquire infections. Still, if diabetic patients with infections have a worse prognosis is unclear.

Importantly, "stress hyperglycemia" is common in acutely ill patients as a result of the stress response with different stress hormones increasing insulin resistance (e.g., endogenous catecholamine and cortisol) (16). Acute hyperglycemia in critically ill patients has a different pathophysiologic effect in patients without diabetes compared with patients with diabetes. That could explain why there is an association between hyperglycemia and increased mortality in patients without diabetes but not in patients with a known diabetes. There must be several features associated with diabetes that influence host response to infection. It is known that hyperglycemia impacts different components of the host response including function of immune cells and regulation of cytokines (17). In correlation with these differences in patients with diabetes and in patients without diabetes there is an association between mean glucose concentrations and adverse clinical outcomes in patients without diabetes with an acute infection, but no such associations were found in patients with a known diabetes (16).

Despite insulin therapy seems to have protective effects because of the correction of hyperglycemia and also through direct effects on cells (17), the importance for intensive insulin treatment in critically ill septic patients remains controversial. Initial studies suggested a lower overall mortality rate in patients in the intensive care unit associated with tight glucose control. Later trials however, did not replicate the initial promising findings or even report higher complication rates with this tighter glucose control (16). Several factors may explain these differences in trials results including different feeding protocols, different insulin protocols with increased risk of hypoglycaemia and different target glucose levels in the control and intervention groups, among others. In 2009 the largest yet trial—the NICE-sugar trial—showed that intensive glucose control compared with conventional glucose control, increased the absolute risk of death (18). Today, there is thus less enthusiasm in regard to intensive glucose lowering and a mild hyperglycemia is often tolerated and seen as a part of the physiological stress response with no adverse effects on patients' outcomes.

Loss of appetite, malnutrition and feeding strategies

Loss of appetite and anorexia is part of the acute physiologic response to severe illness that can be either adaptive or maladaptive. If a healthy person is fasting, the catabolic response is distinctly smaller than it is in acute critical illness because there is an energy deficit in acutely ill patients and additionally there is an immobilization and distinct inflammatory and endocrine stress response. In chronic disease there is a nonspecific wasting syndrome. This means that despite feeding there is protein which get lost from vital organs and tissues because of activated degradation and suppressed synthesis. And this wasting is accompanied

by hypoproteinemia, hypercalcemia, intracellular water and potassium depletion, and hypertriglyceridemia. This protein hypercatabolism gets important after several weeks of a severe disease. It leads to muscle atrophy and weakness and as well to failure of the muscular ventilatory system, which leads to the need for mechanical support. There are also trophic effects of enteral nutrients in the integrity of the gut mucosa. This knowledge led to the conviction to begin enteral nutrition early during critical illness. Furthermore, the inability to provide enteral nutrition early could be a marker of the severity of illness (19). It is not desirable to interfere with the early catabolic response to critical illness, either with macronutrients (19) or with anabolic hormones (15). To test the hypothesis that early parenteral nutrition to reach caloric and protein goals is generally beneficial in patients compared to a slower start of nutrition, Casaer *et al.* performed a large trial comparing these two strategies. There was no difference in mortality associated with late *vs.* early initiation of parenteral nutrition, but there was faster recovery and fewer complications in patients with late initiation of parenteral nutrition compared with early initiation (20). Critically ill patients have oxidative stress and therefore have increased mediators of oxidant stress and a higher incidence of multiorgan failure. However, Heyland *et al.* showed that antioxidant supplementation was not associated with any effect on mortality. In critical illness happens a rapid depletion of plasma glutamine levels, therefore glutamine seems to be essential. But despite this assumption, there was even a nonsignificant increase in 28-day mortality and significant increases in in-hospital 6-month mortality with the use of glutamine. That most of the patients in this study did not have glutamine deficiency early in the course of the critical illness could be one explanation. But the mechanism through witch glutamine causes harm remains unknown (21).

Although the optimal use of nutrition in critical illness is not fully clear, a less aggressive approach is currently favoured by many physicians, and a more aggressive approach—particularly with parenteral nutrition—may in fact be harmful for patients.

Calcium and procalcitonin

The hormone calcitonin, which is produced in the thyroid c-cells, has been found to play a role in bone metabolism. However, studies found that the precursor hormone of calcitonin—procalcitonin (PCT)—increases in patients with bacterial infection independent of bone metabolism and calcium concentrations. In fact, PCT has now emerged as an important diagnostic and prognostic marker for critically ill patients with sepsis and a guide for antibiotic management (22). PCT has a higher specificity for bacterial infections compared to other inflammatory markers (23) and its kinetics provide prognostic information (24). Trials found that monitoring PCT results in shorter antibiotic treatment courses with also lower risk for adverse outcome and lower mortality (25). This is important especially considering that unnecessary antibiotic use leads to increasing bacterial resistance and increases the risks of drug-related adverse events and medical costs (26-28).

Conclusions

Hormonal changes in acutely critically ill patients are often a physiological response to the overwhelming reaction of the body to the sepsis. They may play an adaptive role to help the organism cope with the severe disease. Because these adaptations seem to be useful for the organism, they should often not be treated. In severe chronic disease, however, the hormonal changes could be harmful for the organism and could thus represent a promising therapeutic target. Therefore, the option of a treatment of these hormonal changes should be considered.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jlpm.2018.07.02). Dr. Schuetz reports grants from Thermofisher, grants from Roche Diagnostics, grants from Nestle, from Abbott, outside the submitted work. Dr. Widmer has nothing to disclose. The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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