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**Review**

# Hormonal supplementation in endocrine dysfunction in critically ill patients

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**Abstract:**
One of the greatest challenges for a physician is a critically ill patient. Regardless of the reason for an admission to the Intensive Care Units (ICU) (e.g. myocardial infarction, severe pneumonia, trauma or many others) each of the above-mentioned conditions impairs homeostasis including instability of the endocrine system. The observed alterations in serum glucose level or clinical signs of hormonal imbalance alarm practitioners and prompt them to an intervention. However, side-effects of administered drugs have to be always considered, because every intervention in the endocrine system may have various consequences or prove itself maleficent. Since critical condition causes numerous changes in the hormonal system, the definition of endocrine gland failure in the ICU patients should differ from the definition related to the general population.
This review is aimed at describing alterations, diagnosis and treatment options for an impaired carbohydrate metabolism and inadequate response of the adrenal and thyroid endocrine axis. It has been written in order to aid the choice between "the watch and wait strategy" and aggressive pharmacological intervention. Furthermore, several standard and innovative therapeutic procedures were described and, if possible, compared. Recent articles have been included in order to show current views on the up-to-date clinical approach.

**Key words**:
critical illness, glycemia control, adrenal insufficiency, euthyroid sick syndrome

**Abbreviations**: ACTH – adrenocorticotropic hormone, ADMA – asymmetric dimethylarginine, AI – adrenal insufficiency, APACHE – acute physiology and chronic health evaluation, DIGAMI – diabetes mellitus, insulin glucose infusion in acute myocardial infarction, eNOS – endothelial NO synthase, ESS – euthyroid sick syndrome, GHRP-2 – growth hormone releasing peptide – 2, GnRH – gonadotropin-releasing hormone, ICAM-1 – intercellular adhesion molecule – 1, ICU – Intensive Care Units, MOF – multiple organ failure, IL – interleukin, NO – nitric oxide, rT3 – reverse triiodothyronine, T3 – triiodothyronine, T4 – thyroxine, T4S – thyroxine sulfate, TNF-α – tumor necrosis factor α, TSH – thyroid-stimulating hormone

## Introduction

Owing to the implementation of advanced technology in medical care, more and more patients may be saved after severe trauma and infections. However, the increased probability of saving human lives has led to new problems. Although potent drugs, sophisticated appliances and more sensitive laboratory tests facilitate solving some of those problems, it is necessary to return to the backgrounds of pathophysiology, in or-

der to be able to use the above-mentioned resources properly. Serum hormone concentrations in patients admitted to the Intensive Care Units (ICU) usually differ much from that of a healthy population. Acute stress disrupts physiological feedbacks, which makes the effect of drugs hard to predict. Intervention in hormonal homeostasis seems to be reasonable when laboratory results are outside the reference range. Unfortunately, such actions may worsen patient's outcome because of the incomplete knowledge about homeostasis in a critical illness, which can be easily disturbed. This review is aimed at discussing recent clinical findings in endocrine issues among ICU patients. Special emphasis is put on glycemia control, and on adrenal and thyroid hormones in severely ill patients.

## Glycemia control

Many Intensive Care Unit (ICU) patients, with or without a history of diabetes, often experience hyperglycemia [57, 86, 94]. For many years, the increased glucose level in severely ill subjects was considered as a normal and physiological reaction to stress. On the basis of the recent studies, it is presently assumed that increased glycemia in the severely ill results predominantly from the enhanced production of endogenous glucose and insulin resistance [16, 83]. In one study, blood glucose level in severely ill patients was about 50% higher than in healthy volunteers, despite the fact that the basal and total parenteral feeding-induced insulin level in the former was on average 3 times higher. Furthermore, to maintain similar levels of glycemia during parenteral feeding with infusion of insulin, it was necessary to achieve 30 times higher blood insulin level in the patients than in the control group [84].

Hyperglycemia seems to be disastrous in many ways: it impairs cytokine network [73] enhancing tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6)-induced pro-inflammatory response [49], accelerates apoptosis due to enhancing free radical formation [86], increases the risk of septicemia, which at least partly may be a consequence of an altered function of leukocytes [66], disturbance of opsonic activity [77] and excessive immunoglobulin glycation [35], and may lead to secondary polyneuropathy and multiple organ failure (MOF). What is more, the endothelium is also often damaged and produces less NO due to accumulation of asymmetric dimethylarginine (ADMA) an endothelial NO synthase (eNOS) [80] inhibitor, which together with platelet hyperactivity results in a hypercoagulable state [34, 86]. Although the serum NO level is elevated in ICU patients [51], the increase is caused by the induction of iNOS, which mediates inflammatory response and may lead to organ damage during ischemia or reperfusion. Furthermore, elevated glucose level results in higher amounts of adhesion molecules such as ICAM-1 and E-selectin. The above-mentioned deleterious effects of hyperglycemia may be corrected by intensive insulin treatment. It should be stressed that not insulin itself but lowered blood glucose level is the benefactor [33].

Many clinical trials support the thesis that adjusting blood glucose levels leads to the improvement in patients' outcome. Van den Berghe et al. [90] evaluated the protocol of maintaining patients' blood glucose level between 4.4 and 6.1 mmol/l (intensive treatment) in comparison with the conventional regimen. In the latter, glycemia was maintained between 10 and 11.1 mmol/l and insulin was administered only if glucose level exceeded 11.9 mmol/l. The authors observed a 42% decrease in mortality in the intensive-treatment patients (8.0% *vs*. 4.6%). This difference was even more pronounced in patients receiving intensive care for more than five days (20.2% *vs*. 10.6%). Other benefits observed in patients receiving intensive insulin therapy were a 46.0% reduction in the incidence of septicemia and a 22.0% reduction in the risk of polyneuropathy. Intensive insulin treatment patients who spent in the ICU more than 5 days had a significantly shorter duration of intensive care than conventionally treated patients (12 *vs.* 15 days, $p = 0.003$). Normoglycemia, intensive insulin therapy, or both prevented renal failure and reduced the need of blood transfusions, probably due to decreased hemolysis and/or owing to a reduced toxic effect of excessive glucose level on hemopoiesis. Because the discussed study was conducted mainly on surgical intensive care patients, whose condition is usually more severe, the question whether these beneficial effects may be present in the medical ICU patients for some time remained unresolved. A recently published large analysis of 1200 patient in the Medical ICU [89] has confirmed that intensive insulin therapy reduces morbidity owing to the prevention of renal failure, earlier weaning from mechanical ventilation and earlier discharge from ICU and hospital. However, contrary to

the study carried out among surgical patients, no significant benefit on the risk of bacteremia or severity of hyperbilirubinemia was observed. Additionally, analyzing 1200 patients in the Intention-to-Treat group, there was no significant reduction in in-hospital mortality at day 3 (3.6% *vs.* 4.0%, p = 0.72) and mortality in the ICU at day 3 (2.8% *vs*. 3.9%, p = 0.31). However, when patients stayed in the ICU for more than three days (n = 767), it appeared that intensive insulin treatment significantly reduced the risk of in-hospital death (43.0% *vs*. 52.5%, p = 0.009) as well as total deaths during intensive care (31.3% *vs*. 38.1%, p = 0.05). In a group of 433 patients who stayed in the ICU for less than 3 days, 56 patients in the intensive-treatment group and 42 in the conventional-treatment group died and statistical significance depended on the analytical approach. Both above-mentioned studies suggest that maintaining patients in the range of normoglycemia appears to be beneficial, although further analysis should be performed to verify the potential negative outcome in patients receiving intensive insulin treatment for less than three days.

Promising results were obtained during Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study [56] in which diabetic patients with myocardial infarction receiving intensive insulin treatment were followed up on average for 3.4 (1.6–5.6) years. The authors observed an 11.0% reduction in mortality in these patients compared to the control group. The subsequent study, DIGAMI 2 [58], carried out on a larger population of patients did not confirm the benefits of the above-mentioned therapy on mortality applied during a mean 2.1-year (1.03–3.00) follow-up. However, during glucose-reducing treatment blood glucose was higher than the target range and HbA1c did not differ between the study groups. Therefore, this may suggest that more strict glycemia control is necessary in order to show a reduction in mortality.

In a meta-analysis of randomized controlled clinical trials examining insulin therapy in critically ill patients, carried out by Pittas et al. [75], a 15.0% reduction in short-term mortality was found when cumulative data from all trials were calculated. Additional analysis was performed to investigate the effects of glucose-insulin-kalium (GIK) treatment and other than GIK insulin infusion methods. GIK infusions appeared to be ineffective in lowering mortality (RR, 0.90; 95% CI, 0.77–1.04) whereas other than GIK solution therapies led to a 27% reduction in a relative risk of death (RR, 0.73; 95% CI, 0.56–0.95). In patients receiving insulin, hypoglycemia was observed 3 times more frequently (RR, 3.4; 95% CI, 1.9–6.3). GIK solution caused hypo- as well as hyper- or normoglycemia but when a trial was targeted at maintaining normoglycemia, hypoglycemia occurred more often. In addition, no adverse effects of hypoglycemia were noted in all of the trials included in the meta-analysis.

Krinsley [48] in his large retrospective study examined the relationship between glucose level in critically ill patients and their outcome. The mortality rate increased in parallel with the mean glucose level. The lowest mortality (9.6%) was found in a subgroup of patients with glucose values in the range of 4.4–5.5 mmol/l, while the highest one (42.5%) in a subgroup with glucose level above 16.7 mmol/l. Even a minimal increase in a mean glucose level (5.5–6.6 mmol/l), resulted in 12.2% mortality, which meant a 27.1% increase in a relative risk. Interestingly, in a subgroup with glycemia lower than 4.4 mmol/l mortality again increased to 22.9%, which might be attributed to the episodes of hypoglycemia occurring probably more frequently in this subgroup or more severe course of the underlying disorder. It should be stressed that non-survivors had significantly higher glucose level than survivors ((9.5 *vs*. 7.7 mmol/l, p < 0.001) and that the initial glycemia was also significantly higher in the former (9.6 *vs*. 7.6 mmol/l, p = 0.02) in patients with APACHE II score 0–14.

Not all the results of intensive insulin treatment studies are promising. The prospective, randomized, multi-center study on the effect of colloid *vs*. crystalloid volume replacement therapy and of intensive *vs*. conventional insulin therapy on organ functions and survival in patients with severe sepsis and septic shock (VISEP) study [13], carried out in Germany, has been interrupted prematurely. Only 488 patients of 600 planned were recruited. No beneficial effect on hospital mortality was observed (21.9% *vs*. 21.6%, p = 1), whereas incidence of hypoglycemia was 6-fold higher (12.1% *vs*. 2.1%, p < 0.001) Another large multicenter study, the Glucontrol, was designed to investigate the influence of hypoglycemic treatment in the broad ICU patients population. It was discontinued after obtaining results from 1109 patients, when the study population was planned to reach around 3000. The mortality in the intensive treatment group with intended glucose level 80–110 mg/dl did not differ significantly from the control group (12.3% *vs*.

9.8%, p = 0.19) and the hypoglycemia occurred more often (9.8% *vs*. 2.7%, p < 0.0001). In the German study, the study population consisted of elderly patients with sepsis, both known as risk factors for hypoglycemia [93]. Both studies from Leuven also reported higher incidence of hypoglycemia in intensive insulin treatment group. Lack of influence on mortality in the studies may originate from frequent episodes of hypoglycemia. As mentioned before, Krinsley [48] observed a high mortality rate in a subgroup with glycemia below 4,4 mmol/l in contrast with glucose level 4,5–5,5 mmol/l (22.9% *vs*. 9.6%). Therefore, to achieve a mortality reduction it is probably necessary to make more effort on preventing hypoglycemia. The ongoing trial Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) [65], which targets at including 6100 patients, considers hypoglycemia as a serious adverse effect, and several measures to reduce its incidence are included in the study protocol. To sum up, it seems vital to avoid hypoglycemia during intensive insulin treatment, but further research on this issue is necessary.

Taking into consideration that hyperglycemia worsens patient outcome in ICU and that maintaining normoglycemia reduces mortality and prevents other undesirable effects of hyperglycemia, several strategies of blood glucose reduction were investigated.

The simplest method to achieve this aim is an implementation of sliding scales which enable to calculate insulin dosage on the basis of patient's blood glucose level and weight. Unfortunately, this simple method gives only a weak control of glycemia [26, 76]. Furthermore, it is non-standardized and often needs revisions that leads to additional work for the staff.

Protocols that aim at maintaining glucose values as close as possible to normoglycemia are another measure of achieving normoglycemia. Krinsley et al. [47] designed one, which is executed by nurses under a physician's supervision. The target glycemia was set below 7.8 mmol/l. As a result, mean glucose level decreased by 14.4% in the study group (from 8.5 to 7.3 mmol/l). There was no statistical differences in incidents of severe hypoglycemia and a significant drop of hyperglycemia, defined as a glucose level above 11.1 mmol/l, in the study group vs. control group, 7.1% and 16.2%, respectively. Hospital mortality decreased by 29.3% and length of stay by 10.8%. It is important that these effects were obtained without a significant change in a working routine.

Similar results were obtained during evaluation of an insulin nomogram designed by Chant et al. [17] in which the desired blood glucose level was set between 5 and 8 mmol/l. The nomogram was nurse-directed and self-adjusting. Fifty-two percent of blood glucose measurements were within the target range. Mean morning glycemia, the primary objective of the study, decreased significantly in a treatment group by 27% (9.7 ± 2.8 *vs*. 7.1 ± 1.8 mmol/l, p < 0.001). Additionally incidents of hyperglycemia, defined as glucose level above 10 mmol/l, occurred less often (53% *vs*. 14%, p < 0.001) and an insignificant increase in severe hypoglycemia was observed (0.2% *vs*. 0.4%). Mean ICU stay and mortality were reduced in the nomogram group. However, this study was not powered enough to show significance of these findings.

Both the above-mentioned studies suggest that the reduction of blood glucose level may be achieved without additional workload of the staff as well as may be easily implemented in most of the ICUs. Despite the fact that glycemia, set as a goal in these studies, was higher than normoglycemia, a beneficial effect on mortality could be seen.

Another attempt to reduce elevated glucose level, developed by Chase et al. [18], was two-compartment system model which was able to estimate the amount of insulin necessary to decrease glycemia to a desirable level. The aim of the treatment was to diminish blood glucose level by 10–20% in comparison with previous hour glycemia but no less than to 4.5 mmol/l. Seventy-five percent of the measured values were within 7% measurement error. The average absolute error reached 9%. Larger errors ranging from 17 to 21% were the effects of external factors. In another study [37], a mathematical model was used to capture glucose and insulin kinetics using retrospective data from 17 ICU patients. The error in one-hour glucose level prediction oscillated between 2 and 11%. These promising results were obtained from small groups of patients and, therefore, further studies are necessary to verify the accuracy of this model. Furthermore, there is a lack of studies on the effects of this protocol on mortality. The above-mentioned model may also be used in a completely automated insulin infusion model [28].

Despite the fact that many clinical studies show that hyperglycemia may be disastrous, it is still a common finding in ICU patients. Conquering this state seems to be crucial in order to reduce mortality and morbidity in the ICUs. There are several ways to re-

duce blood glucose level. Simple sliding scales are not sufficient in fighting hyperglycemia [26]. Mathematical models, though promising, still need more investigations. They require much effort from the staff as well as a personal computer to calculate the data. The best way to reduce elevated blood glucose seems to be protocols or nomograms that provide reasonable efficacy compared to staff workload and patient safety. Additionally, these protocols should be easily implemented in the ICUs. Further researches are necessary in order to evaluate methods of lowering hyperglycemia, which would be safer and easier to use. What is more, these studies should concentrate not only on reducing elevated glucose level but mostly on maintaining euglycemia. A very important matter seems to be ICU staff education. According to a survey by McMullin et al. [63], physicians and nurses appear to be very concerned about glycemic control and are aware of many problems associated with glycemia control (e.g. glucometer accuracy, patients discomfort, glucometer availability, workload and cost). However, the surveyed clinicians assume too high glucose level (about 10 mmol/l) as a clinically important threshold for hyperglycemia. Therefore, educational programs and spreading recent clinical findings about the need of strict glucose control should improve patients' outcome.

## Adrenal cortex

Cortisol, an endogenous glucocorticosteroid, is one of the vital hormones for homeostasis. It coordinates an electrolyte and fluid equilibrium and participates in the carbohydrate and protein metabolism. Increased serum cortisol levels have been reported in acute stress reactions to infection, shock, burns, surgery and trauma. Even though hypercortisolemia promotes infections, there is no doubt that in long-term therapy (e.g. supplementary for patients with adrenal insufficiency – AI) glucocorticosteroid dose should be increased significantly in case of infection, surgery or any stressful situation [68]. Unfortunately, hormone constellation and endocrine reaction is not so homogenous and well described in prolonged critical illness.

Cortisol level has been proven to be a predictive factor for mortality and severity of the disease [5, 41, 91]; it correlates positively with APACHE II score [41]. In some studies, the correlation between its level and mortality was U shaped-like, with both low and high levels of cortisol associated with increased mortality [30, 79]. Possible explanations for better outcome of patients with moderately increased cortisol levels, which are descending arm of a mortality curve, are positive hemodynamic (fluid retention, increased number of catecholamine receptors and influence on inotropic and vasopressor responses and prevention of receptor destabilization) [3, 10, 62] metabolic (the energy supply for important organs) [74], and immunological (crucial for adjusting excessive immune response) effects [95]. Presumably, the combination of the above-mentioned aspects or even some others could fully explain the observed influence.

Although diagnosis of absolute AI seems to be clearly marked, severe illness may bring about relative AI, when cortisol levels are insufficient to meet the demand of organism in the protracted disease [50] or systemic response is insufficient to available hormone [46]. Despite low ACTH secretion [92], cortisol level remains high, probably with activation of alternative pathways. Nevertheless, it is not elevated enough. The clinical pattern of AI is not diagnostic; additionally non-specific signs might be induced by serious illness (e.g. hemodynamic instability in all kinds of shock, muscle weakness, coma, gastrointestinal symptoms) or be caused by treatment. Also primary disease treatment may distort AI clinical picture. In the majority of severely ill patients, basal plasma cortisol exceeds 0.49 mmol/l, which does not meet criteria of AI for otherwise healthy subjects [36]. However, increasing needs lead to relative AI and more appropriate threshold in the considered population would be 0.68 mmol/l [10, 21, 59, 60, 62]. Moreover, a single measurement of cortisol level is difficult to interpret, due to its significant fluctuations [30]. The insulin tolerance test is the golden standard for AI diagnosis, but it is contraindicated in patients with any cerebrovascular, cardiovascular or seizure disorders and unsafe in critically ill patients [68]. In that case, ACTH stimulation tests seem to be applicable. Most but a few investigators assume that ACTH test measures adrenal sufficiency rather than functional reserve [59, 60].

Two general types of adrenal stimulation test are in use: high-dose and low-dose in which cosyntropin is administered at the dose 250 μg and 1 μg, respectively. Both ACTH doses produce ACTH plasma level higher than physiological level induced by stress

(e.g. surgery). In the high-dose test, plateau lasts for about 90 min compared to 30 min in the low-dose test. It may be the point to the suggestion that the high-dose test better simulates a protracted stress reaction [29, 61]. Considering plateau duration, the test with 8 h infusion of ACTH might be in some aspects even better than the two mentioned above. However, its value is limited by the fact that it is more expensive and time consuming and not always available. In fact, Kozyra et al. [46] carried out a meta-analysis of the trials from 1966–2004 to assess whether 1 μg ACTH test can be used to evaluate AI. They concluded that it seems very adequate to make therapeutic decisions using the 1 μg test. The supraphysiologic 250 μg dose produces corticotropin concentration as high as 26 400 pmol/l (during the stress its level is usually between 8.8 pmol/l and 44 pmol/l) [29], which overcomes the resistance of patients who do not respond to endogenous ACTH. The low-dose test may pick out more patients with AI, including all who would be identified using the high-dose test. Its specificity is compared with the golden standard, the insulin–induced hypoglycemia test [1, 23, 67, 78, 96, 97]. In the analyzed trials, the increase in the number of adverse events associated with steroids was not observed. The other possible approach, according to Ligtenberg et al. [53, 54], is the administration of a single low dose of hydrocortisone (200–300 mg). According to these authors, patients with rapid clinical and hemodynamic improvement suffer from relative AI.

Two meta-analyses [22, 52] covering the trials published in period of dramatic decrease in the use of steroids, concluded that steroids were not beneficial in sepsis and septic shock. However, recent publications suggest inappropriate patient selection, excessive dosage, suboptimal timing and duration of treatment. Burry and Wax [15] clarified neutral or even deleterious effect of steroids in trials from the abovementioned analyses with heterogeneity of patient populations and high dosage. They also pointed out that management of sepsis, like antibiotics usage, was not standardized. They also analyzed trials published after 1997 [4, 10, 12, 19, 43, 97] to evaluate the use of low-dose corticosteroids. None of those trials suggested increased mortality in septic shock after the administration of low-dose hydrocortisone (i.e. 200–300 mg). Such low-dose steroids are well tolerated, with minimal adverse effects; they should be administered to patients with sepsis and septic shock until the relative AI is excluded.

However, the problem of steroid use in septic shock is still being investigated. The Corticus study (results expected in May 2007) designed to determine whether steroids reduce mortality in patients in septic shock has recently stopped enrolling patients (personal communication from Prof. Charles Sprung).

Patients with cirrhosis are specially susceptible to septic shock due to severe sepsis. Tsai et al. [85] found that relative AI was very frequent in that population. Adrenal capacity was evaluated by a short corticotrophin stimulation test and AI was observed in 51.5% of patients. Lack of an adequate cortisol increment was an independent mortality risk factor and the cortisol response was inversely correlated with the severity of the disease. In another study, Fernandez et al. [32] reported 68% incidence of AI, as well as a significantly higher shock resolution and survival rate after hydrocortisone administration. Transient AI has been also proven to be the possible cause of refractory shock in a group of preterm, very low birth weight infants [64]. In that study, corticosteroid therapy with hydrocortisone or dexamethasone was life-saving in infants who had not responded to treatment with inotropic agents and volume supplementation. Inadequate adrenal function was also connected with worse outcome of patients with respiratory failure. Hydrocortisone supplementation increased the success of mechanical ventilation weaning and shortened a weaning period [38].

Ligtenberg et al. [54] reviewed trials performed before 2004 in more than 1000 patients proving that the administration of low-dose corticosteroids to catecholamine-dependent patients with septic shock helped to restore hemodynamic stability (shock reversal). Therapy should be continued in patients who responded rapidly to the initial hydrocortisone administration, as they suffer from relative shortage of adrenal hormones. Challenge with repeating low-dose steroids could be worth trying if hypotension occurs again in a hydrocortisone-tapering scheme.

## Thyroid gland

Thyroid hormones play a crucial role in human metabolism. They promote anabolism, are involved in the function of the cardiovascular system (increasing heart contractility and cardiac output and decreasing

vascular tone) [39, 40, 46], respiratory system (ensuring central respiratory drive) [14] and skeletal muscles (preventing muscle weakness and myopathy) [44]. The absence of thyroxine (T4) and triiodothyronine (T3) leads to heart dysfunction [9] and ventilation disorders [100]. Disturbances in the hypothalamic-pituitary-thyroid axis are frequently observed in the ICU patients. However, the relevance of these findings is difficult to interpret because of great inter-study differences in TSH and thyroid hormone levels in various studies. Spencer et al. [81] reported that as many as 17.2% of hospitalized patients had TSH level outside the reference range. Physiologically most of T3 is produced as a result of peripheral 5'-deiodination of T4. However, during severe illness the metabolism of T4 often changes and the T3 production lessens in favor of reverse T3 (rT3). This phenomenon occurs as a result of an impaired elimination of rT3 and a decreased function of 5'-deiodinase [55, 71] or the increased production of rT3 [25]. This leads to the reduction in a T3/rT3 ratio and is often accompanied by low or normal TSH and T4 levels [27, 72]. The above-mentioned serum hormone constellation in the absence of true thyroid disease is called euthyroid sick syndrome (ESS) or low-T3 syndrome. Among the ICU patients, this state is much more common than true hypothyroidism. Owing to the changes in thyroid hormones, Chinga-Alayo et al. [20] decided to examine the use of T3 and TSH as prediction factors in patients treated in the ICU. It was shown that combining measurements of the above-mentioned hormones with the APACHE II score resulted in the improved prediction of the mortality versus sole APACHE II scale (area under ROC curve 0.88 *vs*. 0.75). Additionally non-survivors had lower TSH and total T3 concentrations, although no difference was found in total and free T4. Logistic regression analysis revealed a 49% increase in odds of decease in the ICU for every 10 ng/dl decrease in serum total T3 level.

Another interesting study was conducted on patients after cardiac arrest or with myocardial infarction [40]. Not only has it been shown that non-survivors had lower T3 level than survivors (0.72 *vs*. 0.9 ng/ml, $p < 0.02$) but also duration of resuscitation affected the level of T3. The longer resuscitation lasted, the lower serum level was found. In neither of the groups a significant increase in serum TSH was observed despite the low T3, which suggested the occurrence of ESS. After 2 months of follow-up all patients, except for two remaining in vegetative state, had neither clinical nor laboratory signs of ESS. Similar results were obtained by Pavlou et al. [69]. In addition, low total T3 seemed to correlate with severity of myocardial infarction.

All patients with meningococcal sepsis in pediatric ICU presented symptoms of ESS [27]. It has been proved that dopamine infusion markedly decreased TSH level in patients with septic shock. However, this had no effect on serum thyroid hormone concentrations in dopamine-treated patients which remained at a similar level as in non-dopamine-treated subjects (FT3 16.9 *vs*. 17.6 nmol/l, $p = 0.87$). Interestingly, high rT3 levels were noted in 89% of study population but total T3/rT3 ratio was significantly higher in non-survivors. This unexpected finding may be explained by an insufficient time period to develop all clinical signs of ESS. In a subgroup of patients (34 patients including one non-survivor) the concentration of thyroxine sulfate (T4S), a metabolite of T4, was lower than in the healthy control group which is contradictory to the findings of Peeters et al. [70] where T4S levels in adult critically ill patients were significantly higher than in a reference group. This inconsistency is probably caused by the fact that the study groups were not comparable, as in the later only non-survivors were enrolled.

The imbalance in the thyroid hormones may partly result from the impaired function of the hypothalamus, which leads to an inappropriate secretion of TSH [42]. Normally, TSH is released in a pulsatile manner but during critical illness not only TSH level is lower but also the pulsatile pattern of its secretion is lost. Administration of TRH alone elevates the TSH, T3 and T4 levels, however, only infusions with both TSH and growth hormone releasing peptide-2 (GHRP-2) stimulated a pulsatile TSH secretion [88]. Probably the most holistic effect on metabolism can be obtained by combined treatment with TRH, GnRH and GHRP-2. A combined administration of these hormones reactivated the pituitary-thyroid axis and had beneficial anabolic effects such as increased levels of testosterone (maximum 312% from the baseline), estradiol (> 80% from the baseline), and osteocalcin and a significant reduction in ureagenesis [87].

Thyroid hormone supplementation in the ICU patients with ESS remains undoubtedly controversial. Encouraging results were obtained by Taniguchi et al. [82] in potential organ donors in whom exogenous thyroid hormones stabilized the function of the cardiovascular system. Similar findings were noted by

Zuppa et al. [99]. Additionally, during T4 infusions in the study population, lower doses of vasopressor agents were required. There are studies supporting the idea of administering T3, which improves the left ventricle function after ischemic injury [31] and cardiac surgery in children [8]. However, this treatment is not considered safe and may also lead to the increase in mortality [2, 11]. Certainly, it is vital to substitute thyroid hormones if hypothyroidism is diagnosed (about 3% of the ICU patients). This procedure facilitates cessation of the mechanical ventilation [24].

It is easier to diagnose ESS than to treat it properly Watch and wait strategy and avoidance of a thyroid hormone substitution seems to be reasonable option in many cases [98]. Owing to the fact that hepatic deiodinase is a selenoprotein, sensitive to selenium deficiency [6], its supplementation may result in a quicker normalization of T4 and rT3 concentrations [7]. The most evident benefits of thyroid hormone supplementation are observed in supporting organ donors, therefore, they are included in the schemes for organ procurement. Patients treated with dopamine and adrenal steroids which tend to decrease serum levels of TSH require a second thought when a decision about ESS treatment is made. Another interesting treatment option is the combined use of hypothalamic releasing factors, because they improve hormonal balance as well as impaired metabolism, nevertheless, this strategy needs further investigation to prove its efficiency in reducing mortality.

## Conclusions

The clinical studies of the recent years conducted on ICU patients have provided some new data on the effectiveness of the hormonal therapy in critically ill patients. Insulin infusions used for normalization of glycemia have proved to be beneficial for diabetic patients in many clinical trials and meta-analyses. Protocols carried out by nurses under supervision of physicians seem to be the easiest and effective method of glycemia control.

Steroid supplementation is beneficial for patients with absolute and also relative AI, but it is hard to strictly demarcate the level of relative AI. Because relative AI is not well defined, low doses of hydrocortisone (100–200 mg) seem to be appropriate therapeutic management in refractory shock. This treatment should be continued in patients responding to the initial dose (e.g. by decreased requirement for vasopressors). The administration of thyroid hormones is even more controversial and at least now it seems that the best strategy is to use them only if hypothyroidism is confirmed or in potential organ donors.

It would be interesting to investigate in detail the safety of intensive insulin treatment, especially to what extent the increased risk of hypoglycemia reduces the beneficial effects of strict glycemia control. Another interesting direction of future studies is to consider implementation of a combined hormonal treatment (e.g. administration of insulin to maintain normoglycemia in patients treated with adrenal steroids or thyroid hormones). Finally, it should be kept in mind that most drugs intended to improve a patient's condition do have their own side effects and balancing these two sides of equation is undoubtedly a matter of the greatest importance.

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