Dysglycemia in critically ill children
Wahania glikemii w stanach krytycznych u dzieci

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Abstract
Stress hyperglycemia remains a significant and unsolved medical condition in critically ill children. Treatment for hyperglycemia is controversial and, to date, no recommendations exist from pediatric professional society regarding the management of hyperglycemia in critically ill children. This review summarizes recent work investigating the pathogenesis of stress hyperglycemia, the importance of hypoglycemic episodes and glycemic variability among critically ill patients.

Key words: glycemic variability, stress hyperglycemia, hypoglycemia, critically ill children

Streszczenie
Wahania glikemii w stanach zagrożenia życia u dzieci pozostają nadal nierozwiązanym problemem. Leczenie hiperglykemii w tej grupie chorych jest kontrowersyjne i jak dotąd nie zostały opracowane standardy postępowania w leczeniu tych stanów. Niniejsza praca stanowi podsumowanie patogenezy zjawiska oraz jego znaczenia u dzieci w stanach zagrożenia życia.

Słowa kluczowe: zmienność glikemii, „stresowa hiperglykemia”, hipoglikemia, dzieci w stanie zagrożenia życia

Introduction
High glycemic variability commonly observed in critically ill children remains an unsolved matter and controversial field for pediatric critical care practitioners.

Stress hyperglycemia, hypoglycemia and high fluctuations within blood glucose values occur in both critically ill adults and children. It is estimated that stress hyperglycemia with blood glucose concentration > 150 mg/dl occurs in 49–72% of critically ill children, whereas blood glucose concentrations higher than 200 mg/dl are recorded in as many as 20–35% of them [1–3].

The term dysglycemia describes the form of hyperglycemia, hypoglycemia, and/or marked glucose variability. It is a characteristic feature of critical illness, whether patients have previously diagnosed diabetes or not [4]. Moreover, this phenomenon is associated with poor outcomes and an especially increased risk of mortality due to spontaneous hypoglycemia (SHG). SHG in critically ill children correlates with worse neurological outcomes and an increased intensive care unit stay [5–6].

The following article provides an overview of the so-called “stress induced dysglycemia” as a major concern among critically ill pediatric population.

Pathophysiology

Hyperglycemia
Stress hyperglycemia has often been thought of as an adaptive mechanism during an acute phase of illness. Per-
sistence of hyperglycemia in critically ill patients has been shown to be associated with many adverse outcomes [6–11]. Stress hyperglycemia results from complex interactions between counterregulatory hormones i.e. catecholamines, glucagon, growth hormone, cortisol as well as an increase in pro-inflammatory mediators such as tumor necrosis factor-α (TNF-α) and interleukins. These reactions lead to an intense and non-inhibitable production of glucose as the response of insulin resistance of the tissues to which the glucose uptake is insulin-dependent [4, 13–15]. Prolonged and persistent hyperglycemia during critical illness may cause harmful effects due to glucose overload caused by an increased hepatic output of glucose. Glucogenesis is primarily triggered by catecholamines and maintained under the influence of epinephrine and cortisol. Glucogenesis is activated by glucagon more than epinephrine and cortisol. Moreover, among large numbers of inflammatory mediators secreted during acute illness, TNF-α may promote gluconeogenesis by stimulating glucagon production. Furthermore, skeletal muscles and adipocytes are unable to take up glucose, which is related to the change in insulin signaling and downregulation of type 4 glucose transporters (GLUT-4) [13–15]. Glucose also has a significant influence on human brain and represents the brain’s only substrate under normal physiologic conditions. 90% of glucose uptake in neurons is aerobically used for the production of energy to maintain ionic homeostasis. Astrocytes, but not neurons, are able to store glycogen and, due to this ability, play a key role in the regulation of brain responses to activity, as they can rapidly convert glycogen to pyruvate or lactate to be next metabolized in the tricarboxylic acid cycle or used for glutamate synthesis [16–19]. A concept known as the astrocyte-neuron lactate shuttle glutamate-induced glycolysis in astrocytes provides lactate as a preferential oxidative substrate to neurons. According to recent in vivo rat studies, the brain preferred lactate as the energy substrate over glucose when both substrates were available and lactate appeared readily metabolized by a non-injured brain in an activity dependent manner. The neuroprotective influence of exogenous lactate has been previously documented in different conditions like prolonged starvation, diabetes, and ischemia. Data focusing on the beneficial effects of lactate on the acutely injured human brain are still lacking [17–19].

Stress hyperglycemia and brain damage are mostly observed in patients with an acute brain injury. It is associated with an increased risk of death and poor functional recovery in survivors. In cerebral ischemia, hyperglycemia causes increased infarct volume, impaired recanalization and decreased reperfusion [20–21]. Some data suggest that after ischemia and reperfusion injury, hyperglycemia affects neurons and leads to astrocytes death by increased DNA oxidation. In patients who died due to septic shock, the association between hyperglycemia and microglial apoptosis was suggested. The harmful influence of hyperglycemia for human brain injury is multifactorial. An upregulation of neuronal and astrocytic glucose transporters through regulators that are increased in critical illness and acute brain injury may lead to excessive passive transport of glucose into the brain [20–22]. Sepsis and systemic inflammation could cause the disruption of the blood-brain-barrier. As the consequence of neuronal glucose overload, the exaggerated oxidative stress (NADPH oxidase overactivation) may occur.

In addition, an increased glucose reabsorption or a decreased renal glucose clearance has also been reported and contributes to hyperglycemia in acute conditions [22–25].

**Hypoglycemia**

Hypoglycemia is physiologically reversed counterregulatory mechanism activated in a cascade sequence. Steps include the inhibition of insulin secretion, followed by the secretion of glucagon, epinephrine, growth hormone and cortisol in cases of worsening hypoglycemia. Glucagon stimulates the production of glucose by glucogenolysis and gluconeogenesis at the liver while epinephrine helps to increase blood glucose concentration by inhibiting glucose utilization by several tissues. IT activates glycogenolysis and gluconeogenesis at the liver, acting via beta-2-adrenergic receptors. Glucose production is stimulated by cortisol and growth hormone. In adults, normally fasting circulation glucose levels range from 4.4–6.1 mmol/l. Decreasing plasma glucose levels activate response against hypoglycemia [12–14].

Firstly, when glucose levels drop below the lower limit of normal range, insulin secretion decreases. Below glucose level 3.8 mmol/l increments in pancreatic β-cells’ glucagon and epinephrine secretion occur. If these mechanisms fail, lower glucose levels (below 3.5 mmol/l) induce autonomic symptoms including anxiety, tachycardia, sweating, mydriasis. If glycemia falls below 2.8–3.0 mmol/l, neuroglycopenic symptoms such as delirium or seizures may be observed. Stupor and coma may occur at glucose levels below 2.3–2.7 mmol/l. Theta waves increase and delta waves appear on electroencephalograms when blood glucose levels drop to the range of 1–2 mmol/l [26,27].

The mechanism of brain injury after severe hypoglycemia is complex and associated with: decreased glycolytic flux, lower tissue levels of lactate and pyruvate, shortage of acetyl CoA, increased levels of aspartate and a decreased level of glutamate in brain tissue. Meanwhile, both (aspartate and glutamate) are increased in extracellular space. The extracellular aspartate released during hypoglycemia damages neurons by a toxic mechanism. The other mechanisms are NADPH oxide dependent [28].

Hypoglycemia in critically ill patients may occur spontaneously or can be triggered by iatrogenic factors such as the result of insulin infusion, interruption of infusion of a nutritional solution. Spontaneous hypoglycemia include end-stage liver failure and adrenal failure during the septic shock. Hypoglycemia at intensive care unit is still a feared complication [29]. Patients may be unable to recognize or communicate hypoglycemic symptoms, because of an altered mental status, intubation or severity of diseases. Clinical symptoms of the autonomic response to hypoglycemia (sweating, tachycardia, tremor) and central nervous symptoms (dizziness, blurred vision, confusion, seizures) may be masked by coexisting diseases or treat-
Glycemic control in critically ill adults and children – what we know so far?

Glycemic management among critically ill patients has been a topic of extensive study over the past two decades. The American Diabetes Association recommends a blood glucose target of 140–180 mg/dl in critically ill adults, while the Society of Critical Care Medicine recommends a target range of 100–150 mg/dl. In recent years, there has been an increased focus on the potential harmful effects of glycemic variability, though it remains unclear how best to avoid fluctuations in blood glucose levels [13]. In 2001, original Leuven study, reported by van den Berghe et al. was the first major prospective trial to investigate the effects of tight glycemic control in critically ill adults. A majority of patients (63%) had undergone cardiac surgery. Upon intensive care unit admission, patients were randomly assigned to receive either “intensive” or “conventional” insulin therapy. The results of the study strongly favored the intensive insulin therapy group, with observed benefits in terms of both morbidity and mortality. Compared to patients in the conventional insulin therapy group, those receiving intensive insulin therapy also experienced reduced rates of renal replacement therapy, prolonged mechanical ventilation and extended intensive care unit (ICU) stays [31]. The next major prospective trial was again done by the same group in Belgium. On the contrary, second Leuven study showed no overall mortality benefit to intensive insulin therapy, as both ICU and in-hospital mortality rates were similar among patients in the intensive and conventional insulin therapy groups [32]. Between 2008 and 2009, a series of studies focusing on glycemic control among ICU patients were reported. Brunnkhorst et al. trial involved patients with severe sepsis or septic shock admitted to ICU in Germany. The patients were randomized to receive either intensive or conventional insulin therapy for glycemic control and, either hydroxyethyl starch or modified Ringer’s lactate for fluid resuscitation. In the study group there was no documented benefit of intensive insulin therapy, as there were no statistical differences in rates of mortality, rates of acute renal failure or renal replacement therapy, use of vasopressor medications, number of ventilator-free days, or length of ICU stay [33]. Arabi et al., De la Rosa Gdel et al., conducted studies in a variety of settings and, similarly, failed to demonstrate clear benefits of tight glycemic control in critically ill patients, consistently highlighted an increased risk of hypoglycemia among patients treated with intensive insulin protocols [34–35]. The most comprehensive study of glycemic control strategies among ICU patients performed to date remains NICE-SUGAR trial. The study included 6104 medical and surgical patients admitted to ICUs at 42 hospitals in Australia, New Zealand, Canada and the United States. As with previous studies, patients were randomized to intensive or conventional insulin therapy groups. In the intensive insulin therapy group, the target blood glucose was 81 to 108 mg/dl, while in the conventional insulin therapy group, the target blood glucose was 120 mg/dl or less, with insulin administration reduced and then discontinued if blood glucose level fell below 144 mg/dl. With the exception of rates of severe hypoglycemia, markers of morbidity did not differ according to treatment groups as thy were similar between-group ICU and hospital lengths of stay, durations of mechanical ventilation frequencies and durations of renal replacement therapy, rates of organ failure and occurrences of positive blood cultures. Severe hypoglycemia (blood glucose level less than or equal to 40 mg/dl) occurred in 6.8% of patients in the intensive insulin therapy group vs. 0.5% of those in the conventional therapy group (P<0.001) [36].

While the efficacy of tight glycemic control (TGC) remains controversial, TGC may lead to an increased risk of insulin-induced hypoglycemia. Although pediatric intensivists believe that hyperglycemia is harmful for their patients, the fear of insulin-induced hypoglycemia remains a barrier to the practice of TGC. To date no recommendations exist from pediatric professional society regarding the management of hyperglycemia in critically ill children [37].

First randomized controlled trial on TGC in critically ill children was conducted by Vlasselaers et al. In this study, 700 children (0–16 years) were randomized to the TGC group with blood glucose controlled at age-adjusted normal fasting values or the control group receiving standard care with blood glucose maintained at less than 215 mg/dl. In the TGC group, children less than 1 year of age had blood glucose targets of 50–80 mg/dl, whereas children 1–16 years of age had a target range of 70–100 mg/dl. The majority of patients (75%) were postoperative cardiac surgery patients and over half were less than 1 year of age. A significant reduction in C-reactive protein (CRP), the study’s primary outcome measure, was noted in the TGC group compared with the control group. The investigators also demonstrated an absolute risk reduction in mortality by 3% (relative risk reduction of 54%), as well as a decrease in the risk of secondary infections and duration of ICU stay in the TGC group. The risk of hypoglycemia (blood glucose <40 mg/dl) was significantly elevated in the TGC group [38].

In the Safe Pediatric Euglycemia after Cardiac Surgery (SPECS) trial authors showed that tight glycemic control as compared with standard care in the cardiac ICU did not change the rate of health care-associated infections, mortality, the length of stay in the cardiac ICU, or several organ-specific end points. In contrast to previous trials involving adults, this study showed no benefit of tight glycemic control in critically ill...
children who had undergone cardiac surgery, though the reasons are unclear. Normoglycemia was achieved in all the children in standard care-group without insulin therapy in first 48 hours after surgery. Moreover, that study did not lead to widespread adoption of tight glycemic control in children because of an unacceptably high rate of severe hypoglycemia resulting from the extremely low target glucose values [39].

In the Control of Hyperglycemia in Paediatric Intensive Care (CHiP) trial 1369 patients at 13 centers in England underwent randomization (694 to tight glycemic control and 675 to conventional glycemic control), 60% of them had undergone cardiac surgery. In this multicenter study, TGC did not increase the number of days that children were alive and free from mechanical ventilation for 30 days. Although tight glycemic control was associated with a smaller proportion of patients receiving renal-replacement therapy than was conventional glycemic control, it resulted in more episodes of hypoglycemia. In that trial also, continuous glucose monitoring (CGM) was used and acted as another level of protection against hypoglycemia. TGC was associated with a shorter length of stay in the hospital and the lower total health costs at 12 months. CHiP trial highlights the importance of designing pediatric ICU trials with longer-term clinical and economic end points [40].

**Summary**

It remains unclear as to how intensively the blood glucose levels in critically ill patients need to be controlled. The occurrence of hypoglycemia due to tight glycemic control with intensive insulin therapy is the major concern among pediatric critical care practitioners resulting in their hesitancy to embrace this strategy more widely. The use of glucose control algorithms and implementation CGM could improve efficacy and safety of blood glucose control. Glucose algorithms could result in preventing hyperglycemia and hypoglycemia. This type of glycemic control may be widely used in clinical practice.

Use of CGM could result in use of less blood, reduction of nursing time, and also, possibly, the improvement of metrics for blood glucose control. These potential beneficial effects need to be addressed in future trials, after extensive testing of the glucose algorithms and CGM devices [41].

**References**


