Commentary

Admission hyperglycemia and outcome in ICU patients with sepsis

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Stress hyperglycemia is a very common feature in the intensive care (ICU) setting and it is related to multiple causes that include inflammatory and neuro-endocrine derangements in critically ill patients, which lead to insulin resistance and high hepatic glucose output (1). The target for glucose management in this population and its relationship with the patients' outcome is not clear, and results from literature are contrasting. Some evidences state that hyperglycemia, with a threshold value of 180 mg/dL, relates to an increased risk of death and morbidity due to infection in ICU patients (2). The main multicentric studies assessing the role of glucose management in critically ill patients found inconclusive results and the doubt was cast upon the benefits of tight glycemic control. In particular, the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation) trial compared 2 groups of patients with glucose target of 4.5 to 6.0 mmol/L versus 8.0 to 10.0 mmol/L and reported an absolute increase in deaths at 90 days in patients with intensive insulin treatment, suggesting that there is no additional benefit from lowering blood glucose levels below a "moderate" target range (3). Over time, optimal blood glucose target range has dramatically changed; recent evidence demonstrates that a tailored blood glucose target range should be adopted in specific subgroups of patients and that even the timing and type of nutrition is associated with changes in outcome, suggesting that in critically ill patients, an accurate nutrition protocol as well as a strict control of the duration of insulin infusion is mandatory (4).

In critical care patients, both hypoglycemia and hyperglycemia as well as variable high blood glucose values are associated with are associated with an increased risk of death. A recent retrospective study examined the relation between mean glucose strata values and mortality (1). For each patient, the mean overall glucose values measured during admission and the mean morning glucose from the first value available between 5 and 7 a.m. per patient per day was calculated. The authors found that mean overall glucose during ICU admission was related to mortality by a U-shaped curve, with a safe range of mean glucose regulation approximately between 7.0 and 9.0 mmol/L. Thus, as well as the variability of increased rates of blood glucose seem to be associated with higher and attention should be paid to prevent both hypo and hyper glycemia and to minimize changes in blood glucose values variability needs to be deleted; consequently, bolus insulin injection, both intravenous and subcutaneous, and bolus infusion of high glucose concentration solutions should be strictly avoided (5), and therapeutic strategies in order to minimize the risks related to active management of blood glucose control (in particular induction of iatrogenic hypoglycemia) should be adopted (6).

The management of blood glucose becomes even more crucial in some groups of patients such as in the neurocritical care population and in patients with sepsis. The relationship between hyperglycemia and worse neurological outcome after acute brain injury has been confirmed in a review with meta-analysis (7). According to the authors, blood glucose levels must be monitored appropriately and administered along with adequate enteral or parenteral nutrition; moreover, iatrogenic hypoglycemia must be always avoided, but a 'moderate' target range of 110 to 180 mg/dL with adequate nutrition before and during insulin infusion, and careful and accurate glycemic monitoring is raccomanded (8). In a retrospective study of 86 traumatic brain injured patients, mean arterial glucose concentrations

during the first 5 days since admission were correlated with an impairment of cerebrovascular reactivity (9), potentially explaining the link between increased blood glucose and poor outcome; this study confirmed the strict relationship existing between insulin and the brain, as discussed by Bilotta *et al*. (10) who underlight the effects of glucose management on memory, learning abilities, and motor functions suggesting that a wider understanding of the effects of glucose and insulin on cerebrovascular dynamics is necessary.

All in, the effects of hyperglycemia on the outcome of critically ill patients, especially in diabetic population, and the pathophysiological mechanism contributing to a link between increased blood glucose and poor outcome remain unclear.

The large prospective observational cohort study performed by van Vught *et al*. (11) explored the relationship between admission blood glucose concentration and outcome in septic patients admitted to ICU and addressed some important points regarding this topic.

The main endpoint of this research was to investigate the association between hyperglycemia on ICU admission and the outcome of sepsis, in diabetic and non diabetic patients and to provide insight into the effect of hyperglycemia on key host responses involved in the pathogenesis of sepsis.

A total of 1,483 patients consecutively admitted to ICU for sepsis were evaluated for possible enrollment. Out of these, 496 were excluded from this study: 250 patients (16.9%) because re-admission, 164 (11%) because transferred from other ICU's, 60 patients (5.7%) had an admission glucose level ≤70 mg/dL and 22 patients (2%) didn't meet the criteria because the first blood glucose concentration measurement took place more than 4 hours after admission, thus leading to the enrollment of a total 987 patients. Enrolled patients were categorized into three groups according to the blood glucose values: euglycemia (71–140 mg/dL), mild hyperglycemia (141–199 mg/dL) and severe hyperglycemia (≥200 mg/dL). Admission glucose was defined as the first glucose measurement within a time window of 4 hours before and up to 4 hours after ICU admission. Moreover, acute phase response and cytokine levels (CRP, IL-6, 8, 10), endothelial cell activation markers (soluble E-selectin, Angiopoietin-1, 2 and soluble ICAM-1) and coagulation markers (Antithrombin, D-Dimer, protein C) were measured. According to their results, in non-diabetic patients, severe hyperglycemia was found to be a predictor of increased mortality only when associated with hyperlactatemia. In septic patients without a history of diabetes, severe hyperglycemia on ICU admission was associated with increased risk to develop acute kidney injury and acute myocardial infarction. Severe but not mild hyperglycemia was associated with an increased mortality by day 30 in both diabetic and non diabetic patients.

The peculiar characteristic of this paper is the assessment of blood glucose values at first admission, while that most investigations studied glucose levels during hospital or ICU stay, when insulin treatment was presumably already started. Patients with severe hyperglycemia did not have more severe clinical presentation on admission, but the mechanism associated with worsened outcome in patients with hyperglycemia was found to be unrelated to exaggerated inflammation, coagulation or endothelial cell activation, in contrast with other previous findings (12-14).

Data from van Vught and colleagues, confirm previous evidences and strongly support the need to implement blood glucose concentration monitoring in the standard of care of ICU patients. The authors concluded that severe hyperglycemia on admission, defined as a plasma glucose concentration of 200 mg/dL or higher, is associated with an increased mortality in patients admitted with sepsis and that this association is present in patients with and without a known history of diabetes. The physiopathological mechanisms underlying this process remain unclear, as severe hyperglycemia was associated with just attenuated rises in CRP and IL-6 and a reduced drop in antithrombin and protein C in patients without a known history of diabetes.

This manuscript confirms the need for continuous glucose monitoring devices providing accurate measurement which can contribute to minimize the risks associated with hyperglycemia, as an immediate and effective glycemic management is necessary since the first hours from ICU admission. Glycemic management should be based on accurate blood glucose concentration monitoring and achievement of the optimal blood glucose levels target range by using insulin titration, along with an adequate nutritional protocol.

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Footnote

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