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EDITORIAL

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Treatment thresholds for hyperglycemia in critically ill patients with and without diabetes

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Hyperglycemia is exceedingly common in critically ill patients. Although there is no accepted definition of acute hyperglycemia in the critical care setting, it is generally considered to be above 180–220 mg/dl (10.0–12.2 mmol/l). In the study by Plummer and colleagues reported in this issue of *Intensive Care Medicine* only 22.7 % of ICU patients were normoglycemic [1]. Glycemic control and the optimal blood glucose target are a subject of enormous controversy in critically ill patients. Retrospective and cohort studies in both ICU and hospitalized non-ICU patients have demonstrated a strong association between hyperglycemia and poor clinical outcomes [2]. It had therefore been assumed that "strict" glycemic control would improve patient outcomes. In 2001 van den Berghe et al. [3] reported that tight glycemic control (80–110 mg/dl, 4.4–6.1 mmol/l) improved the outcome of critically ill patients in a surgical intensive care unit. Subsequent studies, the most important being the NICE-SUGAR study, demonstrated that intensive glucose control (81–108 mg/dl, 4.5–6.0 mol/l) increased mortality when compared to conventional glucose control (144–180 mg/dl, 8.0–10.0 mmol/l) [4]. We have previously argued that hyperglycemia is a marker of illness severity rather than a cause of poor outcome [5]. Indeed, the degree of hyperglycemia is related to the degree of activation of the stress response. Stress hyperglycemia is regarded as an evolutionary adaptive response which allows the host to survive during periods of severe stress [5]. The neuroendocrine response to stress is characterized by excessive gluconeogenesis, glycogenolysis, and insulin resistance, with increased hepatic output of glucose (gluconeogenesis) being the major cause of stress hyperglycemia. Insects, worms, and all verterbrates including fish develop stress hyperglycemia when exposed to stress [5]. Stress hyperglycemia provides a source of fuel for the immune system and brain at a time of stress. While mild to moderate stress hyperglycemia is protective it is likely that severe stress hyperglycemia may be deleterious. However, the blood glucose threshold above which stress hyperglycemia becomes harmful is unknown. Furthermore, we suggest that both the duration and the degree of hyperglycemia are important in determining whether hyperglycemia is protective or harmful [5]. It seems most unlikely that a few days of hyperglycemia would be harmful; indeed attempts at rapid correction of blood glucose in these patients may be harmful.

Patients with severe hyperglycemia (blood glucose above 220 mg/dl, 12.2 mmol/l) may benefit from moderate glycemic control measures; however, this postulate is untested. Although the NICE-SUGAR study targeted a blood glucose between 144 and 180 mg/dl (8–10 mmol/l) in the control arm, there is no evidence that targeting an even more tolerant level between 180 and 220 mg/dl (10–12.2 mmol/l) would not, in fact, have been better. The current American College of Physicians Guideline recommends a target blood glucose of 140–200 mg/dl (7.7–11.1 mmol/l) in medical/surgical ICU patients with hyperglycemia [6]. Tight glycemic control (80–110 mg/

dl, 4.4–6.1 mmol/l) is currently considered the standard of care in patients undergoing cardiac surgery. This recommendation is based largely on uncontrolled retrospective studies. Agus et al. [7] performed a prospective randomized controlled trial comparing tight glycemic control (80–110 mg/dl, 4.4–6.1 mmol/l) to standard of care in 980 pediatric patients undergoing cardiac surgery. In this study none of the outcome measures differed between groups. Recent publications recommend a more liberal blood glucose target (140–180 mg/dl) than previously recommended in these patients [8]. The optimal blood glucose target in cardiac surgery patients is unknown and it is unclear if this differs from general medical/surgical ICU patients.

Current criteria used for the diagnosis of diabetes mellitus are (i) HbA1c level above 6.5 % [National Glycohemoglobin Standardization Program (NGSP) certified methods], (ii) fasting glucose concentration above 126 mg/dl (7.0 mmol/l), (iii) 2 h plasma glucose concentration above 200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test (OGTT), or (iv) with classic symptoms of hyperglycemia or hyperglycemic crisis with a random plasma glucose concentration above 200 mg/dl (11.1 mmol/l) [9]. Although diagnostic criteria based on HbA1c may be insensitive and not uniformly applicable to all patients [10], HbA1c level measured at admission to ICU is probably still the most useful test for undiagnosed diabetes, because glucose concentrations in critically ill patients increase even in the absence of diabetes. International guidelines recommend the use of a protocolized approach to avoid acute hyperglycemia irrespective of the presence of diabetes mellitus [9].

Recent studies have shown that the relationship between hyperglycemia and outcomes is altered by the presence of diabetes mellitus [11, 12]. Lowering the blood glucose levels in critically ill patients with chronic hyperglycemia will result in drastic and rapid changes of glucose concentrations. The degree of blood glucose change (glycemic variability) has been demonstrated to be an independent predictor of poor outcome in critically ill patients [13]. In patients with type II diabetes, glycemic variability has been demonstrated to increase oxidative stress [14]. Increased oxidative stress can result in endothelial dysfunction and contribute to vascular damage. It would therefore appear appropriate to have a higher glycemic treatment target in patients with preexisting diabetes and premorbid poor glycemic control to prevent large reductions in blood glucose concentration. In the study by Plummer and colleagues increasing blood glucose levels were associated with an increased risk of death in non-diabetics with stress hyperglycemia and diabetics with an admission HbA1c below 7 %. However in diabetic patients with an HbA1c above 7 % hyperglycemia was not associated with an increased risk of death.

Table 1 Suggested blood glucose targets in diabetic and non-diabetic ICU patients

Patient group	Therapeutic blood glucose target, mg/dl (mmol/l)
Non-diabetic	140–200 (7.7–11.1)
Diabetic HbA1C <7 %	140–200 (7.7–11.1)
Diabetic HbA1C ≥7 %	160–220 (8.8–12.2)
Cardiac surgery, non-diabetic	140–180 (7.7–10.0)
Cardiac surgery, diabetic HBA1C <7 %	140–180 (7.7–10.0)
Cardiac surgery, diabetic HbA1C ≥7 %	160–200 (8.8–11.1)

Egi and colleagues previously demonstrated that in patients with a high HbA1c (above 7 %) there was an inverse relationship between ICU glycemic control and mortality—higher blood glucose levels during ICU stay were associated with lower mortality [15]. Biological adjustment to preexisting hyperglycemia and less glycemic variability might explain this phenomenon. These observations generate the hypothesis that glucose levels that are considered safe and desirable in other patients might be undesirable in diabetic patients with chronic hyperglycemia. In diabetic patients whose glucose has been poorly controlled prior to ICU admission, rapid and substantial lowering of their blood glucose levels during their acute illness/surgery may worsen outcomes. On the basis of this data we suggest that the HbA1c be checked on admission to the ICU in all diabetics with blood glucose therapeutic targets as provided in Table 1.

Conflicts of interest The authors have no financial interest to declare or any real or perceived conflict of interest.

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