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REVIEW

Glycemic control in critically ill patients

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Abstract

Hyperglycemia is common in critically ill patients and can be caused by various mechanisms, including nutrition, medications, and insufficient insulin. In the past, hyperglycemia was thought to be an adaptive response to stress, but hyperglycemia is no longer considered a benign condition in patients with critical illnesses. Indeed, hyperglycemia can increase morbidity and mortality in critically ill patients. Correction of hyperglycemia may improve clinical outcomes. To date, a definite answer with regard to glucose management in general intensive care unit patients, including treatment thresholds and glucose target is undetermined. Meta-analyses of randomized controlled trials suggested no survival benefit of tight glycemic control and a significantly increased incidence of hypoglycemia. Studies have shown a J- or U-shaped relationship between average glucose values and mortality; maintaining glucose levels between 100 and 150 mg/dL was likely to be associated with the lowest mortality rates. Recent studies have shown glycemic control < 180 mg/dL is not inferior to near-normal glycemia in critically ill patients and is clearly safer. Glycemic variability is also an important aspect of glucose management in the critically ill patients. Higher glycemic variability may increase the mortality rate, even in patients with the same mean glucose level. Decreasing glucose variability is an important issue for glycemic control in critically ill patients. Continuous measurements with automatic closed-loop systems could be considered to ensure that blood glucose levels are controlled within a specific range and with minimal variability.

Key words: Critical care; Glycemic control; Hyperglycemia; Hypoglycemia; Insulin

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INTRODUCTION

Hyperglycemia is common in critically ill patients, even those patients who have not been previously diagnosed with diabetes[1,2]. Increasing evidence indicates that the development of hyperglycemia during acute medical or surgical illness is not a physiological or benign condition[3-7]. Alterations in glucose metabolism occur during critical illness and are mediated by various factors, including increased insulin resistance, change in hormone production, and activation of cytokines[8]. In critically ill patients a hypermetabolic state exists[9], with the predominant cause being the intense activation of counter-regulatory hormones and cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1, and IL-6, which may be important mediators of insulin resistance and result in hyperglycemia[10]. Clinicians have increasingly

appreciated the impact of hyperglycemia in patients with diabetes, as well as stress-induced hyperglycemia (SIH) or hospital-related hyperglycemia[11-13]. The vast majority of patients in the intensive care unit (ICU) have SIH, which refers to transient hyperglycemia during illness and is usually restricted to patients without previous evidence of diabetes[14]. Patients without diabetes have a higher mortality risk when admitted to the hospital than do patients with diabetes[15-18].

Hyperglycemia is independently associated with increased ICU mortality[19-23]. Strict control of the blood glucose concentration is considered important because strict control of the blood glucose concentration may reduce mortality and morbidity; however, hypoglycemia is significantly higher in patients with tight glucose control using intensive insulin therapy[24,25]. Glycemic control to a moderately tight range is not inferior to euglycemia and clearly safer in critically ill patients[26,27]. A less than strict approach to managing critical illness-related hyperglycemia while avoiding hypoglycemia is becoming the standard approach in most ICUs.

EPIDEMIOLOGY

The prevalence of hyperglycemia in critically ill patients is difficult to estimate because the diagnosis is variably defined. Approximately 75% of all patients, including diabetics, have blood glucose concentrations > 110 mg/dL at the time of admission, and 12% of all patients have blood glucose concentrations > 200 mg/dL[24]. Another study showed that > 60%, 38% and 23% of patients had blood glucose concentrations > 110 mg/dL, > 150 mg/dL and > 200 mg/dL after admission in the medical ICU of a tertiary care medical center, respectively[28]. Glucose values > 140 mg/dL occur in 51%-58% of patients presenting with acute myocardial infarctions (MIs)[29,30]. Latham *et al*[31] found that 21% of cardiothoracic surgery patients developed post-operative blood glucose levels of > 200 mg/dL. The prevalence rates of hyperglycemia were 86.7%, 61% and 35.2% for pediatric patients with maximal glucose levels of > 110 mg/dL, > 150 mg/dL and > 200 mg/dL, respectively[32]. Faustino *et al*[33] reported prevalence data of 75%, 50.1%, and 26.3% in pediatric patients with cut-off values of 120, 150 and 200 mg/dL, respectively.

CAUSES OF HYPERGLYCEMIA AND PATHOPHYSIOLOGY

The factors contributing to hyperglycemia in patients with critical illnesses include the release of stress hormones and the use of medications (exogenous glucocorticoids, vasopressors, lithium, and β-blockers). Overfeeding, intravenous dextrose, commonly used parenteral nutrition, dialysis solutions, and antibiotic solutions, also contribute to hyperglycemia. Insufficient insulin or volume depletion can cause hyperglycemia[34]. Bed rest, even in the absence of obvious disease, leads to impaired skeletal muscle glucose uptake and promotes peripheral insulin resistance; simple bed rest can further aggravate SIH[35].

In patients with diabetes, the cause of hyperglycemia is a combination of insulin resistance and pancreatic β-cell secretory defects. In patients with SIH, the cause of hyperglycemia is a complex interaction of counter-regulatory hormones, cytokines and insulin resistance[36]. Glucagon, epinephrine, and cortisol increase gluconeogenesis and glycogenolysis. Gluconeogenesis is triggered to a greater extent by glucagon than by epinephrine and cortisol[37-39]. TNF-α may promote gluconeogenesis by stimulating glucagon production[40]. Glycogenolysis is triggered primarily by catecholamines and perpetuated under the influence of epinephrine and cortisol[36].

Insulin resistance may be associated with impaired insulin receptor binding or impairment in the activation of early or intermediate components of the insulin signaling pathway[41] and/or with defects in glucose transporter 4[42]. Epinephrine can inhibit insulin-stimulated glucose transport in skeletal muscle. The action of counter-regulatory hormones on insulin resistance in skeletal muscles may be mediated through an elevation in the circulating free fatty acid level in patients with critical illness, despite hyperinsulinemia[43]. Cytokines such as TNF-α and IL-1, inhibit post-receptor insulin signaling[44,45]. The severity of illness is associated with a proportional rise in serum cytokines and insulin resistance[46,47].

ADVERSE EFFECTS OF HYPERGLYCEMIA

It has been reported that pronounced hyperglycemia might lead to complications or a poor clinical outcome[12]. Elevated blood glucose concentrations are associated with increased morbidity and mortality after burns, surgery, strokes, MIs and head trauma[4,48-54]. In the pediatric ICU, peak blood glucose levels and the duration of hyperglycemia are independently associated with mortality[55]. Hyperglycemia can cause polymorphonuclear neutrophil dysfunction[56], and decreased intracellular bactericidal[57,58] and opsonic activity[56,59] which plays a role in the increased incidence of infections in patients with hyperglycemia. High glucose concentrations in cells can damage mitochondrial protein[60], exacerbate inflammatory pathways, modify the innate immune system, and impair endothelial function[61]. High glucose concentrations also reduce vascular reactivity and endothelial nitric oxide production, which may compromise blood flow to the periphery[62]. In addition, acute hyperglycemia enhances proteolysis[63] and is associated with an increased risk of cardiac complications, hemodynamic and electromyocardial disturbances, acute renal failure, and death[64,65].

INSULIN THERAPY PROTOCOLS

Use of a validated protocol to help maintain the glucose level is effective in critically ill patients. The protocol should be developed by a core group of clinicians, in-

ICU protocol for glycemic management

MD signature_____
Date_____

Goal

The goal of this protocol is to maintain the glucose level between 140 and 160 mg/dL

Monitoring

The initial blood glucose level is monitored every 1-2 h until a stable infusion rate is reached, then decreased to every 4 h while the blood glucose concentration is stable

Management of insulin infusion

Continuous insulin infusion (100 IU of Actrapid HM in 99 mL of 0.9% NaCl) with the use of a pump is started when the blood glucose is > 180 mg/dL on two successive measurements

Blood glucose levels are controlled by the neuro-fuzzy method. The first row at the top of the chart in the appendix displays the range of blood glucose values measured, while the first column on the left displays the range of possible blood glucose values measured 1-4 h previously. The adjusted infusion rate is at the intersection between the perpendicular lines drawn from the present blood glucose values and the blood glucose values found 1-4 h previously

Initial dose: patients received oral hypoglycemic agents or up to 12 U/d of insulin, starting with 0.5 U/h of insulin if patients previously received insulin > 12 U/d, and 0.5 U/h for every 10 U > 12 U/d

Present blood glucose value (mg/dL)

Preceding blood glucose value (mg/dL) (1-4 h before)	≤ 80	81-100	101-120	121-140	141-160	161-180	181-200	201-220	221-240	241-260	> 260
≤ 80	-0.3	-0.2	0.1	0.5	0.8	1.2	1.3	1.4	1.5	1.5	1.5
81-100	-0.5	-0.4	-0.2	0.2	0.6	1	1.2	1.4	1.4	1.5	1.5
101-120	-0.7	-0.7	-0.4	0.0	0.4	0.8	1.1	1.3	1.4	1.4	1.5
121-140	-0.9	-0.8	-0.6	-0.3	0.2	0.6	1	1.2	1.3	1.4	1.4
141-160	-1	-1	-0.6	-0.5	0.0	0.6	0.9	1.1	1.3	1.4	1.4
161-180	-1.2	-1.1	-1	-0.7	-0.2	0.3	0.7	1	1.2	1.3	1.4
181-200	-1.3	-1.3	-1.1	-0.8	-0.4	0.1	0.6	0.9	1.2	1.3	1.4
201-220	-1.4	-1.4	-1.2	-1.0	-0.8	-0.1	0.4	0.8	1.1	1.3	1.4
221-240	-1.4	-1.4	-1.3	-1.1	-0.5	-0.3	0.2	0.7	1	1.2	1.3
241-260	-1.5	-1.5	-1.4	-1.2	-0.6	-0.5	0.1	0.6	0.9	1.2	1.3
> 260	-1.5	-1.5	-1.4	-1.3	-1	-0.6	0	0.5	0.9	1.1	1.3

Management of hypoglycemia

If the blood glucose concentration is ≤ 60 mg/dL, the protocol directs the nurses to stop the insulin infusion, and notifies physicians to administer 50% dextrose immediately, with blood glucose measurements repeated after 30 min

Switch to subcutaneous insulin-injection

If the insulin dose is < below 3 IU/h, a conversion of the intravenous infusion to a subcutaneous insulin injection is considered. The insulin infusion is often discontinued before the patient is discharged from the ICU

Figure 1 Example of glycemic control protocol in an adult intensive care unit. ICU: Intensive care unit.

cluding physicians, nurses, pharmacists, and dietitians with guidelines that provide targeting a specific glucose level, insulin dose adjustment, the interval of glucose monitoring, and time for stopping infusion or decreasing the infusion rate to accommodate changes in patient feeding regimes for tests or medications. The risks of complications, such as hypoglycemia, must be addressed. Intravenous insulin therapy is suggested. The initial blood glucose level is monitored every 1-2 h until a stable infusion rate is reached, then decreased to every 4 h while the blood glucose concentration is stable[66]. A protocol is shown in Figure 1 as an example which can be modified for local needs.

Published glycemic management protocols have been documented to significantly improve glucose levels without a significant increase in the risk of hypoglycemia[67]. The advantages of an algorithm or protocol include more consistent glucose control, less of a trial-and-error pattern of treatment, the ability to maintain glycemic control closer to the target range of near-normal, and earlier intervention for hypoglycemia[68,69]. A lack of protocol-based care might be expected to increase glycemic variability[70].

Regular measurement of blood glucose is a burden for nurses; glycemic control by continuous glucose monitoring with automatic closed-loop systems can reduce the clinical burden[71]. Glycemic management protocols in the ICU should focus more on the variability of glycemic control as the treatment target, because glycemic management is related to patient outcome. Continuous monitoring of glucose would allow for the early identification of rapid fluctuations in status associated with changes in insulin requirements. Continuous monitoring of glucose may help prevent the extremes of glucose variability and can maintain optimal blood levels without causing hypoglycemia, thus decreasing the variability in blood glucose concentrations in patients admitted to the ICU[72]. Conversion of an intravenous infusion to subcutaneous insulin injection therapy is often necessary before or at the time of discharge from the ICU[73].

OUTCOMES

Hyperglycemia has been linked to worse outcomes in critically ill patients[74-76]. The SPRINT study showed that tight glycemic control to a mean of 6.0 mmol/L mitigated organ failure faster than conventional control at a higher mean level of 7.2 mmol/L[77]. In 2001, van den Berghe *et al*[24] published the Leuven study, which demonstrated that tight glycemic control with a target of blood glucose level between 80 and 110 mg/dL had better outcome than conventional control in critically ill surgical patients. ICU mortality, the risk of multi-organ failure, systemic infection and sepsis, the incidence of acute renal failure, critical illness-related polyneuropathy, the need for blood transfusion, and the need for prolonged mechanical ventilator support were reduced from 8% to 4.6%, 34%, 40%, 41%, 44%, 50%, and 50%, respectively. Based on the Leuven study, tight glycemic control was adopted as the standard for critical care patients worldwide. In 2004, Krinsley *et al*[67] demonstrated that patients in whom the blood glucose concentrations were controlled to < 140 mg/dL had superior survival rates than did patients in whom the blood glucose concentrations were controlled to < 200 mg/dL in medical-surgical ICUs. In 2006, Van den Berghe *et al*[25] repeated the Leuven study in a medical ICU, but did not demonstrate a survival benefit with tight glycemic control in all critically ill medical patients; however, better outcomes, including ICU, ventilator, and hospital days were noted. For patients in the ICU > 3 d, a survival benefit was reported in the tight glycemic control group. Other studies in which tight glycemic control in the ICU was achieved did not demonstrate a lower mortality rate, less frequent acute renal failure, decreased need for renal replacement therapy, decreased vasopressors, and a lower number of ventilator-free days in the intensive insulin treatment group[26,78-81]. A significantly higher mortality rate was reported in the NICE-SUGAR study[26]. Furthermore, the NICE-SUGAR study did not demonstrate shorter ventilator, ICU, and hospital days, and a lower rate of renal replacement therapy, positive blood cultures, and red cell transfusions, but significantly higher rates of severe hypoglycemia were noted. Wiener *et al*[82] reviewed 29 randomized controlled trials with a total of 8432 patients in a meta-analysis. Wiener *et al*[82] showed that hospital mortality did not differ between patients with tight glucose control and patients with usual care, and there was also no significant difference in mortality when stratified by glucose goals. Another meta-analysis study showed that intensive insulin therapy may be beneficial in patients admitted to the surgical ICU, but not the medical ICU or a mixed ICU[83].

Patients with SIH had worse outcomes than patients with a known diabetic history. Umpierrez *et al*[2] reported that newly diagnosed hyperglycemia (admission or fasting glucose level > 125 mg/dL or random glucose level > 200 mg/dL) was associated with a 16% mortality rate compared to a mortality rate of 3% among patients with known diabetes and a rate of 1.7% among patients without hyperglycemia. Three cohorts of ICU patients concluded that hyperglycemia during an ICU admission had a more significant impact on the risk of mortality among patients without diabetes than among patients with diabetes[72,84,85].

GLYCEMIC VARIABILITY

Blood glucose levels in critically ill patients fluctuate widely, even when continuous feeding and an insulin infusion are used[69]. Glycemic variability is usually expressed as the standard deviation around the mean glucose value or as the mean amplitude of glycemic excursions[86]. Glycemic variability is also associated with outcome in critically ill patients; specifically, greater glycemic variability is associated with a significantly higher mortality rate[87-89]. Non-survivors of critical illnesses were shown to have a higher standard deviation and coefficient of variation (CV) of glucose (standard deviation/mean glucose level) during the ICU stay. A blood glucose level standard deviation > 20 mg/dL was associated with a 9.6-fold increase in mortality compared with a blood glucose level standard deviation < 20 mg/dL[89]. A deleterious effect resulting from increased glycemic variability was noted among non-diabetic patients, but not among patients with diabetes. The mortality rate among non-diabetic patients with a mean glucose level of 70-99 mg/dL during the ICU stay was 10.2% for patients with a glucose CV of < 15% *vs* 58.3% for patients with a glucose CV above 50%[88]. Increased glycemic variability not only increased the mortality rate, but also morbidities, such as nosocomial infections and hospital length of stay[90]. In a recent retrospective study involving surgical ICU patients, Hermanides and coworkers reported serum glucose variance and combined with high serum glucose levels was associated with the highest mortality, and glucose variability was more important than glucose levels in predicting outcome[91]. Dossett *et al*[92] reported that glucose variability was associated with increased mortality, but the mean blood glucose level was not associated with increased mortality in patients with sepsis.

Why is glycemic variability associated with poorer outcomes? Glycemic variability may reflect more attention to detail in medical and nursing care, which may be the real determinants of better outcomes. Less glycemic variability may be associated with severe illness[93]. Induced fluctuation in glycemic levels is more likely to produce apoptosis than sustained hyperglycemia[94,95]. These effects may be mediated *via* wide changes in osmolarity that in turn could affect cellular and organ function[96]. Oxidative stress was produced in much higher concentrations by alterations in glycemic levels than by sustained hyperglycemia[97]. Indeed, increased oxidative stress can result in endothelial dysfunction and contributed to vascular damage. Oxidative stress may be one of the unifying mechanisms underpinning the vasoconstriction, microvascular thrombosis, and inflammation associated

with hyperglycemia and glycemic variability[98,99]. Rapid changes in glucose levels can also induce monocyte adhesion to endothelial cells[100]. Another reason why increased glycemic variability may be associated with poorer ICU outcomes is the fact that significant hypoglycemia could occur undetected[101].

In past trials involving intensive insulin therapy, there were discrepancies in mortality outcomes. All of the data regarding glycemic variability were unavailable in these trials; however, glycemic variability may account for the different mortality rates.

HYPOGLYCEMIA

A plasma glucose concentration < 70 mg/dL is the most common threshold used to define hypoglycemia[102]; however, most of the studies involving glucose control in the ICU have defined severe hypoglycemia arbitrarily as values < 40 mg/dL whether or not the patients had associated symptoms[24,25,67,79,81]. Emerging data suggest that hypoglycemia may have a negative impact on the clinical status and outcome of ICU patients[103,104]. ICU patients may tolerate hypoglycemia poorly and also exhibit impaired counter-regulatory responses or have delayed detection of hypoglycemia. The most severe complications of severe hypoglycemia, such as seizures and death, are easy to measure; more subtle manifestations of neuroglycopenia, such as headaches, fatigue, confusion, dysarthria, or impaired judgment, may be difficult or impossible to diagnose in critically ill patients[105,106]. Hypoglycemia is more common in medical and septic sub-groups of patients[107]. Female gender, a history of diabetes, the APACHE Ⅱ score, mechanical ventilation, continuous veno-venous hemodialysis, and ICU length of stay are independent predictors of hypoglycemia[108]. Spontaneous episodes of severe hypoglycemia are rare and observed mainly in patients with fulminant hepatic failure and adrenal failure secondary to septic shock, and especially in patients with severe co-morbidities, such as liver cirrhosis, chronic renal failure, and malnutrition[26,109].

Based on the Leuven study in 2001, intensive insulin therapy was widely used in many ICUs. Many studies have shown that intensive insulin therapy is associated with significantly more episodes of severe hypoglycemia than conventional insulin therapy[78-81,110]. In the VISEP[80] and Glucocontrol trials[81], the studies were terminated early because of significantly more hypoglycemic episodes in the intensive insulin treatment group. In two meta-analyses studies, intensive insulin therapy also showed a significantly increased risk of hypoglycemia[82,83]. Because intensive insulin therapy has been associated with a significantly higher risk of hypoglycemia, there is increased concern about the safety of intensive insulin therapy, which has become an obstacle to strict glycemic control.

Is the hypoglycemic episode directly responsible for an increased risk of death in patients with critical illnesses? One study revealed the degree of hypoglycemia parallels the increase in the risk of death[111]. Even a single episode of severe hypoglycemia is independently associated with an increased risk of mortality[104]; however, some studies have shown that the occurrence of hypoglycemic is not associated with an increased risk of mortality[108,112].

GLYCEMIC GOAL

Considerable uncertainty remains regarding the optimal target levels of glucose for patients in the ICU. A safe upper limit for blood glucose level during insulin therapy has not been precisely determined in critically ill patients. The Surviving Sepsis Campaign Guidelines advocate a goal of glucose control < 150 mg/dL, in part to limit hypoglycemia[64]. A large body of observational cohort study data from heterogeneous populations strongly suggests that a J- or U-shaped mortality curve exists among acutely and critically ill patients[28,113,114]. Both high and low blood glucose values are independently associated with hospital mortality, with the lowest mortality occurring among those patients with mean glucose levels during their stay in the range of 5.60-8.69 mmol/L and higher rates of mortality for those patients with levels below or above this range[107]. In a recent study, moderate glycemic control was superior to tight glycemic control with decreased mortality and major complications for patients undergoing isolated coronary artery bypass grafting[27]. Patients with a glucose level of 127-179 mg/dL had the lowest mortality and major complications; specifically, sepsis, prolonged ventilation, post-operative renal failure, and the need for new dialysis were highest in the tight glucose control group. Another study also showed that a glucose level of 140-180 mg/dL was associated with the best risk-benefit ratio[103]. The American Association of Clinical Endocrinologists and the American Diabetes Association have increased the treatment threshold to values > 180 mg/dL and a target glucose level between 140 and 180 mg/dL for ICU patients[115].

CONCLUSION

Acute hyperglycemia associated with insulin resistance is common in critically ill patients. Both hyperglycemia and hypoglycemia harm our patients. The appropriate glycemic target has not been established and may indeed be different for different patient populations. At the same mean blood glucose value, the nature of glycemic control can be quite different with respect to glycemic variability. Not only is the blood glucose level important, but glycemic variability is also important. An attempt to minimize glycemic variability might have a significant beneficial impact on the outcomes of patients without diabetes. New strategies should be developed to achieve glycemic control with a minimal risk of hypoglycemia and large glucose variations. More effort should be focused on the quality of blood glucose measurement devices and blood glucose monitoring modalities.

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