

Glycemic management in critically ill patients

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Abstract

Hyperglycemia associated with critical illness, also called "stress hyperglycemia" or "stress diabetes", is a consequence of many pathophysiologic hormonal responses including increased catecholamines, cortisol,

glucagon, and growth hormone. Alterations in multiple biochemical pathways result in increased hepatic and peripheral insulin resistance with an uncontrolled activation of gluconeogenesis and glycogenolysis. Hyperglycemia has a negative impact on the function of the immune system, on the host response to illness or injury, and on infectious and overall outcomes. The degree of glucose elevation is associated with increased disease severity. Large randomized controlled trials including the Van den Berghe study, the NICE-SUGAR trial, VISEP and GLUCONTROL have shown that the control of glucose levels in critically ill patients has implications on outcome and that both hyperglycemia and hypoglycemia are detrimental and should be avoided. Glucose variability has also been shown to be detrimental. Aggressive glucose control strategies have changed due to the concerns of hypoglycemia and therefore intermediate target glucose control strategies are most often adopted. Different patient populations may vary with regards to optimal glucose targets, timing and approach for glucose control, and with regards to the prognostic significance of glucose excursions and variability. Medical, surgical, and trauma patients may benefit at different rates from glucose control and the approach may need to be adapted to various medical settings and to correspond to the workflow of health providers. Effect modifiers for the success of insulin therapy for hyperglycemia include the methods of nutritional supplementation and exogenous glucose administration. Further research is required to improve insulin protocols for glucose control, to further define glucose targets, and to enhance the accuracy of glucose measuring technologies.

Key words: Hyperglycemia; Hypoglycemia; Critically ill; Intensive care unit; Glucose control

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Core tip: Hyperglycemia is not innocuous, especially in the critically ill; and glucose control has been shown to significantly impact morbidity and mortality. In this review, we describe the pathophysiology of the "diabetes

of stress"; we summarize the major investigations that constitute the body of evidence and the reasons behind current practices. Further, we emphasize glucose considerations in special populations, especially trauma and postoperative populations. Finally, we provide insight on the relative importance of avoiding hyperglycemia, hypoglycemia, and glucose variability.

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INTRODUCTION

Historically, elevation in blood glucose has been considered to be a compensatory response that exemplifies the metabolic changes required to cope with injury or illness. This view has radically changed since the seminal study by Van den Berghe *et al.*^[1] in the early 2000s. Glycemic control has been shown to have an important impact on outcome, especially in critically ill patients. Relevant glucose derangements include hyperglycemia, glycemic variability, and hypoglycemia. The ideal target for glucose control continues to be under debate. In this review, we will discuss the evidence behind current practices of glucose control with emphasis on glucose considerations in special populations, such as trauma and postoperative patients. We will also summarize the pathophysiology of hyperglycemia in the critically ill.

HYPERGLYCEMIA IN CRITICALLY ILL PATIENTS

Hyperglycemia is defined as an acute sustained rise in serum glucose levels^[1]. Stress hyperglycemia is associated with the physiologic response to stress, including illness or injury. It is a multifactorial occurrence resulting from multiple metabolic derangements as well as the effects of medical treatments. Hyperglycemia is not innocuous; it incurs a range of adverse events, including abnormal immune function, increased infection rate, and hemodynamic and electromyocardial disturbances^[2-6]. It is associated with increased insulin resistance and is partially due to the patient's inability to meet the increase in insulin demands that accompanies the metabolic stress response^[3,6]. The clinical impact of hyperglycemia has been investigated in large clinical trials.

The landmark study by Van den Berghe *et al.*^[1] conducted in Leuven, Belgium, is a randomized interventional trial that enrolled 1548 patients admitted to a single intensive care unit (ICU) with a predominantly surgical population. In that study, intensive insulin therapy (IIT, target glucose range 80 to 110 mg/dL achieved by a titratable infusion of fast-acting insulin) resulted in a reduction in overall mortality of 32% compared

to conventional glucose therapy (CGT, target glucose range 180 to 200 mg/dL, with insulin infusion only started at > 215 mg/dL). Furthermore, in this study, IIT decreased blood stream infections by 46%, acute renal dialysis requiring dialysis or hemofiltration by 41%, and transfusion requirements by 50%. The greatest reduction in mortality involved deaths due to multiple-organ failure with a septic focus, and involved long-stay patients defined as being in ICU for more than 5 d. The study was stopped early for safety reasons since CGT was inferior. Hypoglycemia occurred in 5.1% in IIT compared to 0.8% in CGT.

The Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation (NICE-SUGAR) trial^[7] was a multi-centered randomized interventional trial that was designed to address whether the benefit of IIT is generalizable to critically ill patients in general. The study was multi-centered and included 6104 patients of a mixed population of medical and surgical patients. Only patients expected to require ICU treatment for 3 or more days were enrolled. The results were opposite to the landmark study by Van den Berghe *et al.*^[1]. IIT (target glucose range 81 to 108 mg/dL) increased the risk of death by 2.6% compared to CGT (target glucose 180 mg/dL or less). The rate of hypoglycemia was 6.8% in IIT compared to 0.5% in CGT group. Interestingly, however, these results did not apply to the trauma subgroup in this study. The trauma subgroup of this study consisted of 886 patients. These patients were analyzed separately and a trend for decreased likelihood of death with IIT was found in this trauma subgroup.

Other studies aimed at determining the optimal target for blood glucose in the overall intensive care population. GLUCONTROL^[8] was a multi-centered randomized interventional trial comparing IIT (target glucose range 79 to 110 mg/dL) and an intermediate glucose control (IGT, target glucose range 126-180 mg/dL). A total of 1078 patients were analyzed. The study was stopped prematurely because a high proportion of glucose values were outside the predetermined groups for the study. The study did not show a benefit for IIT. There was an increased rate of hypoglycemia in IIT (8.7% vs 2.7%). VISEP^[9] (Volume Substitution and Insulin Therapy in severe Sepsis) trial, was a multicenter two-by-two factorial trial that randomized patients with severe sepsis to receive IIT (target glucose range 80 to 110 mg/dL) or CGT (target glucose range 180 to 200 mg/dL) and either 10% pentastarch or lactate ringer. The IIT arm was stopped first, after the inclusion of 537 patients, because of an increased rate of hypoglycemia (12.1% vs 2.1%). There was no significant difference in mortality, morbidity, or rate of organ failure between IIT and CGT.

A second Leuven study by Van den Berghe *et al.*^[10] was conducted in a medical ICU setting with the same glucose targets as the initial trial and found a reduced morbidity and length of stay with IIT but no effect on mortality among the 1200 patients. However, there was a reduction in mortality in the subgroup of patients

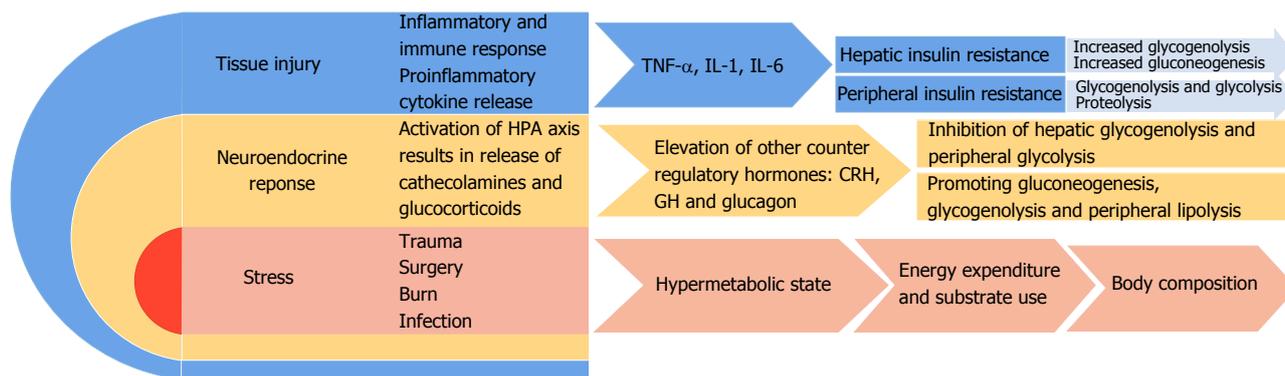


Figure 1 Response to metabolic stress. The metabolic homeostasis is affected once a stressor is identified. The response involves a series of neuroendocrine activations/inactivations and an inflammatory/immune component. The neuroendocrine response involves the activation of the hypothalamic-pituitary-adrenal axis resulting in an elevation of catecholamines and cortisol^[73]. Other counter-regulatory hormones found also elevated during physiologic stress are CRH, GH and glucagon. These hormones inhibit hepatic glycogenesis and peripheral glycolysis while activating gluconeogenesis, hepatic and muscle glycogenolysis, and peripheral lipolysis^[11]. The presence of glucagon activates the hepatic pathways of glycogenolysis and gluconeogenesis. Increased gluconeogenesis fueled by proteolytic, lipolytic, and glucolytic metabolites combined with hepatic insulin resistance are considered the main causes of stress-induced hyperglycemia, but more obvious factors such as exogenous dextrose, enteral or total parenteral nutrition, and simple bed rest can further aggravate this picture^[11]. $TNF\alpha$: Tumor necrosis factor α ; IL: Interleukin; GH: Growth Hormone; CRH: Corticotrophin.

remaining more than 3 d in ICU by a subgroup analysis. The rate of hypoglycemia in this study is elevated, 3.1% in CGT compared to 18.7% in IIT.

A direct comparison between the initial Leuven^[1] study and NICE-SUGAR^[7] is difficult due to important differences in the target blood glucose and in the patient population. Reducing hyperglycemia incurs an increased rate of hypoglycemia, to varying degrees. Furthermore, there are significant treatment differences in these patients, such as enteral vs parenteral feeding and the instruments of glucose measurement. The reasons for these discrepancies in results are thus numerous. Some important qualifiers for the effect of glucose control in critically ill patients, will be addressed in depth in this review.

PATHOPHYSIOLOGY OF HYPERGLYCEMIA IN CRITICAL ILLNESS

The metabolic response to stress

Critically ill patients commonly enter a hypermetabolic state with distinct alterations in carbohydrate, protein, and lipid metabolism as part of the physiologic stress response. The pathways involved in the metabolic response are depicted in Figure 1. The magnitude of the metabolic response is proportional to the severity of injury. These effects are mediated by hormonal and neuroendocrine components as well as by cytokines released locally in response to injury.

The stress response involves the activation of the sympathoadrenal and hypothalamopituitary-adrenal axis, resulting in increased levels of catecholamines and glucocorticoids^[11]. The effects of catecholamines include the increase in glycogenolysis in the liver and muscle and in peripheral lipolysis, which increases glucose and lactate^[11,12]. Glucocorticoids increase glucose by similar mechanisms as well as by inhibiting glucose uptake and contributing to insulin resistance^[11]. Sympathetic

stimulation of the pancreas leads to an increase in glucagon secretion and a decrease in insulin secretion^[13]. Insulin production is low in comparison to the level of glucose associated with the state of physiological stress.

Growth hormone, corticotropin, and glucagon are elevated in response to stress^[12]. These hormones are counter-regulatory to insulin; they increase glucose levels in blood by increasing gluconeogenesis, hepatic and muscle glycogenolysis, and peripheral lipolysis while inhibiting hepatic glycogenesis^[11]. The breakdown of glycogen, lipids, and muscle protein provide the substrates for hepatic gluconeogenesis, further increasing blood glucose in the critically ill^[14,15]. Furthermore, pro-inflammatory cytokines such as tumor necrosis factor alpha and interleukin-6 (IL-6) can contribute to the state of peripheral and hepatic insulin resistance^[16-18].

Glucose transport is altered in critical illness. There is usually a net rise in serum glucose levels in spite of the increase in glucose uptake^[11,15,19]. The overall picture is that of an increased supply of substrates due to the catabolic state, as well as insulin resistance and relative insulin deficiency. There is a threefold lower intestinal absorption of glucose in the gut in the setting of critical illness^[20,21], indicating that there is a homeostatic drive against hyperglycemia in critical illness. However, inflammatory cytokines, such as endothelin-1, transforming growth factor-beta, and tissue hypoxia increase the insulin-independent transport of glucose into various tissues, including neurons^[22-24]. This provides needed energy for tissue repair regeneration; however, it also exposes these cells to the untoward effects of hyperglycemia.

Insulin resistance and compensatory mechanisms

Insulin resistance culminates in the inability to stimulate glucose uptake, mainly into skeletal muscle, or to inhibit gluconeogenesis in the liver. Insulin resistance mainly occurs *via* the intracellular signaling pathway

involving the insulin receptor/insulin-receptor substrates/phosphatidylinositol 3-kinase/Akt through a loss of insulin-mediated phosphorylation^[25]. Insulin regulation of the hepatic pathway, Ras/mitogen-activated protein kinase/extracellular signal-regulated kinase, is less affected^[25]. There is the added problem of increased substrates available for gluconeogenesis due to catabolism and the effect of counter-regulatory hormones as previously described. This issue is potentially compounded by the iatrogenic doses of glucose contained in therapeutic medications or treatments.

The development of insulin resistance is not a uniform process across disease processes or tissue types. Animal studies suggest that there are tissue-specific differences in the development of insulin resistance following injury^[25]. Furthermore, the effect of a combination of trauma and hemorrhage in skeletal muscle with regards to insulin responsiveness, appears to occur by a distinct mechanism that is poorly understood. Trauma alone causes less insulin resistance than the combination of trauma and hemorrhage^[25]. Glucagon has been shown to be a major factor in the development of hyperglycemia in burn patients. Add to this that there are individual-based variations in the degree of insulin resistance in the patient population.

In humans, glucose transporter channel protein-4 (GLUT-4) is specifically and reversibly upregulated by insulin^[26] by the mechanism described above. The failure of this mechanism leads to decreased glucose uptake into skeletal muscle and adipose. GLUT-1 and GLUT-3, however, are basally active, and the concentration dependent increase in uptake due to hyperglycemia, leads to higher intracellular concentrations of glucose in glucose-sensitive tissues such as neurons and endothelial cells^[26]. On the other hand, GLUT-2 which is responsible for glucose transport across the intestinal wall is downregulated in critical illness, which affords some systemic protection against the exacerbation of hyperglycemia in illness by intestinal uptake^[20,21]. This is a protective mechanism that must be recognized in the setting of insulin-therapy.

Immune and inflammatory effects of hyperglycemia

Injury and acute illness, including states of shock, cardiac arrest, and acute respiratory distress, are associated with increased oxidative stress. The magnitude of the oxidative stress and the severity of the condition^[27,28]. Acute inflammation, ischaemia-reperfusion, hypoxia, and hyperoxia, all involved in the state of acute injury or illness and its treatment, further enhance this imbalance between reactive oxygen species and anti-oxidants^[29]. Oxidative stress increases the inflammatory response, which further increases the production of ROS like a vicious circle, and the resultant imbalance causes severe damage on essential structures such as protein, membrane lipids, carbohydrate, and DNA, which need subsequent repair^[30].

The ability of monocytes to present antigen has been shown to be compromised in acute hyperglycemia^[31].

Further there is an increased level of pro-inflammatory cytokines such as TNF-alpha, IL-1beta and IL-6 with hyperglycemia and an increased rate of neutrophil apoptosis in response to LPS challenge^[31]. A new paradigm for the human immunological response to severe injury based on the pattern of gene expression by leucocytes after injury postulates that the early leucocyte genomic response is consistent with simultaneously increased expression of genes involved in the systemic inflammatory, innate immune, and compensatory anti-inflammatory responses, and also with the simultaneous suppression of genes involved in adaptive immunity^[32].

There is significant endothelial dysfunction associated with even transient hyperglycemia^[26]. High glucose levels are also known to impair the microvasculature's ability to relax in the presence of vasodilating stimuli such as nitric oxide, and to promote the adherence and sequestration of neutrophils and monocytes into peripheral tissue^[31]. This could be a reason why morbidity and mortality are increased in association with hyperglycemia in diseases directly related to the vascular endothelium, as described later in this review.

EFFECT OF FEEDING

The association between the development of hyperglycemia during total parenteral nutrition (TPN) and poor clinical hospital outcome is well established^[33]. Patients with hyperglycemia during TPN have higher incidence of death, infection, and renal failure^[34]. Furthermore, the blood glucose values before and within 24 h of initiation of TPN may have special predictive value of mortality and complications, as shown in a study of 276 predominantly critically ill medical and surgical patients^[33].

Enterally and parenterally supplied carbohydrates do not have an equal effect on the insulin response or on the resultant blood glucose concentrations^[34]. Parenteral feeding bypasses the first-pass control mechanisms of the liver, where splanchnic glucose uptake by first-pass extraction from the portal vein and hepatic artery does not occur. Furthermore, the transit of glucose and fats through the patient's gut liberate glucagon-like peptide 1 and glucose-dependent insulinotropic peptide, among other hormones, that stimulate insulin secretion and decrease gut motility, thereby controlling the rate of nutrient absorption^[34,35]. These adaptive mechanisms for regulated clearance of metabolites are absent when nutrients are given parenterally.

In addition to this, the insulin response has been found to be higher when the carbohydrate load is administered parenterally in healthy volunteers^[36]. There is no clear explanation for this phenomenon. However, this clearly has an implication on the amount of insulin needed to cover a parenteral glucose load as compared to an enteral load, which may not be attainable by a critically ill patient. Furthermore, the type of fat included in parenteral feeding affects glucose metabolism indirectly with polyunsaturated fatty acids contributing to worse insulin resistance and hyperglycemia compared to monounsaturated fatty

acids^[34]. On the other hand, none of the enteral formulations have been shown to be distinctly superior to prevent hyperglycemia in the critically ill (standard vs elemental, high fiber or diabetes-specific formulas)^[37-43].

In the initial Leuven trial^[1], parenteral nutrition supplemented insufficient enteral feeding, whereas in the NICE-SUGAR^[7] study, patients were fed enterally exclusively. The administration of insulin during hypocaloric feeding may have increased the risk of hypoglycemia in the NICE-SUGAR^[7] study. On the other hand, the administration of insulin in the initial Leuven trial may have counterbalanced the parenteral carbohydrate load.

A meta-analysis of prospective randomized controlled trials (pooled study population of 11425) by Marik *et al.*^[44] demonstrated a significant relationship between the proportion of calories provided parenterally and the treatment effect of insulin therapy (defined as 28-d mortality in this study).

SPECIAL POPULATIONS

Newly diagnosed hyperglycemia in a study of 2030 patients admitted to a general medical center was associated with a higher rate of ICU admission and with an increased risk for adverse outcome compared with patients who had diabetes and those who were normoglycemic^[45]. In fact tight glucose control may be more beneficial in patients without diabetes^[46].

A meta-analysis of 35 randomized control trials in surgical ICUs showed that insulin therapy decreased short-term mortality by 15%^[47]. Numerous studies have shown a direct relationship between the extent of stress hyperglycemia and mortality in patients in the ICU. In critically ill non-diabetic patients who sustained a myocardial infarction, a meta-analysis of 15 observational studies reported an almost fourfold higher risk of death in patients whose glucose levels ranged from 110-144 mg/dL^[48]. Similarly, a meta-analysis of 32 observational studies demonstrated that acute hyperglycemia after stroke was associated with an increased risk for in-hospital mortality and poor functional recovery^[49].

A very large retrospective cohort study of over 250000 patients demonstrated that admission diagnosis was a modifier of the effect of admission hyperglycemia on outcome^[50]. In other words, specific diagnoses have a greater association between initial hyperglycemia and mortality, including acute myocardial infarction, unstable angina, arrhythmia, pulmonary embolism, sepsis, and intracerebral hemorrhage^[50]. This suggests that benefit from tight glucemic control and the glucose control strategies that are most may vary by patient population. IIT may be especially beneficial in the surgical ICU^[46,47,51]. Furthermore, the list of diagnoses with the high association between initial hyperglycemia and mortality are those that involve the vascular endothelium, which leads to the hypothesis that tight glucose control may exert its beneficial effect on the endothelium.

Operative patients

The appropriate target glucose level for elective perioperative cases is currently under investigation. A large study of 11633 patients by Kwon *et al.*^[52] associated perioperative hyperglycemia in elective colorectal and bariatric surgery with increased risk of infection, reoperative intervention, and death^[52]. The authors defined hyperglycemia as a serum glucose > 180 mg/dL and best effectiveness of glucose control as being < 130 mg/dL.

We initially evaluated the impact of preoperative hyperglycemia in a series of 252 non-diabetic trauma patients^[53]. Elevated serum glucose on admission, defined as glucose greater than 200 mg/dL, was found to be a predictor of postoperative infection, hospital and ICU length of stay, and mortality.

Bláha *et al.*^[54] conducted a single center randomized controlled trial with 2383 cardiac surgery patients and showed that the initiation of insulin therapy perioperatively reduced postoperative complications (23.2% vs 34.1%, 95%CI: 0.60-0.78). This effect was seen most prominently in non-diabetic patients with a risk reduction of 37% (21.3% vs 33.7%, RR = 0.63, 95%CI: 0.54-0.74).

The risk of hypoglycemia may be exacerbated in operative patients as the relationships between hypoglycemia and death in the NICE-SUGAR^[7] study was stronger among postoperative patients^[7]. On the hand, insulin administration itself may have positive implications on the risk of infection, operative intervention, and mortality in cases of hyperglycemia^[52].

Trauma

Trauma is clearly is recognized as a distinct population with respect to the injury-induced hyperglycemic stress response and its adverse effect on outcome. These patients are typically previously healthy and the traumatic effect of glucose elevation and variability on outcome seems to be especially pronounced^[55].

First, hyperglycemia on admission (serum glucose greater than or equal to 200 mg/dL) is a predictor of morbidity and mortality^[56]. Yendamuri *et al.*^[57] evaluated 738 general trauma patients and found that patients who had hyperglycemia on admission had a significantly greater ICU stay and mortality, as wells as higher infectious morbidity including pneumonia, urinary tract infections, wound infections, and bacteremia. Sung *et al.*^[58] conducted a prospective study of 1003 patients also comparing glucose levels on admission in trauma patients and found a 2.2 fold greater risk of mortality in patients who had hyperglycemia on admission than patients who are normoglycemic on admission and a significantly higher overall infection rate (52% vs 32%). The effect persisted after adjustment for age and injury severity.

Second, glucose control was found to be most beneficial in the first week of hospitalization in trauma patients. This time course fits the clinical course of

trauma patients, as the highest peak of infection is at the end of the first week of hospitalization and a peak of deaths occurs in the second week as a result of sepsis and organ dysfunction. Glucose control in the first week significantly influences these events. Bochicchio *et al.*^[59] evaluated 942 critically ill trauma patients' glucose levels and glucose patterns prospectively. Glucose levels were categorized as all low, all moderate, all high, improving, worsening, and highly variable. When controlling for age, ISS and gender, high, worsening and highly variable hyperglycemic patterns were highly predictive of increased ventilator days, ICU and hospital days, infection, and mortality. The changes in blood glucose over time, namely glucose variability, has thus been shown to be associated with outcome in trauma patients. In another study over 28 d, Bochicchio *et al.*^[56] studied 894 patients and found a 17-fold increase in odds of death in patients with high glucose levels over the first week and a 1.5 fold increase in infection. This effect persisted regardless of subsequent glucose control. To further elucidate this, Bochicchio *et al.*^[60] evaluated both degree of glucose elevation and variability post trauma. By combining both of these variables and creating an acute glucose elevation score (AGE score) via a computational algorithmic model, an AGE score of 4 was found to have a 91% positive predictive value for diagnosis of infection^[60].

Third, glucose control in trauma patients is associated with improved outcomes. In a large prospective quasi-experimental time series of 2120 patients^[61], patients assigned to the experimental group (glucose target 100-150 mg/dL) had fewer infections and greater survival. The benefit from glucose control in trauma patients is expected to be greatest when glycemic control is initiated early.

HYPOGLYCEMIA

The benefits of tight glucose control are counterbalanced by the harm of hypoglycemia. In the first Leuven study^[1] where intensive glucose therapy was shown superior, the rate of hypoglycemia in the treatment group was 5.1% compared to 0.8% in the control group. In the NICE-SUGAR^[7] trial, the rate was 6.8% compared to 0.5%. Patients with moderate hypoglycemia in the latter study (41 to 70 mg/dL) have a 40% increased risk of death compared to patients without hypoglycemia, while patients with severe hypoglycemia had twice the risk of death than the control group. Note that the conventional glucose targets in these two studies^[1,7] are different, meaning that the maximum size of the benefit from controlling glucose is likely different in the two studies.

The trade-off between the benefit of preventing hyperglycemia and the harm of hypoglycemia is elegantly exemplified by a sensitivity analysis conducted on a large retrospective cohort of critically ill patients by case-matching sentinel cases of hypoglycemia against cases with no hypoglycemia at a ratio of 1:3^[62]. The result was that in this cohort, the benefit of tight glucose control

would have been eliminated if the rate of hypoglycemia was four times higher and the mortality attributed to severe hypoglycemia was twice as high. This question of risk-vs-benefit comes into sharp focus with the closure of two large intensive glucose management trials, the German VISEP^[9] and European GLUCONTROL^[8]. Importantly, the mortality rate in the latter study was significantly increased in patients with similar severity scores who experienced hypoglycemia^[8].

Thus one must ask, what is the appropriate target of glucose that optimizes the benefit of reducing hyperglycemia at an acceptable rate of hypoglycemia? The answer, in the opinion of the authors is dependent on multiple factors. First, not all glucose measurement meters are created equal. Many widely used methods are fraught with inaccuracies and are especially problematic in the critically ill population^[63,64]. Protocols and the adherence to them also affect the rate of hypoglycemia. Different institutions have different abilities to implement complex protocols. Disease processes are likely different in the glucose patterns that they generate and in the degree and timing of glucose control that is most beneficial. Having said this, the authors believe that continuous or near continuous glucose monitoring would provide a much needed solution to glucose control. The true answer is normal glucose range (80-110 mg/dL) if performed safely without hypoglycemia.

GLUCOSE VARIABILITY

In addition to hyper and hypoglycemia, variability in the glucose measurements of a particular patient seem to have a bearing on outcome. Several studies have addressed this issue. In a cohort of 7049 critically ill patients, the coefficient of variability calculated from the standard deviation of glucose measurements for each patient showed increased mortality risk with greater variation^[65]. Interestingly, in patients who had diabetes, the variability of glucose measurements had a higher correlation with ICU mortality than the absolute value of blood glucose^[65].

More time spent in range (glucose level within protocol) is a strong predictor of outcome. In a study of 784 patients admitted to ICU, it was found that the more time spent in the 72-126 mg/dL range, the better the outcome, with 50% of the time in each day being the minimal acceptable threshold based on outcome^[66]. A post-hoc analysis of the GLUCONTROL^[8] showed similar findings with patients spending more than 50% of the time in the glucose range of 70-126 mg/dL having better outcome^[67]. Glucose variability, however, was not addressed in the initial large randomized trials.

In a large study involving 20375 patients of a prospectively collected multicenter dataset, metrics of glycemic variability were measured^[68]. In the medical patients, outcome was associated with standard deviation of glucose measurement and the mean of the differences in glucose levels that were more aberrant than the standard deviations^[68]. In the surgical patients, the

Table 1 Summary of recommendations for glycemic management

Recommendations	Ref.
In operative patients including trauma, cardiac, and elective surgical patients, it is advised to start a fast acting insulin regimen in the emergency room and perioperatively whenever applicable	[11,32,55]
In trauma patients, glucose control with a target of 100-150 mg/dL is reasonable and most important through the first week of hospitalization	[57,61,62]
In elective surgical patients, glucose control with a target of less than 130 mg/dL is advised perioperatively	[32,53]
In patient who will receive parenteral nutrition, intensive insulin therapy is recommended in anticipation of feeding and especially within the first 24 h of initiation	[34,37,42,45]
In patients receiving hypocaloric feeding or with interruption of enteral feeding, less strict glucose control is recommended	[1,11,45]
The rate of hypoglycemia should be a widely adopted quality control parameter. Elevated rates of hypoglycemia should prompt corrective action and changes in policy as needed	[1,8,9,63]
It is important to avoid excursions in glucose levels by titrating insulin treatment conscientiously, especially in diabetic patients, in trauma, and in surgical patients	[61,66,68,69]
Frequent glucose monitoring is advised. To prevent increasing clinician workload, continuous glucose monitoring may be indicated	[64,65,71,72]
Unexplained rises or falls in glucose levels may be a sign of worsening clinical status or infection	[56,60]

latter variables were also significant. In addition to this, a measure of the mean of the differences in glucose levels adjusted for the time between measurements was significant^[68]. This indicates that the amount of glucose variability over time may be more important in surgical patients than in medical patients within the surgical population. Bochicchio *et al.*^[59] reported in a study of 942 critically ill trauma patients, that highly variable glucose patterns were highly predictive of increased ventilator days, ICU and hospital days, infection, and mortality^[59].

INSULIN DOSING

It is difficult to make specific recommendations regarding insulin protocols and administration because these depend heavily on the resources of the care facility, the nursing workload, and importantly, the accuracy of the glucose measurement techniques used as point of care. In addition, patients may vary widely in their requirements for insulin dosing and the optimal strategy of glucose control.

The authors believe that there is an under appreciation of the contribution of the primary diagnosis to the requirements of glucose control. For example, in a randomized controlled trial of 2383 cardiac surgery patients^[54], starting an insulin protocol as of time of surgery whenever blood glucose reached greater than 110 mg/dL reduced postoperative complications compared to starting an insulin protocol after the patients have greater than 180 mg/dL or are admitted

to ICU. In an analysis of prospectively collected data in elective bariatric and colorectal patients, hyperglycemia was associated with increased infectious morbidity and this effect was absent in hyperglycemic patients in the non-extreme range who received insulin on the day of surgery^[52,69]. Surgical patients appear to benefit from the initiation of an insulin protocol early in the perioperative period. In trauma patients, early glucose control is important and reduces morbidity and mortality and patients would likely benefit from an insulin protocol started immediately in the emergency department.

One of the major differences between the Leuven study and the NICE-SUGAR trial is the use of parenteral nutrition to supplement insufficient enteral feeding in the Leuven study but the strict adherence to the latter in the NICE-SUGAR^[1,7,8] study. Since parenteral feeding causes a greater rise in blood glucose and requires more insulin than an equivalent enteral load^[36], it is reasonable that the treatment effect of insulin is increased in these patients. Therefore, patients deserve individual assessment of predicted insulin requirements prior to initiation of feeding and more liberal dosing in anticipation of increased needs.

It is unlikely that one size fits all for insulin protocols. We recommend that hospitals and individual departments develop glucose protocols per patient population and taking into account the patient's diagnosis and plan of therapy, premorbid glucose status, and nutritional support, as well as the personnel resources and best accuracy of glucose measurements available. The target of glucose therapy and starting insulin doses and rate of change should be updated with the existing evidence for each patient population as well as the feedback of hypoglycemia rates in each hospital service. Recommendations for glucose management in critically ill populations are summarized in Table 1.

Advances in glucose monitoring technology including near continuous glucose monitors and neural prediction networks^[70-72] are under development to improve glucose measurement accuracy, decrease staff workload, and self-adjust for changing insulin needs by real-time prediction of glucose levels.

CONCLUSION

Glucose control is of therapeutic importance in critically ill patients. Hyperglycemia is the result of the metabolic response to stress and is modulated by the treatment of the critically ill, including exogenous glucose sources and nutrition. Glucose levels in critically ill patients have both prognostic and therapeutic value. Glucose control is best applied by consistent control of glucose in a therapeutic range without incurring hypoglycemia or variability. Patients with different diagnoses may have different needs for glucose management. The advent of more precise glucose monitors and automated systems would help improve the degree of glucose control possible without the harmful effects of hypoglycemia and therefore improve outcome.

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