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REVIEW ARTICLE

Intensive Glycemic Control in Intensive Care Unit

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Abstract: *Glycemic control has received intense scrutiny in the last decade as an important aspect of patient care. Earlier studies suggested that tight glycemic control (target level of 80–110 mg/dL) improved outcomes in intensive care unit (ICU) patients. Subsequent trials did not confirm the same benefit. Moreover, increased mortality was found in association with such tight control compared with a less strict target. As a result, tight glucose control has become less popular. The interaction between diabetic status and outcomes in relation to glucose control strategies and/or chronic glycemic state in perioperative and critically ill patients was examined. Tight glucose control appears to be more beneficial in patients without diabetes than in those with known diabetes. It may also be more beneficial in improving outcomes in surgical rather than nonsurgical ICU patients, and in decreasing sepsis rather than mortality. Tight glycemic control was associated with a high incidence of hypoglycemia, which may offset some of its potential benefits. Tight glycemic control in the perioperative and intensive care settings should not be totally abandoned either as a clinical practice or as a subject of future research. Beneficial effects of tight glycemic control may be demonstrated when the appropriate glycemic targets are matched to the appropriate population. This article discusses in depth the role of intensive glycemic control in the ICU.*

Introduction

The biggest challenge to physicians in treating critically ill patients is stress-induced hyperglycemia.[1] This is often confounded by insulin resistance and pre-existing impaired glucose tolerance. Higher blood glucose levels are commonly observed in patients at intensive care units (ICUs) and the outcomes correspond to a J-shaped curve with the lowest risk being associated with normal glucose values (Fig. 1).

The mortality rate in ICU patients is at least 20% after 2 weeks and 30% after 3 weeks with more than 30% requiring intensive care for more than 5 days.[2] Sepsis, excessive inflammation, multiple organ failure, and weakness prolong the need for intensive care in critically ill patients.[3]

The usual practice to treat elevated blood glucose in the ICU setting was to follow a sliding scale insulin regimen. However, the sliding scale has been found to have a number of disadvantages. Moreover, physicians consider moderately elevated blood glucose to be ideal in the acute care setting. The long accepted concept of stress hyperglycemia as an adaptive response was challenged when intensive insulin therapy (IIT) was used by van den Berghe *et al*. to control blood glucose to normal levels and

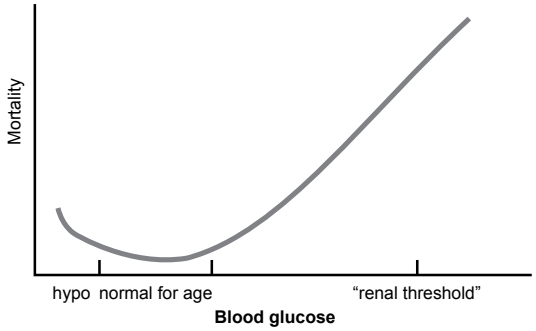

Figure 1. The J-shaped curve observed in ICU patients.

reported a reduction in ICU mortality from 8% to 4.6%.[4] Furthermore, the deleterious effects of hyperglycemia and the beneficial effects of intensive glycemic control on diabetes complications were also proved by major landmark trials.[5–7]

These results led to widespread endorsement of the IIT, and in 2004, the American College of Endocrinology (ACE) and the American Diabetes Association (ADA), with the participation of prominent cardiology, critical care, and anesthesiology organizations, issued a consensus statement that supported intensive glycemic control for inpatients.[8] In 2005, ADA endorsed IIT for treatment of hyperglycemia in hospitals.[9] In 2006, the ACE and ADA published the consensus statement on inpatient diabetes and glycemic control.[10] However, the trials that followed including the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR), Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP), etc. yielded inconsistent results with a higher mortality rate in the intensively treated group due to incidence of hypoglycemia.[11] The results of the ACCORD and ADVANCE trials also raised concerns on the benefits of intensive glycemic control.[12–14]

In view of the confusion and conflicting data, the ACE and ADA brought up a revised consensus statement that advocates a less stringent glycemic control and safe glycemic targets for management of inpatient hyperglycemia.[15]

Why Hyperglycemia in ICU?

Earlier, in critically ill patients, stress-induced hyperglycemia was regarded beneficial with high blood sugar providing fuel to the vital organs such as brain, heart, and skeletal muscles.[16,17] In critical illness, the generation of neuroendocrine responses by acute insults such as the stress of surgery and anesthesia, trauma, or sepsis (i) alters carbohydrate metabolism, (ii) causes excessive secretion of counter-regulatory hormones like catecholamines, cortisol, glucagon, and growth hormone, (iii) promotes insulin resistance, (iv) increases hepatic glucose production via enhanced glycogenolysis and gluconeogenesis, and (v) impairs peripheral glucose utilization and insulin action. Four glucose transporters, namely GLUT-1, GLUT-2, GLUT-3, and GLUT-4, facilitate insulin-independent glucose transport in these tissues. In critical illness, cytokines, VEGF, TGF-β, and hypoxia appear to upregulate the expression and membrane localization of GLUT-1 and -3 transporters in different cells types.

This "stress response" may over-rule the normal protection of cells against hyperglycemia, thus allowing cellular glucose overload. Therefore, all organ systems that take up glucose independent of insulin may be at high risk for direct glucose toxicity by the consistently attained high levels of these regulators during critical illness.

Some of the common reasons leading to risk for hyperglycemia and hypoglycemia in ICU may be enumerated as follows:

- Changes in caloric or carbohydrate intake[18]
- Change in clinical status or medications (e.g., corticosteroids or vasopressors)[19,20]
- Failure of the clinician to make adjustments to glycemic therapy based on daily blood glucose patterns[21]
- Prolonged use of sliding scale insulin as monotherapy[22,23]
- Poor coordination of blood glucose testing and administration of insulin with meals[24]
- Poor communication during times of patient transfer to different care teams[25]
- Use of long-acting sulfonylureas in elderly patients and those with kidney or liver insufficiency
- Errors in order writing and transcription[21,25]

Deleterious Effects of Hyperglycemia

Stress-induced hyperglycemia has been proven to increase oxidative injury, potentiate the proinflammatory responses, promote clotting, cause abnormal vascular reactivity, and impair leukocyte and mononuclear cell immune responsiveness.[5] Increases in the blood glucose and A_{1C} levels have been associated with significant cardiovascular and all-cause mortality.[26,27] Furthermore, various studies suggest that in cardiac surgery perioperative hyperglycemia is associated with an increased risk of postoperative infections, length of stay in the hospital, and increased mortality.[28,29] In the cardiovascular system, hyperglycemia contributes to myocyte apoptosis, impaired ischemic preconditioning, and increased infarct size.[30]

Hyperglycemia (with a threshold value of 180 mg/dL) is associated with longer length of hospitalization, higher infective morbidity in ICU patients, and an increased risk of death. Hyperglycemia in critically ill patients also seems to adversely affect numerous clinical parameters like duration of stay in the ICU, duration of ventilatory support and inotropic and vasopressor treatment, number of transfusions, duration of antibiotic therapy, presence of critical illness polyneuropathy, and survival (Fig. 2).[31]

Tight control of blood glucose alleviates hyperglycemic damage and restores islet-graft function by ensuring normal development of new vessels and preservation of endothelial lining in experimental animals.[32,33]

It is a paradox that critically ill patients without diabetes have a significantly higher mortality rate than the known diabetes patients.[34,35] Adults with new-onset hyperglycemia in nondiabetic individuals were associated with a threefold ICU and fivefold increased hospital mortality rate compared to known diabetes patients.[36] The reason for this contradiction though unknown may probably be due to a sudden increase in blood glucose concentration with acute illness that may produce dysregulation of the immune system. It could also be related to potential benefits of traditional medication

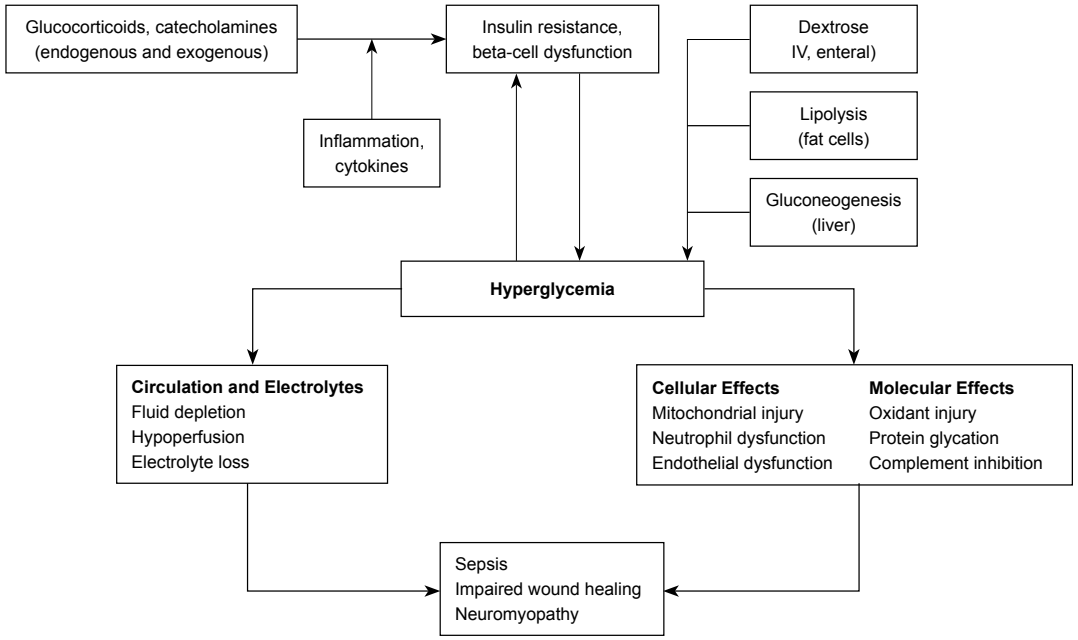

Figure 2. Deleterious effects of hyperglycemia.

given to the diabetics as an outpatient (statins, ACEI, aspirin, etc.), which may help reduce inpatient mortality. An additional possibility is the fact that known diabetes patients may receive insulin administration sooner than those with new-onset hyperglycemia.[37]

However, it is interesting to note that critically ill nondiabetic patients who were provided intravenous insulin demonstrated a mortality benefit over that seen in diabetes patients.[38]

Benefits of Intensive Insulin Therapy

The benefits of IIT are primarily due to glycemic control and reduction in mortality and prevention of liver, kidney, and endothelial dysfunction. Increased myocardial contractility occurs only when normal blood glucose values are maintained, which emphasizes the importance of glycemic control. High blood glucose may negatively affect cellular immune function, but this may be rescued in part by glycemic-independent actions of insulin.[39]

Insulin-stimulating endothelial nitric oxide synthase, which subsequently enhances nitric oxide, results in arterial vasodilation in addition to a variety of other beneficial effects on oxidation and inflammation. Insulin is supposed to inhibit proinflammatory cytokines, adhesion molecules, and chemokines and acute-phase proteins when blood glucose level is normal or near normal. It is assumed that one or more of these mechanisms are responsible for the improved outcomes reported with insulin-treated hyperglycemia.

Reduction in mortality in critically ill patients with intravenous insulin infusion may be attributed to favorable alterations in myocardial and skeletal muscle metabolism.[40,41] These alterations may downregulate the overutilization of free fatty acids that occurs during the hyperglycemia and stimulate oxidative glycolysis. Favorable improvements in cell membrane stability, myocardial contractility, and endothelial function result along with decreases in inflammatory mediators and increase in nitric oxide. Reduction in infectious complications may occur because of the apparent eradication of nonenzymatic glycosylation of proteins critical to adequate function of the immune system.[42] These complications include inactivation of immunoglobulin G, impaired opsin binding of complement, activation of collagenase, and inhibition of neutrophil functions, including delayed chemotaxis, impaired phagocytosis, and hindered bactericidal capability.[43–45]

Prevention of hyperglycemia-induced dysfunction in cellular systems (such as central and peripheral nervous system, endothelial, epithelial, and immune cells) that allow insulin-independent glucose uptake would explain some of the protective effects of insulin therapy in critically ill patients.[46] In clinical practice, achievement of normoglycemia before a surgical procedure ensures proper activation of the basic steps of the healing process like normal vascularization and inflammatory response.[47,48] IIT also maintained normal blood glucose levels during prolonged critical illness by only transiently elevating circulating insulin levels, suggesting improved overall insulin sensitivity after a few days of IIT. The higher serum adiponectin levels in the IIT group may explain the improved insulin sensitivity. Adiponectin is a protein hormone that is exclusively produced and secreted by adipocytes. Adiponectin is known to increase the tissue response to insulin.[49]

The three early proof-of-concept, single-center, randomized controlled trials by van den Berghe *et al*. in surgical, medical, and pediatric ICUs of the Leuven University in Belgium[4,50,51] demonstrated the beneficial response of IIT within age-adjusted narrow limits (80–110 mg/dL in adults, 70–100 mg/dL in children, and 50–80 mg/dL in infants). Analysis of data from 1,548 patients in surgical ICU revealed that maintenance of blood glucose concentrations ≤110 mg/dL in the intensive-treatment group reduced mortality by 42% (from 8.0% in the conventional-treatment group to 4.6% in the intensive-treatment group). The benefit of IIT was attributable to its effect on mortality among patients who remained in the ICU for more than 5 days (20.2% with conventional treatment vs 10.6% with IIT; $P = 0.005$). The greatest reduction in mortality involved deaths due to multiple-organ failure with a proven septic focus. IIT also reduced overall in-hospital mortality by 34%, bloodstream infections by 46%, acute renal failure requiring dialysis or hemofiltration by 41%, the median number of red-cell transfusions by 50%, and critical-illness polyneuropathy by 44%. Patients receiving intensive therapy were less likely to require prolonged mechanical ventilation and intensive care (Fig. 3).

In the study by van den Berghe *et al*. in medical ICU, IIT significantly reduced morbidity but did not reduce mortality among all patients. In this intention-to-treat analysis of 1,200 patients, IIT reduced blood glucose levels but did not significantly reduce in-hospital mortality (40% in the conventional-treatment group vs 37.3% in the intensive-treatment group, $P = 0.33$). However, morbidity was significantly reduced by the prevention of newly acquired kidney injury, accelerated weaning from mechanical ventilation, and accelerated discharge from the ICU and the hospital. Among 433 of the 1,200 patients who stayed in the ICU for less than 3 days, mortality was greater among those receiving intensive insulin therapies. In contrast, among 767 patients who stayed in the ICU for 3 or more days, in-hospital mortality in the 386 who received IIT was reduced from 52.5% to 43% (P=0.009) and morbidity was also reduced.[50]

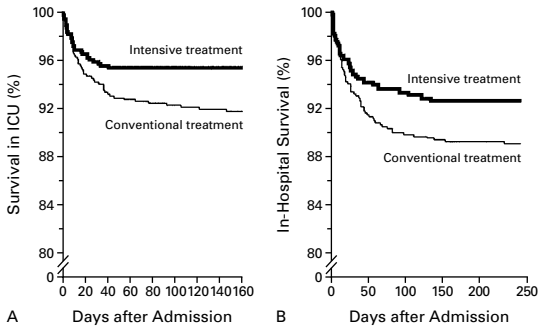

Figure 3. Kaplan–Meier curves showing cumulative survival of patients who received intensive insulin treatment.

The third trial by van den Berghe *et al*. in the pediatric ICU (PICU) was performed among 700 infants and children who were randomly allocated to the IIT group or the conventional insulin therapy (CIT) group. A significant reduction in the duration of PICU stay, inflammatory response, and mortality was noted.[51] A review on the clinical outcomes of glycemic control suggests improved glycemic control and reduced morbidity and mortality in critically ill patients on IIT.[52]

Insulin therapy has shown to benefit adult patients hospitalized for critical illness,[53] but according to some studies, the effect may be on short-term mortality and strongly influenced by the clinic settings.[54] In the study by van den Berghe *et al*. in medical ICU, targeting blood glucose levels to below 110 mg/dL with insulin therapy prevented morbidity but did not significantly reduce mortality among all patients. However, IIT in patients who stayed in the ICU for at least 3 days was associated with reduced morbidity and mortality. Mode, timing, and adequacy of nutritional support also affect glycemic control and outcomes in critically ill patients. The delivery of correctly formulated and safely administered nutritional and metabolic support plays critical role in surgical and critical care units.[55]

It was observed that a 26% higher insulin requirement was required to maintain normoglycemia for identical amounts of calories in patients who received exclusively parenteral feeding compared with those who received enteral nutrition. This may be explained by the incretin effects on insulin secretion with enteral feeding in nondiabetic subjects.[56] Furthermore, endogenous insulin released by enteral feeding is likely to induce more pronounced suppression of hepatic gluconeogenesis and more hepatic glucose uptake than peripherally infused insulin.[57] The higher insulin requirements to obtain normoglycemia in patients fed with parenteral compared with enteral feeding indicate that parenterally fed patients are more at risk for hyperglycemia. Furthermore, the outcome benefits of IIT were present regardless of the feeding regimen.

The Controversy

Given the benefits of IIT in critically ill patients, several studies tried to replicate the study findings of the Leuven studies. However, majority of the studies came up with conflicting results; some showed reduced mortality, others failed to match these results and many with no clinically significant difference.[1] It was also noted that in the Leuven study in PICU, IIT led to an increased incidence of short-lasting hypoglycemia with approximately 25% patients having at least one hypoglycemic event during their entire stay.[51] Three large multicenter studies (VISEP, GLUCONTROL, and NICE-SUGAR) that could not confirm the survival benefit of the Leuven studies also showed significantly higher rates of hypoglycemia in the patients receiving IIT.

The multinational NICE-SUGAR trial,[58,59] designed to test the hypothesis that intensive glucose control reduces mortality at 90 days in critically ill patients, proved that intensive glucose control led to moderate and severe hypoglycemia, both of which were associated with an increased risk of death.[60] Mortality in the intensive-control group was significantly higher than that in the conventional-control group (27.5% vs 24.9%, $P = 0.02$). Severe hypoglycemia was also higher in the intensive group than in the conventional group (6.8% vs 0.5%). The excess deaths in the intensive-treatment group were predominantly cardiovascular, which is consistent with evidence from other studies that severe hypoglycemia might be associated with adverse cardiovascular events. In NICE-SUGAR, no appreciable differences were observed between the two groups for other outcomes, such as length of stay in the ICU, total duration of hospitalization, number of days of mechanical ventilation, rate of positive blood cultures, or red blood cell transfusion.

The VISEP trial designed to determine the influence of colloid versus crystalloid volume resuscitation and of intensive versus CIT on morbidity and mortality of patients with severe sepsis and septic shock also reported increased risk for serious adverse events related to hypoglycemia with the use of IIT in critically ill patients with sepsis.[61] The trial was terminated due to safety reasons and the flaws[62] in the study design of the VISEP trial were widely discussed.[63,64]

The Glucontrol Study, a prospective randomized controlled trial, that compared the effects of IIT on ICU mortality with an intermediate glucose control, which was also prematurely stopped due to an increased incidence of hypoglycemia, also failed to prove the clinical benefit of IIT.

A series of other studies including meta-analysis also could not confirm the benefits associated with tight glycemic control.[60,65–69] A recent study shows that in patients with critical illness in ICU, high levels of insulin were independently associated with in-hospital mortality.[70] In a post hoc analysis of the NICE-SUGAR trial, in critically ill adults, intensive glucose control increased moderate and severe hypoglycemia more than conventional glycemic control. Moderate and severe hypoglycemia were associated with increased risk for mortality, independent of glycemic targets.[71] Another meta-analysis of studies conducted in critically ill patients including the NICE-SUGAR trial concludes that IIT significantly increased the risk of hypoglycemia and conferred no overall mortality benefit among critically ill patients.[72]

Leuven Studies versus NICE-SUGAR Study

Analysis of the landmark studies by van den Berghe *et al*. and the NICE-SUGAR study has revealed interesting facts that explain the discrepancies in the results of both the landmark trials.[73–77] The factors included in these trials are given here (Fig. 4):[78]

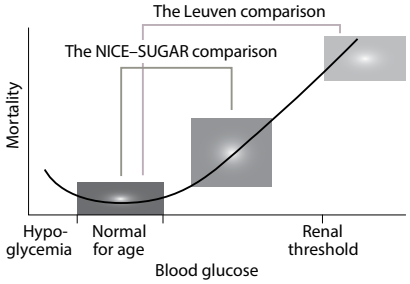

Figure 4. Comparison of Leuven and NICE-SUGAR studies.

- Differences in populations of patients (e.g., reasons for admittance to the ICU)
- Insulin-treatment protocols
- Mortality
- Glucose goals
- Glucose concentrations actually achieved
- Use of parenteral nutrition
- Expertise and experience of nursing staff at a particular institution
- Statistical power of the studies

1. The target blood glucose level of <110 mg/dL in the intensive arm of van den Berghe study was compared with the target ranges of 140–180 mg/dL in the NICE-SUGAR study and 180–215 mg/dL in the Leuven studies, making the studies fundamentally different.
2. In the 2001 study by van den Berge *et al*., glucose measurements were based on arterial blood samples using an accurate arterial blood gas analyzer. The advantage of using a blood gas analyzer is the simultaneous measurement of a set of parameters (e.g., potassium, oxygen, lactate, and hemoglobin) rather than taking a blood sample just for glucose value measurement. Many parameters like adjustments of mechanical ventilation settings have to be measured frequently (e.g., 4-hour time interval) in an ICU environment. Strict procedures were followed to avoid misinterpretations when using one multiple-lumen catheter for both sampling venous blood and administering glucose nutrition and/or medication.
3. The NICE-SUGAR study used glucose meters that are considerably less precise than blood gas analyzers or central laboratory analyzers. Many point-of-care glucose meters that are widely used by diabetes patients are not adequate sensor devices for use in the specific setting of the critically ill patient. Acidosis, high partial pressure of oxygen levels, anemia, and several drugs are typical disturbance factors that preclude accurate glucose measurements. Patient-specific factors also contribute to inaccurate results with glucose meters, especially in individuals who are critically ill. Reduced tissue perfusion in hypotensive patients results in large differences in glucose concentrations in capillary blood samples, despite the minimal alterations in arterial

blood samples. Furthermore, the glucose concentrations in arterial, venous, and capillary blood also differ, and though the differences are minimal in fasting individuals, postprandial capillary glucose values are higher than that observed in venous blood. It was also observed that many of the subsequent studies also used capillary blood and measured glucose with point-of-care meters and in many of them the sample type and/or method of analysis were not specified.

4. Increased number of cardiovascular deaths in the NICE-SUGAR trial may also be attributed to the use of the variety of glucometers, which were unsuitable for the study. The different glucose values produced by these diverse methods and samples might have led to different insulin doses and potentially wide variations in the true glucose concentrations among patients. The range for the intensive control target set by the NICE-SUGAR investigators exceeded the most widely accepted criteria for adequate glucose-meter performance. Thus, undetected hypoglycemia, large fluctuations in glucose levels, and possibly hypokalemia were tolerated or even induced.
5. In the NICE-SUGAR study, patients received enteral nutrition exclusively, whereas in the Leuven studies, parenteral nutrition supplemented insufficient enteral feeding. The administration of insulin during hypocaloric feeding in the NICE-SUGAR study may have been deleterious.
6. An element of bias may also be suspected in the unexplained early withdrawal of care in the NICE-SUGAR study, which was not balanced between the two treatment groups.[73]
7. As a consequence of differences in water content, glucose concentrations in plasma are approximately 11% higher than those in whole blood if the hematocrit is normal. Some, or perhaps all, of these factors might have contributed to the results reported by the NICE-SUGAR investigators.

The protocol followed in the Leuven studies was totally different from that followed in the NICE-SUGAR study. The bedside nurses control the blood glucose levels particularly based on their intuition and experience. This "intuition" was based on the variations in blood glucose, insulin, and nutrition. The varying insulin resistance were anticipated when changes were caused by external factors. Moreover, both the nutrition load and the insulin infusion were stopped for any transportation of the patient. IIT was stopped when the majority of the caloric intake was through the oral route. Glucose control was to be continued based on their insulin infusion regimen that they were used to before their admission to the PICU.[76]

In the Leuven studies, since the arterial blood sample measures other parameters such as the potassium level using blood gas analyzer, hypokalemia that can subsequently induce arrhythmias were corrected. However, in the NICE-SUGAR, the use of bolus insulin injections, volumetric insulin pumps, and handheld glucometers that cannot detect potential hypokalemia could have enhanced the risk of hypokalemia.

The negative outcomes in the Action to Control Cardiovascular Risk in Diabetes (ACCORD), The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE), and the Veterans Affairs Diabetes Trial (VADT) are also in line with the results of the NICE-SUGAR study. Going by the clinical judgment, hypoglycemia-induced consequences could probably have been the etiology that triggered the negative outcomes. It may also be due to altered brain serotonin concentrations and autonomic dysregulation in addition to the low-grade systemic inflammation, decreased endothelial nitric oxide and enhanced free radical generation, diminished antioxidant defenses, and altered metabolism of essential fatty acids present in patients with type 2 diabetes.[79,80]

Although the NICE-SUGAR trial adds to the accumulating data on the use of tight glucose control protocols in patients in the ICU, considering the flaws in the study design, further large trials are necessary to resolve the debate on whether IIT improves the outcomes of selected ICU patients.

Insulin Infusion Protocols

The pharmacodynamics of insulin makes it suitable for adapting to the changing physiology of the patient. Moreover, it has a predictable delivery, short biological effect, minimal side effects except for hypoglycemia, minimal drug–drug interactions, can be easily titrated, and has no dosage threshold.

Sliding scale regular insulin (SSI) introduced as early as 1934 was the norm in inpatient glycemic control where only fast- or rapid-acting insulin was given subcutaneously. Traditional sliding-scale insulin regimens were used to measure blood glucose preprandially and at bedtime if the patient was eating, or on a schedule of every 6 hours if the patient was taking nothing by mouth. Hence, it responds to hyperglycemia after it has happened, rather than preventing it before. The sliding scale was based on the clearly inaccurate assumption that insulin sensitivity is uniform among all patients.[81] Also, the patient's previous medication regimen, diet type and amount, and personal characteristics like weight, diabetes duration, etc. were not considered while determining the SSI dosage. No basal insulin was given in sliding scale and patients were not given insulin coverage for prolonged periods. Moreover, the patient's diabetes management were in the hands of the nursing staff where the patient's progress toward an acceptable blood glucose level was not monitored and the physician was often contacted only when the concentration is <60 or >400 mg/dL. Although the nurses found the sliding scale easy

to use, the patients suffered from huge fluctuations in the blood glucose levels due to the innumerable flaws of SSI, including insulin stacking.[82–86]

In view of the inadequacies of the sliding scale, numerous paper-based and computer-based continuous insulin infusion algorithms were developed. These physiologic insulin regimens used the basal, nutritional, and correctional insulin approach. Research shows the various continuous insulin infusion protocols to be effective in achieving glycemic control, with low rate of hypoglycemic events, and in improving hospital outcomes.[20,87–90] The Randomized Study of Basal Bolus Insulin Therapy in the Inpatient Management of Patients with Type 2 Diabetes (RABBIT 2) trial is the only prospective randomized controlled study that compared traditional SSI with a basal–bolus subcutaneous insulin glargine (for long-acting insulin) and insulin glulisine (Apidra; for nutritional and supplemental doses). In this study, the mean admission blood glucose was 229 ± 6 mg/dL and A_{1C} was 8.8 ± 2%. A blood glucose target of <140 mg/dL was achieved in 66% of patients in the glargine and glulisine group and in 38% of those in the SSI group. The mean daily blood glucose between groups ranged from 23 to 58 mg/dL, with an overall blood glucose difference of 27 mg/dL ($P < 0.01$). Despite increasing insulin doses, 14% of patients treated with SSI remained with blood glucose >240 mg/dL, with no significant differences in hypoglycemia or length of the hospital stay.[91]

The common themes in the insulin infusion protocols were the use of regular insulin for continuous insulin infusion and a basal/bolus subcutaneous insulin regimen including a long-acting insulin analog (insulin glargine or detemir) and prandial and correctional doses of a rapid-acting insulin (insulin aspart, glulisine, or lispro). Continuous infusion of regular insulin is suggested for critically ill ICU patients, pre- and postoperative patients, peripartum women with hyperglycemia, severe hyperglycemia like diabetic ketoacidosis and hyperosmolar nonketotic states, and any patient in whom tight glycemic control is clinically indicated. A basal–bolus insulin regimen is preferred for all noncritically ill patients, whereas for patients who are eating, a scheduled mealtime insulin dose with a rapid-acting insulin analog helps prevent the glucose from rising from carbohydrate intake. Whether eating or not, when blood sugars are outside the glycemic target range, a correctional dose of rapid-acting insulin may be administered. Insulin analogs are preferred for basal, mealtime, and correction doses instead of human insulins (regular and NPH). Moreover, insulin analogs have a more predictable absorption and action profile in addition to less pharmacokinetic fluctuation in patients with renal insufficiency. Premixed insulins are generally not recommended for use in the hospital setting, as there is an increased risk of hypoglycemia in patients with variable oral intake. Regular insulin should be avoided for SC postprandial blood glucose correction. Isophane insulin (NPH) historically has been used safely in pregnancy. Nutritional insulin in patients who are eating requires coordination with nursing and dietary staff for timing the doses zero to 15 minutes before each meal. The key concepts covered in a typical insulin infusion protocol are given in Table 1. Table 2 outlines the types of insulin used for physiologic subcutaneous insulin protocols.

Table 1 | Key concepts covered in a typical insulin infusion protocol

Step	Action	Comment
1.	Measure blood glucose before meals and at bedtime, or every 6 hours if nothing by mouth; stop oral agents; order A_{1C} if none obtained in the past 30 days	Initiate protocol for patients with known diabetes mellitus and anyone with two or more random blood glucose readings >180 mg/dL or fasting glucose >126 mg/dL
2.	Calculate initial total daily dose of insulin	0.3 units per kg: underweight; older age; hemodialysis 0.4 units per kg: normal weight 0.5 units per kg: overweight ≥0.6 units per kg: obese; glucocorticoids; insulin resistance
3.	Administer 50% of the total daily dose as long-acting basal insulin	Insulin glargine (Lantus) every 24 hours, or insulin isophane (NPH) or detemir (Levemir) every 12 hours
4.	Administer 50% of the total daily dose as short-acting nutritional insulin given in three divided doses 0 to 15 minutes before meals (if eating) or before bolus tube feeds	If continuous tube or parenteral feeds, consider every 6-hour dosing of short-acting or regular insulin; hold if nothing by mouth
5.	Select a scale of short-acting correctional insulin given 0 to 15 minutes before meals	Use patient's insulin sensitivity as a guide for initial scale selection
6.	Subsequent daily adjustment of total daily dose based on previous day's total units given	-

Table 2 | Types of insulin used for physiologic subcutaneous insulin protocols[85]

Type of insulin	Time of onset (hour)	Duration of action (hour)
Basal insulin		
Glargine	1–2	24
Detemir	1–2	18–24
Isophane (NPH) (every 12 hour)	1–2	10–20
Nutritional and correctional insulin		
Lispro, aspart, glulisine (If patient is eating, dose 0–15 minutes before meals)	5–15	3–6
Regular human insulin (Consider dosing for every 6 hours only if patient is taking nothing by mouth or is on continuous parenteral or tube feeding)	1–2	6–10

Conversion from IV to subcutaneous insulin is needed when the critical illness resolves. The insulin dose given to the patient during the previous 6 hours should be extrapolated to a 24-hour dose, and then reduced by 20% as a safety factor to calculate the new total daily dose.[92] The total daily dose is then divided according to the guidelines in Table 1. The basal insulin injection should be given at least 1–2 hours before discontinuation of the insulin infusion to prevent rebound hyperglycemia. If a faster discontinuation of the infusion is required, a portion of basal insulin is given with a more rapid analog to cover until the basal insulin can take effect or the preferred administration time is reached.[93] If the patient is starting to eat and the infusion can be continued, bolus insulin injections are added in addition to the drip to cover these new requirements.

Continuous Glucose Monitoring in ICU

Continuous glucose monitoring (CGM) systems use a tiny sensor inserted under the skin to check glucose levels in tissue fluid. The sensor measures the level of glucose in the tissue every 10 seconds and automatically provides an average glucose value every 5 minutes for up to 72 hours (Fig. 5).[94]

The use of CGM is slowly gaining momentum in view of the scientific evidence that suggests tight glycemic control in ICU patients. A survey assessing the current mindset of healthcare professionals toward CGM in the ICU setting and resulting implications to industry reports that 93% of

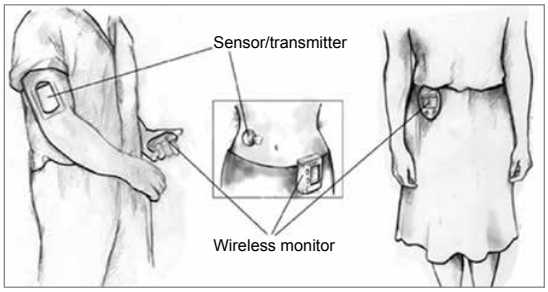

Figure 5. Components of continuous glucose monitoring,

respondents cited nurse labor savings and 24% referenced improved patient comfort as the potential benefits of CGM (Fig. 6). The respondents thought that it significantly reduced the 2 hours of direct nursing time per patient required per day to implement a tight glycemic control protocol.[95] Approximately 38% respondents cited an interest in a CGM device that could provide assistance with insulin dosing, moving toward a semiclosed/closed-loop system especially in the context that insulin is among the most commonly reported products involved in ICU medication errors.

The second most frequently cited potential gain from adopting CGM in the ICU was improved inpatient glycemic control due to benefits such as immediate feedback regarding therapeutic adjustments (28%), predictability of glucose levels (trend data) (24%), and hypo/hyperglycemic detection (17%). Nurses' fear of inducing hypoglycemia has been cited as a major impediment toward tight glycemic control adoption, and studies have demonstrated that patients treated under such protocols experienced on average more episodes of hypoglycemia than conventionally treated patients.[96]

In the commercially available real-time CGM devices, the hypo- and hyperglycemic alerts that can be programmed to beep at a customized threshold value are available. The nursing staff can intervene at least 30 minutes before a potential crisis, proving a great value in the ICU setting.[97] Studies from our own center have shown this technology superior to the conventional blood glucose monitoring in therapeutic decision making in routine diabetes care.[98]

Despite the clear value added with CGM technology, nearly 44% of respondents indicated that accuracy and precision of CGM technology would have to be proven. Additionally, 31% of participants considered higher supply costs associated with CGM technology to be a major drawback, particularly in light of absence of reimbursement. Tight glycemic control may be time consuming for ICU staff, and pathophysiologic, technical, and personnel factors impact the accuracy of point-of-care glucose monitoring. Tight glycemic control in the ICU requires safe, accurate, robust, rapid, and CGM that lack interference from drugs or other substances.

Apart from measured blood glucose value, the fluctuations in glucose termed "glycemic variability" is gaining more popularity as a factor contributing to endothelial damage

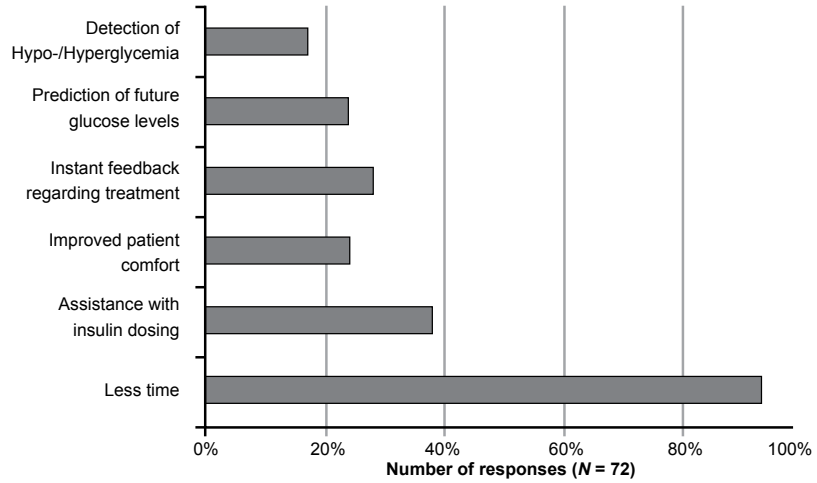

Figure 6. Responses from the survey.

and may be influenced by choice of treatment regimen.[99] Glycemic variability and glucose complexity have also been considered to be the independent predictors of mortality in critically ill patients. Clinical data would not only have to address concerns about CGM accuracy and risk of infection but also have to demonstrate improved patient outcomes, for example, the avoidance of hypoglycemia. Starting with the lag time associated with interstitial fluid (ISF)-based CGM sensors[100] to the risk of infection, ICU professionals are seeking more accommodating technologies such as the need for CGM to measure blood glucose in the ICU, given the impact on ISF from metabolites and diuretics administered to surgical patients.

Retrospective analyses were conducted for two prospective, randomized, controlled trials in which 174 critically ill patients either received IIT according to a real-time CGM system (n = 63) or according to an algorithm (n = 111) guided by selective arterial blood glucose measurements with simultaneously blinded CGM for 72 hours. The study showed that loss of glucose complexity was significantly associated with mortality and with the presence of diabetes mellitus.

CGM technology has the potential to improve glycemic control with low glucose variability and low incidence of hypoglycemia. Studies evaluating the accuracy and reliability of CGM devices, based on a whole blood sample in perioperative and ICU settings, are needed since ISF CGM may not be useful in perioperative and ICU settings. Once a reliable CGM sensor for ICU use is identified, a large, prospective, controlled, multicenter study could determine if optimal IIT with a low or zero incidence of hypoglycemic events improves mortality.[101]

A study by Shulman *et al*. with the use of the computerized decision supported IIT protocol calls for more sophisticated methods like CGM with automated insulin and glucose infusion adjustment to achieve tight glycemic control.[102] In one of the largest studies conducted in critically ill children in ICU, the role of CGM devices in the identification and management of hyperglycemia in diverse ICU settings has been postulated.[103]

In light of tight glycemic control becoming the new standard of patient care, healthcare professionals in the ICU may embrace CGM technology; however, product acceptance will remain limited in the early stages, given the substantial education, market development, and economic hurdles.

Continuous Subcutaneous Insulin Infusion in ICU

Continuous subcutaneous insulin infusion (CSII) or insulin pump therapy consists of a disposable reservoir for insulin and a disposable infusion set, including a cannula for subcutaneous insertion and a tubing system that connects the insulin reservoir to the cannula. When insulin is administered subcutaneously via a properly programmed insulin pump, the insulin delivery mimics the insulin release pattern of a normal healthy pancreas much better than other modalities of insulin delivery. Although initially meant only for type 1 diabetes, in insulin-requiring T2DM, a judicious use of insulin pumps in selected candidates is beneficial in reducing HbA_{1C} levels,[104] and in minimizing glycemic excursions.

The recent suggested guidelines on the use of insulin pumps in Indian patients enlist the ideal candidate for insulin pump therapy.[105] The chief benefit of insulin pump therapy is customized, flexible basal, and bolus dosing to meet patients' individual insulin requirements while reducing the risk of severe hypoglycemia. Insulin delivery via pump is more consistent and precise than delivery by syringe or injection pen. With a pump, basal insulin can be adjusted in increments as small as 0.25 unit, depending on the model of pump. Bolus insulin can be dosed to within 0.1-unit increments or even 0.05-unit increments on some

pumps. More precise and accurate insulin dosing can better regulate blood glucose levels.

The biggest challenge to the treating doctor in an ICU is that hypoglycemia and landmark trials have data on the increased mortality associated with hypoglycemia. The newer features in the pump including the low glucose suspend (LGS) have the potential to shut off the pump, sensing an impending hypoglycemia.[106] This is similar to results with insulin pump therapy providing the greatest reduction in hypoglycemia in those with the most hypoglycemia at baseline.[107] Since different basal profiles can be programmed in insulin pump, variable basal rates can be set for different hours of the day thereby overcoming the shortcomings of nursing care.

An automated mechanical glucose-responsive, sensor-guided insulin infusion system has been a long-term goal, thereby closing the loop. Closed-Loop Insulin Infusion for Critically Ill Patients (CLINICIP) project evaluated the safety and performance aspects of a closed-loop control system for this patient group using the CS-1 support system. The CS-1 decision support system is composed of three standard infusion pumps – two for the administration of enteral and parenteral nutrition and one for insulin administration. At the bottom of the CS-1 decision support system, a slide-in rack with a central user interface and a central hardware that includes the enhanced model predictive control (eMPC) version algorithm have been implemented. This algorithm has demonstrated safety and efficacy in a previous laptop-based study in medical ICU patients. The central hardware with the user interface is connected to the infusion pumps and permanently reads the actual status and rate of the three infusion pumps. Individual enteral and parenteral nutrition products with the corresponding carbohydrate content are stored in the drug database of each pump (Fig. 7).

Before start of enteral or parenteral nutrition, the nurse has to select the type of nutrition from a pickup list on the display of the pump. Based on the type and on the infusion rate used for the selected nutrition product, the amount of administered carbohydrates is calculated and communicated with the central hardware and the eMPC, respectively. The glucose reading as measured has to be entered manually. Based on this input and available information of administered insulin and nutrition, the eMPC gives advice on the insulin infusion rate and a countdown timer for the next glucose measurement. In addition to other information, this is displayed on the user interface. The countdown timer signals the time until the next glucose measurement in the range from 20 to 240 minutes. In addition, standard optical and acoustical alarm signals are used to alert the staff for upcoming measurements. The suggested insulin infusion is displayed on the screen and has to be entered manually and therefore confirmed by the operating nurse. To avoid the onset of hyperglycemia by means of unattended nutrition changes, insulin infusion is automatically calculated and displayed in case the nutrition rate is changed or stopped at all.[108]

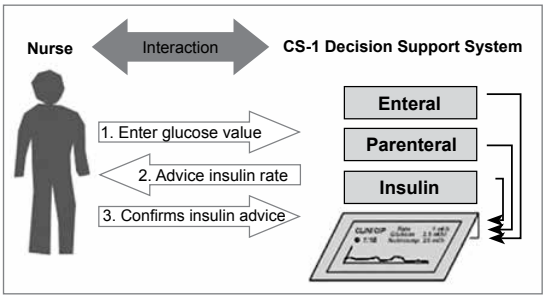

Figure 7. CS-1 Decision Support System.

Guidelines for ICU

In view of the fact that recent clinical trials showed increased morality rate in ICU patients on intensive glycemic control, the ACE and ADA endorsed less stringent glycemic targets for management of inpatient hyperglycemia. Some of the key recommendations are as follows:[109]

Critically ill patients

- Insulin therapy should be initiated for treatment of persistent hyperglycemia, starting at a threshold of not greater than 180 mg/dL.
- Once insulin therapy has been started, a glucose range of 140–180 mg/dL is recommended for the majority of critically ill patients.
- Intravenous insulin infusions are the preferred method for achieving and maintaining glycemic control in critically ill patients.
- Validated insulin infusion protocols with demonstrated safety and efficacy, and with low rates of occurrence of hypoglycemia, are recommended.
- With IV insulin therapy, frequent glucose monitoring is essential to minimize the occurrence of hypoglycemia and to achieve optimal glucose control.

Noncritically ill patients

- For the majority of noncritically ill patients treated with insulin, the premeal blood glucose target should generally be <140 mg/dL in conjunction with random blood glucose values <180 mg/dL provided these targets can be safely achieved.
- More stringent targets may be appropriate in stable patients with previous tight glycemic control.
- Less stringent targets may be appropriate in terminally ill patients or patients with severe comorbidities.
- Scheduled subcutaneous administration of insulin, with basal, nutritional, and correction components, is the preferred method for achieving and maintaining glucose control.

- Prolonged therapy with SSI as the sole regimen is discouraged.
- Noninsulin agents are inappropriate in most hospitalized patients.
- Clinical judgment and ongoing assessment of clinical status must be incorporated into day-to-day decisions regarding treatment of hyperglycemia.

Patients Using Insulin Pump

Patients who use insulin pump therapy in the outpatient setting can be considered as candidates for diabetes self-management in the hospital setting, provided they have the mental and physical capacity to do so.[110,111] The nursing personnel must document basal rates and bolus doses on a regular basis. The availability of hospital personnel with expertise in continuous subcutaneous insulin infusion therapy is essential.[111]

Discussion

The ICU population is unique where the introduction of innovative technologies is challenging and may be met with unintended consequences. ICU patients are often limited in their ability to communicate, receiving sedation or analgesics, and are in a dynamic highly stressed state. They typically receive a host of medications, and many suffer end-organ dysfunctions, including neurologic, cardiopulmonary, renal, hepatic, hematologic, and pancreatic morbidities. Patients are often fed in a relatively nonphysiologic or unique manner, either via total parenteral nutrition or via specialized enteral feedings. Most of them are sedentary too!

Further, all ICUs are not created equal; many are general medical–surgical units, whereas others are highly specialized or subspecialized such as coronary care units or neuro-ICUs where patient characteristics may be quite broad. Further, there are significant differences in how ICUs are staffed, community versus academic centers, and whether physicians who advocate intensive treatment are actively involved in day-to-day care and in the development of protocols and practice guidelines.

Depending on the ICU population, approximately 5–20% of critically ill patients are known to have diabetes.[112,113] The call for tight glycemic control in critically ill patients using IIT frequently continues to grow, yet the optimal level and ranges of glucose still remain questioned. Concerns over under-recognized or underappreciated hypoglycemia remain and are increasingly acknowledged as practitioners become more aware of the limitations of point-of-care measurements and the host of variables involved in providing timely, accurate, and reliable glucose measurements at the bedside. Reliable point-of-care testing is mandatory for implementing tight glycemic control with IIT in daily intensive care practice. In addition to avoidance of an important time delay between the blood sampling and the blood glucose result, which is required for timely adjustment of the insulin infusion, there is a high need for accuracy, particularly in the lower blood glucose ranges, to avoid potentially harmful hypoglycemia. The development and refinement of rapid, reliable, precise, and accurate glucose measurement on a continuous or near continuous basis are increasingly recognized as needed to optimize the metabolic care of critically ill patients. Emerging technologies on the horizon include nanotechnology, microprocessed, and sample separation approaches that may eliminate whole blood sampling issues.[114]

Patients in ICU may require high doses of insulin to reach glycemic targets and might often require correction doses of insulin to treat unexpectedly high blood glucose levels. Using "sliding scale" cannot be encouraged in such situations where the requirement varies according to individual patient parameters. This may be overcome by using standardized protocols developed by multidisciplinary team that addresses the issues like identifying patients prone to or at risk of hypoglycemia.[115] Adjustments may be required for appropriate provision of diabetes care, including timely delivery of meal trays, point-of-care blood glucose testing, and the administration of diabetes medications. Nursing staff should receive adequate and ongoing in-service training on the specialized needs of the inpatient with diabetes, especially with regard to insulin therapy. There is evidence that a multiprofessional team approach reduces the length of stay in hospital and improves clinical outcomes in patients with diabetes.[115–117] In addition to the physician, the team may include specialty staff such as qualified diabetes educators and nursing staff when needed. Discharge planning should also be initiated well in follow-up comprehensive outpatient diabetes care and self-management training like self-monitoring of blood glucose etc. should also be provided.

Innovative technology is being developed to treat hyperglycemia in trauma patients. The link between technology and therapy of trauma hyperglycemia may be explained as follows: (i) trauma may lead to hyperglycemia; (ii) morbidity and mortality of trauma hyperglycemia are related to blood glucose concentrations; (iii) IIT corrects trauma hyperglycemia and improves outcomes; and (iv) future IIT will use CGM, computerized insulin delivery, closed loop control, and physiological monitoring.

The currently available studies do not allow to confidently recommending one optimal target for glucose in heterogeneous ICU patient groups and settings. Provided that adequate devices for blood-glucose measurement and insulin administration are available, together with an extensive experience of the nursing staff, blood-glucose levels may be controlled as close to normal as possible, without evoking unacceptable fluctuations and hypoglycemia.[118] Unresolved issues include whether increased blood glucose variability is inherently harmful and whether even moderate

hypoglycemia can be tolerated in the quest for tighter blood glucose control. Future research must first address whether intensive glucose control can be delivered safely, and whether computerized decision support systems and newer technologies that allow accurate and continuous or near-continuous measurement of blood glucose can make this possible. Until such time, clinicians would be well advised to abide by the age-old adage to "first, do no harm."[119]

Increased insulin administration is positively associated with death in the ICU regardless of the prevailing blood glucose level. Thus, the control of glucose levels rather than of absolute levels of exogenous insulin appears to account for the mortality benefits associated with IIT demonstrated by others.[120] Recent guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients suggests that glycemic control end point such as a blood glucose ≥ 150 mg/dL triggers interventions to maintain blood glucose below that level and absolutely <180 mg/dL. There is a slight reduction in mortality with this treatment end point for general ICU patients and reductions in morbidity for perioperative patients, postoperative cardiac surgery patients, post-traumatic injury patients, and neurologic injury patients. We suggest that the insulin regimen and monitoring system be designed to avoid and detect hypoglycemia (blood glucose ≤ 70 mg/dL) and to minimize glycemic variability.

Important processes of care for insulin therapy include use of a reliable insulin infusion protocol, frequent blood glucose monitoring, and avoidance of finger-stick glucose testing through the use of arterial or venous glucose samples. The essential components of an insulin infusion system include use of a validated insulin titration program, availability of appropriate staffing resources, accurate monitoring technology, and standardized approaches to infusion preparation, provision of consistent carbohydrate calories and nutritional support, and dextrose replacement for hypoglycemia prevention and treatment.[121] Quality improvement of glycemic management programs should include analysis of hypoglycemia rates and run charts of glucose values <150 and 180 mg/dL. The literature is inadequate to support recommendations regarding glycemic control in pediatric patients.

Conclusions

Hyperglycemia, whether stress-induced or existing as part of previously known diabetes, independent of etiological factors, triggers inflammation that results in poor prognosis. Management of diabetes, chronic or acute, becomes complex due to risk of hypoglycemia and subsequent mortality. The impact of hypoglycemia could be more fatal in the critically ill patients.

Since the landmark publication by van den Berghe *et al*. in 2001, hospitals began to implement rational subcutaneous insulin protocols based on the American Diabetes Association technical review, replacing the ineffective practice of SSI. However, logistical challenges have included coordination of multiple hospital departments and achieving multidisciplinary consensus on goals and methods. The subsequent trials including the NICE-SUGAR trial failed to replicate the study findings by van den Berghe *et al*. and consequently the clinician is faced with the dual challenge to maintain normoglycemia during surgery and minimize the untoward effects of hyperglycemia.[122] As a result many of the hospitals focus on avoiding hyperglycemia with less aggressive glycemic targets in the critically ill and rational subcutaneous insulin in the noncritically ill patients.[123,124]

Efficacy and safety of IIT may be affected by patient-related and ICU setting-related variables. Therefore, no single optimal blood glucose target range for ICU patients can be advocated. Aggressive treatment of hyperglycemia in the ICU requires a highly trained multidisciplinary team, avoidance of conventional sliding scale, and expertise in the use of technology. In the absence of such facilities, it is better to maintain blood sugars at acceptable levels, comfortable to the staff in the ICU. A simple fallback position could be to control blood glucose levels as close to normal as possible without evoking unacceptable blood glucose fluctuations, hypoglycemia, and hypokalemia.[125]

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"Health and disease are the same thing—vital action intended to preserve, maintain, and protect the body. There is no more reason for treating disease than there is for treating health."

— Herbert M. Shelton