CHAPTER 79

Blood Glucose Control in Critical Care

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OBJECTIVES

This chapter will:

1. Describe the nature of stress-induced hyperglycemia.
2. Explore the possible significance of normoglycemia in critically ill patients.
3. Discuss the importance of blood glucose control and nutritional support.
4. Describe the risk and incidence of hypoglycemia in relation to pursuing tighter blood glucose control.
5. Review recent recommendations for blood glucose control in critically ill patients.

Acute hyperglycemia is common in critically ill patients. Approximately 90% of all patients develop blood glucose concentrations of more than 110 mg/dL during critical illness.[1] Multiple observational studies and, later, a single-center randomized controlled trial (RCT) showed reduced mortality if blood glucose was normalized using intensive insulin therapy (IIT) in critically ill patients. However, subsequent multicenter randomized controlled trials (RCTs) have not only failed to confirm this finding but also demonstrated a high incidence of potentially harmful hypoglycemia during IIT. Additional concern is reinforced by novel data suggesting a different response to common glucose management in acute ill patients with diabetes mellitus, especially in those with poorly controlled blood glucose before becoming critically ill. Thus lowering blood glucose control remains a focus of critical care.

STRESS-INDUCED HYPERGLYCEMIA

Stress-induced hyperglycemia is common in critically ill patients.[2] There are no accepted criteria to define this acute hyperglycemia, unlike "chronic diabetes mellitus." In acute illness, "stress" in response to tissue injury or infection can have profound effects on carbohydrate metabolism. This type of hyperglycemia occurs despite elevation in insulin levels (insulin resistance). It is assumed that several mechanisms contribute to this stress-induced hyperglycemia.

- *Decreased glucose uptake and utilization:* Insulin-stimulated glucose uptake and utilization is achieved by skeletal muscle for 80% to 85% of all peripheral glucose

uptake and by adipose tissues for 5%. In skeletal muscle, exercise is an important stimulating factor for glucose uptake and utilization. However, in critical illness, this exercise-stimulated glucose uptake is decreased, because patients are typically bed-bound. Furthermore, in critically ill patients, glucose transporter-4 (GLUT-4)–dependent insulin-stimulated glucose uptake is inhibited.[3]

- *Increased glucose production:* The liver is the dominant organ for glucose production from glycogen (gluconeogenesis). In the fasting phase, the liver can produce 2 μg/kg/min of glucose, which represents 85% of whole body gluconeogenesis in healthy subjects. In critically ill patients, this hepatic gluconeogenesis increases because of increased levels of glucagon, cortisol, growth hormone, and cytokines.[4]
- *Depressed glycogen production:* The production of glycogen from glucose (glycogenesis) is one of the key roles of the liver. In critically ill patients, increases in the level of glucagon, epinephrine, and cytokines inhibit glycogenesis by inactivation of glycogen synthase through increased glycogen synthase-kinase.[5]
- *Increased free fatty acids:* In critically ill patients, free fatty acid and triglyceride production from adipose tissue increases secondary to increased activity of hormone-sensitive lipase. The increase in the blood level of glucagon and adrenalin enhance such activity, which in turn decreases peripheral glucose uptake.

It is well known that stress-induced hyperglycemia reflects severity of illness and is associated with mortality and morbidity in various patient groups, such as those with acute myocardial ischemia, cerebral infarction and hemorrhage, and multiple trauma and burns. Until recently, it was suggested that stress-induced hyperglycemia may be an adaptive response, promoting glucose uptake into brain and red cells and facilitating wound healing. Even relative hypoglycemia was considered dangerous and was to be avoided. Thus "optimal" blood glucose concentrations were considered to be in the range of 160 to 200 mg/dL (8.8–11.1 mmol/L).[6] Insulin administration was appropriate only when blood glucose exceeded 215 mg/dL (12 mmol/L), because at such levels it may induce osmotic diuresis and fluid shifts that may be clinically undesirable.

NORMOGLYCEMIA IN CRITICALLY ILL PATIENTS

In 2001, in a single-center randomized controlled study, van den Berghe et al.[1] found that IIT reduced mortality and morbidity in selected surgical patients (Leuven I). In this trial, 1548 mechanically ventilated surgical patients requiring intensive care were allocated randomly to the IIT group (target glucose: 80–110 mg/dL [4.4–6.1 mmol/L]), starting insulin administration when blood glucose levels exceeded 110 mg/dL (6.1 mmol/L), or to a conventional treatment group (target glucose range: 180–200 mg/dL [10.0–11.1 mmol/L]), starting insulin administration when blood glucose levels exceeded 215 mg/dL (11.9 mmol/L).

In this trial, ventilated postoperative intensive care unit (ICU) patients allocated to IIT had a 43% relative risk reduction for ICU mortality (8.0% vs. 4.6%, $p = .04$), when compared with patients receiving conventional glucose control. The benefit of IIT occurred particularly in the patients receiving intensive care for more than 5 days (ICU mortality: 20.2% vs. 10.6%, $p = .005$) and with multiple-organ failure with proven septic focus. IIT also decreased the duration of ventilatory support and ICU stay; reduced the need for blood transfusions; and reduced the incidence of bloodstream infections, critical illness polyneuropathy, and acute renal injury. Logistic regression analysis indicated that the reduction of blood glucose levels, not the administration of insulin, explained the clinical benefit.[7] However, because more than 60% of patients in this trial were postcardiac surgery patients, the benefit of IIT may be altered in other ICUs with a different case mix.[8]

In 2006 the same research group assessed the benefit of IIT in a medical ICU (Leuven II).[9] The protocol of blood glucose management was the same as previously reported in the Leuven I trial.[1] In the intention-to-treat analysis of 1200 patients, IIT did not significantly reduce hospital mortality (40.0% in the conventional treatment group vs. 37.3% in the intensive treatment group, $p = .33$). However, morbidity was significantly reduced by the prevention of newly acquired renal injury, accelerated weaning from mechanical ventilation, and accelerated discharge from the ICU and the hospital. However, in a post-hoc analysis, among 433 patients who stayed in the ICU for less than 3 days, mortality was greater among those receiving IIT. In contrast, among 767 patients who stayed in the ICU for 3 or more days, mortality was reduced in the IIT group from 52.5% to 43.0% ($p = .009$); morbidity also was reduced (Table 79.1).

In 2009 the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study compared IIT (target glucose: 81–108 mg/dL [4.5–6.0 mmol/L]) with conventional glucose control (target glucose: ≤180 mg/dL [≤10.0 mmol/L]) in 6104 ICU patients treated in 42 hospitals across Australia, New Zealand, and Canada.[10] In contrast to the Leuven studies, patients randomized to IIT in the NICE-SUGAR study had a 2.6% excess 90-day mortality compared with patients receiving conventional glucose control (24.9% vs. 27.5%, $p = .02$).

In addition to the Leuven studies and the NICE-SUGAR study, two single-center[11,12] and four multicenter RCTs[13–16] have compared IIT with conventional blood glucose control in a total of almost 6000 patients. Neither of these studies found a significant difference in mortality between the two glucose management strategies in patients with severe sepsis,[13] in patients with septic shock,[15] or in mixed ICU patients[11,12,14,16] (see Table 79.1).

OTHER KEY STUDIES OF GLUCOSE CONTROL AND INSULIN THERAPY

Chronic Glucose Control in Patients With Diabetes Mellitus

In 1993 in the Diabetes Control and Complications Trial of 1441 type 1 diabetes patients, strict blood glucose control (mean blood glucose 155 mg/dL [8.6 mmol/L]) was shown to reduce the rate of progression in retinopathy, nephropathy, and peripheral and autonomic neuropathy over a 6-year follow-up in comparison with conventional treatment (mean blood glucose 230 mg/dL [12.8 mmol/L]).[17] Furthermore, strict blood glucose control was later shown to reduce the risk of any cardiovascular event and the risk of nonfatal myocardial infarction, stroke, or death from cardiovascular disease over a 17-year follow-up.[18] In 1998 the United Kingdom Prospective Diabetes Study showed that strict blood glucose control in patients with type 2 diabetes decreased hemoglobin A1C (HbA1c) by 0.7% and reduced

TABLE 79.1

Nine Randomized Control Trials to Assess the Benefit of Normoglycemia in Intensive Care Patients

	DEATH DURING INTENSIVE CARE[a]			INCIDENCE OF HYPOGLYCEMIA[b]			
	CONVENTIONAL TREATMENT	INTENSIVE INSULIN TREATMENT	P-VALUE	CONVENTIONAL TREATMENT	INTENSIVE INSULIN TREATMENT	P-VALUE	RELATIVE RISK
Leuven I[1]	63/783 (8.0%)	35/765 (4.6%)	<0.04	6/783 (0.8%)	39/765 (5.1%)	<0.001	6.65
Leuven II[9] (ICU stay > 3 days)	145/381 (38.1%)	121/386 (31.3%)	0.05	15/381 (3.9%)	97/386 (25.1%)	<0.001	6.38
Leuven II[9] (all patients)	162/605 (26.8%)	144/595 (24.2%)	0.3	19/605 (3.1%)	111/595 (18.7%)	<0.001	5.94
VISEP[13]	53/241 (21.9%)	53/247 (21.6%)	1.0	5/241 (2.1%)	30/247 (12.1%)	<0.001	6.38
Arabi[11]	44/257 (17.1%)	36/266 (13.5%)	0.3	8/257 (3.1%)	76/266 (28.6%)	<0.001	NR
de la Rosa[12]	78/250 (31.2%)	84/254 (33.1%)	0.6	2/250 (0.8%)	21/254 (8.3%)	<0.001	NR
NICE-SUGAR[10]	498/3014 (16.5%)	546/3014 (18.1%)	0.1	15/3014 (0.5%)	206/3016 (6.8%)	<0.001	14.7
Glucontrol[14]	83/542 (15.3%)	92/536 (17.2%)	0.4	13/542 (2.4%)	44/536 (8.2%)	<0.001	NR
COIITSS[15]	109/254 (42.9%)	117/255 (45.9%)	0.5	20/254 (7.8%)	42/255 (16.4%)	0.003	NR
CGAO-REA[16]	310/1312 (23.6 %)	302/1336 (22.6 %)	0.5	79/1284 (6.2%)	174/1317 (13.2%)	<0.001	NR

[a]In the VISEP trial, short-term mortality was assessed with 28-day mortality; in the COIITSS trial, in-hospital mortality is reported.
[b]Hypoglycemia was defined as a glucose concentration less than 40 mg/dL (2.2 mmol/L).
CGAO-REA, Computerized Glucose Control in Critically Ill Patients; *COIITSS,* Corticosteroid Treatment and Intensive Insulin Therapy for Septic Shock; *ICU,* intensive care unit; *IIT,* intensive insulin therapy; *NICE-SUGAR,* Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation; *VISEP,* Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis.

the incidence of retinopathy, microalbuminuria, cataracts, and myocardial infarction.[19]

However, in 2008 the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study found that intensive glucose lowering therapy to control HbA1c below 6% in patients with type 2 diabetes led to more severe hypoglycemia episodes and increased mortality (hazard ratio, 1.22; 95% CI, 1.01–1.46; $p = .04$) compared with standard therapy (HbA1c target: 7.0%–7.9%).[20] A post-hoc analysis of the ACCORD data revealed that the higher mortality in the intensive therapy group was confined to patients with poorly controlled diabetes at study inception.[21]

Thus improving blood glucose control in chronic diabetic mellitus appears to be effective in preventing complications and is considered desirable for the chronic management of diabetes. However, because intensive glucose control may not be beneficial for all patients, the concept of "personalized" glycemic control is rapidly emerging.

Acute Glucose Control in Patients With Acute Coronary Syndrome

In 1995 the Diabetes and Insulin Glucose Infusion in Acute Myocardial Infarction study assessed the benefit of lowering blood glucose from 277 to 173 mg/dL (from 15.4 to 9.6 mmol/L) in patients with diabetes with an acute myocardial infarction. Patients with the intensive treatment had improved 1-year survival but no change in short-term survival (in hospital and 3 months).[22]

In 2005 the Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction 2 study randomized more than 1000 patients with myocardial infarction to receive either insulin infusion or routine metabolic treatment; the study failed to show any benefit on mortality.[23]

In 2005 the Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation/Estudios Cardiológicas Latin America Study Group study randomized 20,201 patients with acute ST-segment elevation myocardial infarction to a glucose-insulin potassium infusion regimen or usual care.[24] The trial found no benefit in morbidity and mortality from the intervention despite a reduction in blood glucose levels.

In 2013 the BIOMarker study to identify the Acute risk of a Coronary Syndrome-2 (BIOMArCS-2) trial randomized 294 patients with acute coronary syndrome and hyperglycemia (blood glucose 140–288 mg/dL [7.8–16 mmol/L]) to IIT (target glucose: 85–110 mg/dL [4.7–6.1 mmol/L]) or conventional glucose management (target glucose: <288 mg/dL [16 mmol/L]). No difference in myocardial infarct size (defined by elevated high-sensitivity troponin T and myocardial perfusion scintigraphy) was found. However, the composite of death or a second myocardial infarct increased with IIT (5.7% vs. 0.7%, $p = .04$).[25]

Acute Glucose Control in Patients With Diabetes

The uniform approach to glycemic control in critically ill patients with and without diabetes mellitus, as advocated by all RCTs in the field to date, recently has been challenged. Egi et al. demonstrated that an average blood glucose level between 180 and 252 md/dL (10–14 mmol/L) compared to a level between 108 and 180 md/dL (6–10 mmol/L) during ICU admission was associated with lower mortality in patients with diabetes with chronic hyperglycemia (HbA1c >6.8%) before ICU admission (Fig. 79.1).[26] In addition, although more severe hyperglycemia (>14 mmol/L) was associated with greater mortality in patients without diabetes and in patients with diabetes with adequate premorbid control (HbA1c ≤7%), Plummer et al. failed to demonstrate an association between severe hyperglycemia and mortality in patients with HbA1c >7%.[27] Therefore these studies suggest that patients with diabetes adapted to a chronic hyperglycemic state may tolerate higher glucose levels and that conventional glucose targets may not be safe for these patients.

In contrast to hyperglycemia, it is now well established that even mild hypoglycemia (<70 mg/dL [3.9 mmol/L]) is associated with increased mortality in critically ill patients with and without diabetes.[28] However, patients with poorly controlled diabetes not only have a greater risk of developing hypoglycemia but also a higher hypoglycemia-associated

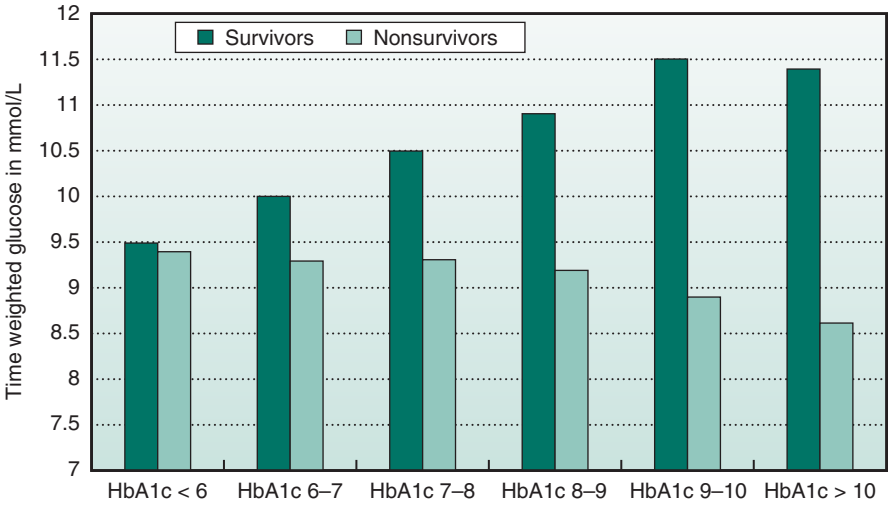

FIGURE 79.1 Relationship between mean blood glucose in ICU, HbA1c, and hospital survival in 415 patients with diabetes mellitus. Survivors with poor pre-ICU glycemic control (HbA1c > 6.8%) had significantly greater mean blood glucose in ICU than nonsurvivors. (Modified from Egi M, Krinsley JS, Maurer P, et al. Premorbid glycemic control modifies the interaction between acute hypoglycemia and mortality. *Intensive Care Med.* 2016;42[4]:562–567.)

mortality risk than patients without diabetes or with well-controlled diabetes.[29] In their aggregate, these observational findings imply that more liberal blood glucose targets may be justified in patients with diabetes. Indeed, recent pilot studies suggest that such "permissive hyperglycemia" (glucose target: 180–252 mg/dL [10–14 mmol/L]) reduces the occurrence rate of hypoglycemia without causing harm in patients with diabetes.[30,31] However, high-level evidence of net clinical gain to support practice change in critically ill diabetics is currently lacking.

BLOOD GLUCOSE CONTROL AND ACUTE KIDNEY INJURY

In the Leuven I trial,[1] IIT was shown to reduce acute kidney injury as defined by (1) a peak plasma creatinine concentration more than 2.5 mg/dL (12.3% to 9.0%, p = .04), (2) a peak plasma urea nitrogen concentration more than 54 mg/dL (11.2% to 7.7%, p =.02), and (3) the need for renal replacement therapy (8.2% to 4.8%, p = .007). Similarly, in the Leuven II trial, IIT was shown to reduce acute kidney injury as defined by either a level of serum creatinine twice that present on admission to the ICU or a peak level of serum creatinine of greater than 2.5 mg/dL (8.9% to 5.9%, p = .04).[9]

In contrast to the two Leuven studies, none of the subsequent RCTs on glycemic control in critically ill patients demonstrated a significant difference in the presence or severity of acute kidney injury and/or RRT requirement between patients managed with IIT or conventional glucose control (VISEP, Arabi, de la Rosa, NICE-SUGAR, Glucontrol).[10–14] In contrast with chronic diabetic nephropathy (where injury is mostly glomerular), the pathophysiology of acute kidney injury in critically ill patients is not clearly identified. Thus the mechanism by which IIT prevented acute renal injury in the Leuven studies remains unclear.

BLOOD GLUCOSE CONTROL AND INFECTIONS

Patients with diabetes are at greater risk of infection. Even acute short-term hyperglycemia may affect the immune response and impair the ability of patients to deal with infection. Experimentally, hyperglycemia impairs (1) neutrophil activity (chemotaxis, formation of reactive oxygen species, phagocytosis of bacteria), (2) microvascular reactivity to dilating agents such as bradykinin, and (3) complement function (opsonization, chemotaxis), despite elevations of complement factors.

In critically ill patients, poor glycemic control defined as more than 200 mg/dL (11.1 mmol/L) is associated with increasing wound infection.[32,33] Introducing stricter blood glucose control reduces wound complication.[34,35] In the Leuven I trial (surgical patients),[1] IIT reduced the incidence of septicemia by 46% and reduced the mortality of patients with a proven septic focus. In 2004 Grey et al.[36] showed that strict glucose control (targeted blood glucose less than 140 mg/dL [7.8 mmol/L]) reduced nosocomial infection significantly when compared with standard glucose control (targeted blood glucose: 180–220 mg/dL [10–12.2 mmol/L]) in 61 predominantly nondiabetic, general surgical ICU patients. However, in the VISEP trial,[13] which specifically targeted septic critically ill patients, IIT had no benefit on mortality in comparison with conventional treatment. Finally, subsequent RCTs comparing infectious complications between patients managed with IIT and standard glucose control have failed to demonstrate any significant difference in the incidence of ICU acquired infections[11,12,15] or the duration of antiinfective therapy in ICU.[14,16]

Thus no strong evidence suggests that targeting normoglycemia is able to reduce the incidence of infection and mortality from sepsis compared with targeted mild hyperglycemia below 200 mg/dL (11.1 mmol/L).

BLOOD GLUCOSE CONTROL AND NUTRITIONAL SUPPORT

Nutritional support should affect blood glucose control. In the Leuven trials, nutritional support in IIT and conventional treatment groups was scheduled in the form of continuous intravenous glucose (800–1200 kcal/day) on admission day, and then 20 to 30 nonprotein kcal/kg/day as total parenteral nutrition, enteral feeding, or both combined. In contrast, less than 100 kcal/day of intravenous glucose and less than 900 kcal/day (approximately equivalent to 11 kcal/kg/day) as total nonprotein calories was administered on average over the first 2 weeks in ICU in the NICE-SUGAR study.

Although there is little information about "optimal" caloric intake in critically ill patients, hypercaloric nutrition (35 to 40 kcal/kg/day) to critically ill patients may be associated with increased rates of infection and metabolic complications.[37] Furthermore, der Voort et al.[38] reported that, in critically ill patients requiring intensive care more than 7 days, the amount of intravenous glucose infusion, not mean blood glucose control, was associated with greater ICU and hospital mortality.

The benefit of a targeted blood glucose strategy may be different with different approaches to nutritional support as suggested by the contradictive results in the Leuven studies and the NICE-SUGAR study, and a high amount of intravenous glucose administration may be harmful. In addition, permissive underfeeding (caloric target: 40%–60% of calculated requirements) as compared with standard feeding (caloric target: 70%–100% of calculated requirements) lowered blood glucose levels and reduced insulin requirements without causing harm in a recent trial.[39] Similarly, using diabetes-specific high-protein formulas for enteral nutrition reduced insulin requirements, mean glucose, the occurrence rate of hypoglycemia, and glycemic variability in another small RCT.[40] Therefore physicians may need to pay attention to their nutritional strategy as much as to blood glucose control in critically ill patients.

INCIDENCE OF HYPOGLYCEMIA RELATED TO LOWERING BLOOD GLUCOSE CONTROL

Although early evidence suggested a benefit from stricter blood glucose control, widespread implementation of such IIT protocols across multiple centers in NICE-SUGAR showed a robust signal of harm. In addition to the workload associated with maintaining normoglycemia in the ICU, the major "cost" of IIT appears to be related to the increased incidence of hypoglycemia (see Table 79.1).

In the Leuven I trial,[1] hypoglycemia, defined as a blood glucose less than 40 mg/dL (2.2 mmol/L), was seen in 5.2% of patients in the IIT group and in 0.8% in the conventional group. This increase in the incidence of hypoglycemia associated with introducing normoglycemia was also seen in medical ICU[9] patients (18.7% vs. 3.1%), and was demonstrated consistently in all the following IIT trials conducted to date. These observations raise the issue of safety with IIT.

To minimize the incidence of hypoglycemia, physicians need to (1) develop a nutritional and insulin administration protocol that is easy to follow, (2) train nurses to achieve targeted blood glucose control, (3) measure blood glucose concentration frequently, and (4) target blood glucose levels within a mild hyperglycemic range as suggested by the NICE-SUGAR trial. If continuous blood glucose measurements could be developed and used as a reliable tool, it should reduce the "cost" of glycemic control.

VARIABILITY (FLUCTUATION) OF BLOOD GLUCOSE CONTROL IN CRITICALLY ILL PATIENTS

In the Leuven I trial, IIT reduced mean blood glucose concentration and mortality. It also reduced the standard deviation of blood glucose concentration, an accepted measure of variability, from 33 mg/dL (1.83 mmol/L) in the conventional control group to 19 mg/dL (1.05 mmol/L) in the IIT group—a relative reduction of 42%. However, the benefit of IIT was ascribed to a reduction in the mean glucose concentration rather than minimization of its variability. Fluctuations in glucose concentration may be pathophysiologically important, especially from a neurologic perspective, and possibly as important as sustained hyperglycemia and episodes of hypoglycemia.

Egi et al.[41] reported data from a large multicenter cohort of patients and set of glucose measurements and found that the standard deviation and coefficient of variation of glucose were independent predictors of ICU and hospital mortality and that their predictive ability was greater than that of the mean blood glucose concentration. This finding is consistent with data on acute hyperglycemia in pediatric critically ill patients[42] and chronic type 2 diabetes mellitus patients.[43]

Decreasing the variability of blood glucose concentration may be an important dimension of glucose management, a possible mechanism by which IIT exerted its beneficial effects in the Leuven studies and an important goal of glucose management in ICU. Continuous glucose measurements may assist in achieving less variability (higher quality) of blood glucose control in critically ill patients.

RECENT RECOMMENDATIONS FOR BLOOD GLUCOSE CONTROL IN THE CRITICALLY ILL

In the Surviving Sepsis Campaign guidelines,[44] maintenance of blood glucose levels less than 180 mg/dL (10 mmol/L) using continuous infusion of insulin was recommended with a Grade 1A recommendation. With use of this approach, measuring glucose frequently—after introducing lowering blood glucose (every 1–2 hours) and on a regular basis (every 4 hours) once the blood glucose concentration has stabilized—also was recommended (grade 1C). The most recent consensus statement from the American Diabetes Association also supported these recommendations.[45]

CONCLUSION

Acute hyperglycemia is a common condition in critically ill patients. Using intensive insulin therapy to normalize blood glucose in these patients is not recommended because of the high risk of hypoglycemia and evidence of harm from a large multicenter, multinational randomized controlled trial. In addition, the previous belief that normoglycemia reduces the incidence of acute renal injuries and ICU acquired infections has been refuted by several randomized trials. Therefore, based on available evidence and consensus guidelines, it is justified to recommend insulin infusion when blood glucose is above 180 mg/dL (10 mmol/L) and adjust the dose to target a blood glucose concentration between 108 and 180 mg/dL (6–10 mmol/L). However, emerging evidence suggest that patients with diabetes with poor premorbid glycemic control may benefit from more liberal glucose targets in ICU. The best approach to glucose management in patients with diabetes must be explored in future trials.

Key Points

1. Acute hyperglycemia is common in critically ill patients. This "stress-induced hyperglycemia" is not yet defined by specific diagnostic criteria.
2. Stress-induced hyperglycemia, up to 215 mg/dL (12 mmol/L), was believed to be a beneficial physiologic response that promoted cellular glucose uptake.
3. The largest multicenter prospective randomized control trial demonstrated that intensive care unit patients allocated to intensive insulin therapy (target glucose: 81–108 mg/dL [4.5–6.0 mmol/L]) had a 2.6% excess mortality when compared with patients receiving conventional glucose control (target glucose < 180 mg/dL [10.0 mmol/L]).
4. Recent recommendations suggest that blood glucose should be kept at less than 180 mg/dL (10.0 mmol/L) using continuous infusion of insulin (Grade 1A).
5. No strong evidence suggests that mild hyperglycemia (108–180 mg/dL) increases the risk of renal injury or nosocomial infections.
6. Physicians should be aware that the benefit of intensive insulin therapy may be altered by different case-mix and nutritional support.
7. Novel observational data suggest that critically ill patients with diabetes with an HbA1c above 7% benefit from moderate hyperglycemia (blood glucose > 180 mg/dL).

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