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MINIREVIEWS

Management of critically ill patients with diabetes

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Abstract

Disorders of glucose homeostasis, such as stress-induced hypoglycemia and hyperglycemia, are common complications in patients in the intensive care unit. Patients with preexisting diabetes mellitus (DM) are more susceptible to hyperglycemia, as well as a higher risk from glucose overcorrection, that may results in severe hypoglycemia. In critically ill patients with DM, it is recommended to maintain a blood glucose range between 140-180 mg/dL. In neurological patients and surgical patients, tighter glycemic control (*i.e.*, 110-140 mg/d) is recommended if hypoglycemia can be properly avoided. There is limited evidence that shows that critically ill diabetic patients with a glycosylated hemoglobin levels above 7% may benefit from looser glycemic control, in order to reduce the risk of hypoglycemia and significant glycemic variability.

Key words: Diabetes mellitus; Critical care; Stress hyperglycemia; Hypoglycemia; Glycemic control; Intensive care unit

Core tip: Diabetes mellitus is a common comorbidity found in critically ill patients. Although strict glycemic control in the past was considered a standard therapeutic intervention, newer clinical trials have shown that moderate glycemic control (*i.e.*, glucose levels between 140-180 mg/dL) reduces mortality and morbidity in such patients.

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INTRODUCTION

Stress-induced hyperglycemia, or diabetes injury as originally described by Claude Bernard in 1877, has become the subject of significant debate, as recent guidelines have called for stricter glucose control in critically ill patients[1,2]. Occurring as a result of catecholamine-induced stress response, this hyperglycemia is a common occurrence in critically ill patients[1]. With the rising population of diabetic and pre-diabetic individuals in the United States, the risk of severe hyperglycemia among critically ill patients is quite high, particularly in patients with undiagnosed diabetes mellitus (DM), who have inadequate glycemic control previous to hospitalization[1,3].

On the other hand, one of the important complications in dealing with stress-induced hyperglycemia is severe hypoglycemia. This significant decrease in blood glucose, however, is not due to some underlying physiological process, but it is often the consequence of inadequate glucose monitoring, and incorrect dosage of hypoglycemic medication, usually insulin. Hypoglycemia in critically ill patients is an important factor that can increase mortality in the intensive care unit (ICU), and is an important complication that needs to be prevented in patients that require glycemic control therapy[4]. Increased glycemic variability may be an issue with inadequate hypoglycemic treatment, which leads to increased oxidative stress and may be more dangerous than persistent hyperglycemia[5].

Appropriate hypoglycemic therapy is required in order to reduce mortality and morbidity of uncontrolled hyperglycemia in critically ill patients[6]. In this article, we review the current state-of-evidence on ideal glycemic goals that should be set for diabetic patients in the ICU.

EPIDEMIOLOGY

In 2014, the United States National Diabetes Statistic Report, documented 21 million individuals suffering from DM, accounting for 6.7% of the total population and approximately 8.1 million undiagnosed DM, which would raise the percentage of American population with diabetes to 9.3%[7]. This report also indicated that the prevalence of diabetes was highest among those older than 65 years of age and above[7]. Patients in this age group, account for up to 45.7% of ICU patients[8]. In addition, approximately 50% of ICU patients, have pre-existing diagnostic criteria for DM[9].

PATHOPHYSIOLOGY

During periods of stress, the body reacts by producing elevated levels of catecholamines[10]. This reaction, is modulated by the suprarenal glands and activated by either the sympathetic nervous system in acute stress and by feedback to the pituitary gland in chronic stress[11,12]. Any period of disease can be considered a period of stress, and therefore, some degree of hyperglycemia is normal during these times, and can be seen as initially protective and part of the adaptive response for survival[13]. However, in acute and severe diseases, the resulting hyperglycemia can be much too high and require glycemic control therapy to manage[1].

Severe hyperglycemia, is a well-documented marker of illness severity, rather than a direct cause of poor outcome[13]. This condition often subsides after the affecting illness (*i.e.*, sepsis) has resolved[1]. In the acute setting, it is believed that the resulting hyperglycemia is due to insufficient insulin secretion that is unable to overcome the hyperglycemic effect of catecholamine.[14] It is also believed that insulin resistance plays a factor in chronic disease with significant amounts of tissue injury[1,14].

Patients with pre-existing DM tend to have a persistent state of hyperglycemia due to insulin resistance (or insulin absence in DM type 1), and hyperglucagonaemia that are the consequences of the disease's natural progression. As a result of these factors, during periods of acute illness, the resulting stress-induced hyperglycemia can be much more severe than in non-diabetic patients, and more likely to require control with hypoglycemic medications and strict glucose monitoring[14]. See Table 1 for factors that lead to hyperglycemia and hypoglycemia in critically ill patients.

STRESS-INDUCED HYPERGLYCEMIA

Stress-induced hyperglycemia (SIH) is a common finding among critically ill patients, particularly among cardiovascular patients, neurocritical patients, and patients undergoing surgical procedures, even in the absence of preexisting DM[14]. In non-diabetic patients, SIH has been arbitrarily defined as a blood glucose level greater than 140 mg/dL or glycosylated hemoglobin (HbA1c) greater than 6.5%[15]. In diabetic patients, SIH is be defined as blood glucose levels greater than 180-220 mg/dL[15]. This clinical condition increases the morbidity and mortality in critically ill patients and leads to poor outcomes and prognosis[15]. Some have advocated that in these patients, it is necessary to maintain a strict glycemic control to directly improve their outcomes[14,15].

Part of the controversy as to the precise level of strict glycemic control started with a clinical study published in 2001, consisting of 1548 patients in a surgical ICU in Belgium[16]. In this study, van den Berghe *et al*[16] reported that intensive insulin therapy, aimed at maintaining blood glucose below 110 mg/dL reduced mortality and morbidity in critically ill patients by 42%. The reduction in mortality was apparent among patients who stayed in the ICU for more than five days[16]. A follow-up study, by the same investigators in 2006, aimed at comparing strict blood glycemic control (blood glucose: 80-110 mg/dL) *vs* a much looser control (blood glucose: 180-215 mg/dL) in this study on 1200 medical

Table 1 Factors leading to hyperglycemia and hypoglycemia in critically ill patients

Hyperglycemia[65]	Hypoglycemia[66]
Release of stress hormones (glucagon, epinephrine, cortisol, and TNF-α)	Severe sepsis
Certain medications (exogenous glucocorticoids, vasopressors, lithium, and β-blockers)	Trauma
Overfeeding	DM
Intravenous dextrose	Prior insulin treatment
Parenteral nutrition	Prior glucocorticoid treatment
Persistent bed rest	Cardiovascular failure
Increased insulin resistance (DM type 2)	Intensive glucose control
Deficient insulin secretion (DM type 1)	

DM: Diabetes mellitus; TNF: Tumor necrosis factor.

ICU patients and found that the strict glucose control group had a mortality reduction rate of 32% in patients who stayed more than three days in the ICU[17]. Of note, in this study, strict glucose control increased mortality in patients with short ICU stays (< 3 d), due to the increased rate of severe hypoglycemia.

A series of additional clinical trials followed these 2 seminal investigations. One of the most quoted in the medical literature was the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) multicenter trial, with 6104 ICU patients that compared strict glucose control (81-108 mg/dL) *vs* a more moderate glucose target (< 180 mg/dL)[18]. This study reported that moderate glycemic control lead to a reduction in cardiovascular mortality in critically ill patients.

Glycemic variability and hypoglycemia

As noted above, in diabetic patients, particularly those with persistent hyperglycemia, significantly lowering glucose levels and strict glycemic control may lead to symptomatic and life-threatening hypoglycemia and glycemic variability[19]. Glycemic variability has been defined as acute glycemic fluctuations; with both upwards fluctuations (in hypoglycemic correction) and downward fluctuations (in initial overbearing hypoglycemic treatment) leading to increased oxidative stress (which in turn leads to endothelial dysfunction and vascular damage). It is well documented that glycemic variability is much more dangerous than persistent hyperglycemia in critically ill patients[19,20].

Two retrospective studies found that glycemic variability conferred an increased risk of mortality in critically ill patients[21,22]. The mortality risk increased by 25.7% in critically ill non-diabetic patients[21,22]. Although no current consensus exists on the adequate range of acceptable glycemic variability in critically ill patients, Monnier and associates proposed a range of 40 mg/dL, as this corresponds to the normal variability found in non-diabetic healthy individuals[20].

Hypoglycemia is another dangerous situation in both diabetic and non-diabetic ICU patients. This clinical entity is directly related to cardiovascular mortality as it has been associated with increased QT waves in the electrocardiogram and changes in cardiac cell repolarization[23,24]. A study performed in 2005 reported that diabetic patients hospitalized with acute myocardial infarction, had a 93% increased mortality rate when hypoglycemia was present during their hospitalization[25]. In another study published last year, 2601 patients were evaluated and analyzed ICU mortality when moderate or severe hypoglycemia was present as compared to no hypoglycemia. Patients with severe and moderate hypoglycemia had a 34% and 18% increase, respectively, in ninty days mortality, when compared to patients with no hypoglycemia. Those patients that presented multiple hypoglycemic events had a 44% increase in mortality when compared to patients with no hypoglycemic events[26].

There is significant evidence that hypoglycemia poses significant risk of cardiovascular mortality among diabetic patients in critical care scenarios. Alongside the theoretical benefits of reducing glycemic variability, having a much looser glycemic control in critically ill diabetic patients, may aid in reducing cardiovascular mortality[27]. Further studies are necessary on the subject of glycemic variability, in an effort to find its real-world impact on diabetic patients in and out of critical care.

GUIDELINES RECOMMENDATIONS

The American Diabetes Association recommends starting insulin in patients with persistent hyperglycemia above 180 mg/dL in critically ill patients, and to maintain the glycemic range between 140-180 mg/dL. It also states that stricter glycemic control (110-140 mg/dL) can be appropriate for certain patients, such as patients with acute cardiac ischemia or patients with acute neurological event, as long as significant hypoglycemia can be avoided[28]. They also recommend active prevention of hypoglycemia by having a treatment plan if hypoglycemia were to develop and to change the current therapy if serum glucose levels fall below 70 mg/dL[28]. These recommendations were based on a consensus form American Association of Clinical Endocrinologists, which involved two meta-analyses of several clinical trials, including the NICE-SUGAR study, the largest randomized controlled trial, addressing this issue[28-31].

The American College of Physicians recommends serum glucose levels between 140-200 mg/dL indepen-

dent of diabetic status, and recommends avoiding blood sugar levels below 140 mg/d, due to the associated risks of hypoglycemia and glycemic variability[32]. The Society of Critical Care Medicine (SCCM) recommends maintaining the serum glucose level between 150-180 mg/dL[33].

However, a 2011 study conducted in the ICU among diabetic patients found that patients with uncontrolled diabetes (HbA1c above 7%) had different mortality when hyperglycemia was present when compared to non-diabetic patients or patients with better controlled diabetes (HbA1c below 7%)[34]. Additional newer studies have concluded similarly, that diabetic patients do not share the same mortality with hyperglycemia as non-diabetic patients, and that these diabetic patients may benefit from higher glycemic ranges to reduce the risk of hypoglycemia and glycemic variability[35-37]. Moreover, another study recommended maintaining serum glucose levels between 160-220 mg/dL in patients with HbA1c above 7%, and to maintain serum glucose levels between 140-200 mg/dL in patients with an HbA1c below 7%[19].

It is recommended that glycemic control be maintained with insulin due to the effectiveness, quick action, and few contraindications as it relates to this therapy[28,29]. However, the use of continuing metformin therapy in ICU patients with type 2 diabetes is seeing resurgence among certain patients, as the risk of hypoglycemia is lower; although its use should be cautious among patient with renal insufficiency, which is very common in the ICU[38].

In the following sections, we describe the evidence and recommendations for glycemic control among different patient groups who may be presenting in the ICU. Details are depicted in Table 2.

Patients in the surgical ICU

The Society of Thoracic Surgeons created guidelines in 2009 for glucose management in adult cardiac surgery patients, including diabetics[39]. For preoperative care, maintenance with insulin therapy with a serum glucose goal below 180 mg/dL was recommended. It was also recommended to check HbA1c level pre-operative for proper glycemic management. Intraopertavely, insulin therapy was also recommended for glycemic values above 180 mg/dL, and intravenous insulin infusion was recommended for persistent glycemic levels above 180 mg/dL intra-operatively or postoperatively in the ICU[39]. The recommendation was to keep a goal of 180 mg/dL throughout their stay in the ICU unless they are expected to remain in the critical care unit more than 3 d, or if the patient is ventilator-dependent, or requires therapy with inotropes, intra-aortic balloon pump, left ventricular assist device, anti-dysrhythmic medications, dialysis, or hemofiltration. In aforementioned cases, it is recommended to have the blood glucose levels below 150 mg/dL[39,40].

A recent study in 447 patients, found that a glucose level of 80-110 mg/dL, when compared to 140-180 mg/dL, reduces surgical site infections[41]. However, this study did not focus on over-all patient mortality and had a challenge of small sample size.

Patients with neurological events

A large clinical trial by van den Berghe *et al*[16] in 2001, suggested that strict glucose control (< 110 mg/dL) reduces mortality in critically ill patients[16]. For a period of time, following the findings of this trial, the standard of care was to maintain neurocritically ill patients blood glucose below 110 mg/dL[16]. However, the publication of the NICE-SUGAR study, and a prospective study of intensive insulin therapy in patients with recent neurosurgery, both published in 2009, showed that strict glucose control led to increased mortality mainly secondary to hypoglycemia[18,42].

In 2012, a systematic review and meta-analysis of 16 clinical trials on optimal glycemic control in neurocritical care patients, revealed that strict glycemic control (70-140 mg/dL) had no impact on patient mortality, but did increased the incidence of hypoglycemia[43]. Loose glycemic control (> 200 mg/dL) was shown to increased mortality when compared to a moderate glycemic control (140-180 mg/dL)[43]. The ADA states that blood glucose level of 110-140 mg/dL may be appropriate if significant hypoglycemia can be avoided[28].

Patient with an acute myocardial infarction

In 2008, the American Heart Association released a statement on glucose management in acute coronary syndrome, which recommended a glucose levels between 90-140 mg/dL in ICU patients with acute coronary syndrome[44]. The recommendations were later updated in 2009, suggesting an upper limit of serum glucose to 180 mg/dL[45].

The European Society of Cardiology published their most recent guidelines in 2012 on management of acute myocardial infarction with ST-segment elevation[46]. They recommend loose glycemic control in the acute phase, by maintaining the patient serum glucose below 200 mg/dL, as hypoglycemia was felt to be an important factor which increases the mortality[46]. This conclusion is based on a consensus reached by the National Institute Health and Care Excellence in 2011, that stated that no high quality studies were available to reach an evidence-based conclusion[47].

A 2012 meta-analysis, focusing on type 2 diabetics with acute myocardial infarction, involving 3 studies (for a total of 2113 patients), concluded that stricter glucose control with intensive insulin therapy did not reduced the patient mortality but significantly increased the incidence of hypoglycemia while offering no overall reduction in cardiovascular mortality[48].

Patients with sepsis

In response to the study on glucose control in surgical ICU patients, a study specifically on patients with sepsis, the Surviving Sepsis Campaign recommended a

Table 2 Glycemic control recommendation based on patient condition

Condition	Glucose control recommendation	Studies with patient number	Ref.
Non-diabetic ICU patients	140-180 mg/dL	29 studies with 8432 total patients and 26 studies with 13567 total patients	Wiener *et al*[30] (2008) and Griesdale *et al*[31] (2009), respectively
Diabetic ICU patients	If HbA1c < 7%: 140-180 mg/dL If HbA1c > 7%: > 200 mg/dL	1 retrospective study with 415 total patients	Egi *et al*[34] (2011)
Surgical ICU	If ICU stay is for more than 3 d, ventilator dependent, on dialysis, or with cardiac comorbidities: < 150 mg/dL	1 prospective study with 4864 total patients across 17 yr	Furnary *et al*[40] (2004)
Neurocritical ICU patients	If not: < 180 mg/dL If hypoglycemia can be prevented: 110-140 mg/dL If not: 140-180 mg/dL	16 studies with 1258 total patients	Kramer *et al*[43] (2012)
STEMI ICU patients	< 200 mg/dL	No high quality studies available Consensus by NICE	Nice Guidelines[47] (2011)
Sepsis ICU patients	< 180 mg/dL	1 randomized control trial with 6104 patients	Based of NICE-SUGAR study[17]
Pregnant ICU patients	No consensus	N/A	Van de Velde *et al*[55] (2013)

ICU: Intensive care unit; N/A: Not applicable; HbA1c: Glycosylated hemoglobin; NICE-SUGAR: Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation.

stricter range of glycemic control, with an upper goal of 110 mg/dL of serum glucose[17,49,50]. With the advent of the NICE-SUGAR trial in 2009, which also included septic patients, the 2013 update of the Surviving Sepsis Campaign modified its recommendation to a looser goal of 180 mg/dL[51]. Due to increased risk of hypoglycemia and hypoglycemia-related mortality, the Surviving Sepsis Campaign deemed that there was no apparent benefit from strict glucose control[51]. Insulin therapy was recommended to be started after two consecutive blood glucose measurements were above 180 mg/dL and to maintain a blood glucose of less than 180 mg/dL[51].

Pregnant patients

Gestational diabetes accounts for 2% to 9% of all pregnancies[52]. Hyperglycemia is an important factor to consider in all pregnancies, especially among hospitalized patients. During pregnancy, maternal cells have increased insulin resistance, due to elevated levels of human placental lactogen, progesterone, and estrogen[53]. This mild increase in insulin resistance is protective, and allows glucose absorption to be prioritized in the fetus, however in some patients, this mild resistance can be combined with insulin resistance, leading to persistent hyperglycemia[53,54].

It is generally agreed that treatment of gestational diabetes-related hyperglycemia is important in reducing perinatal mortality, as well as reducing hyperglycemia in postpartum mothers and improving overall health[52]. No consensus currently exists on the ideal range of serum glucose levels in critically ill pregnant patients[55]. It is difficult to recommend moderate or loose glycemic control in these patients, as even mild hyperglycemia can lead to adverse outcomes in infants[56]. On the other hand, tight glycemic control may lead to increased risk of hypoglycemia, which is also a factor that increases both maternal and infant mortality. Future clinical trials are necessary to be able to reach a consensus on how glycemic care should be managed in this population.

GLYCEMIC CONTROL THERAPY

While several studies have been performed on glycemic control in non-diabetic patients in the ICU, few of such studies have been performed on diabetic individuals. Table 3 depicts recent studies on this topic. Three of the four studies focused on surgical patients, and recommend a stricter glucose control for infection prevention, and hyperglycemia prevention[57-59]. The fourth study takes into account the risk of hypoglycemia, and recommends looser glycemic control to reduce moderate to severe hypoglycemia and glycemic variability[9]. However, all of these studies fail to take into account that diabetic individuals with persistent hyperglycemia (HbA1c above 7%) who are at higher risk from hypoglycemia-related mortality than hyperglycemia-related mortality[19,34]. A 2016 study on diabetic ICU patients, recommended keeping serum glucose levels below 250 mg/dL in patients with HbA1c above 7% upon admission to the ICU[9]. This study found that this loose glycemic control prevented glycemic variability and reduced the incidence of moderate and severe hypoglycemia[9].

Measurement of glucose should be performed every 2 to 4 h to allow for proper monitoring. If the patient's serum glucose concentration is fluctuating, it may be necessary to measure glucose every 30 or 60 min[60]. Currently, technology for continuous blood glucose monitoring using vascular catheter blood sampling is currently undergoing clinical trials and may become the standard of care and can allow tighter glycemic control in addition to preventing severe hypoglycemia or hyperglycemia[61]. Research has shown promise, as the technology is capable of detecting changes in glycemia that may otherwise be missed in our current practice, and has

Table 3 Strict glycemic control *vs* moderate glycemic control in critically ill patients with diabetes

Ref.	Study design/cohort	Sample size	Control group	Therapies employed	Conclusion	Favored therapy
Lecomte *et al*[57] (2011)	Diabetics undergoing off-pump cardiac bypass surgery	60	Matched 60 non-diabetics	Strict glycemic control (80-110 mg/dL)	Strict glycemic control was feasible and efficient Minimal risks for hypo- or hyperglycemia	Strict glycemic control
Yuan *et al*[58] (2015)	Diabetic patients receiving enteral nutrition after gastrectomy	212	None	Strict glycemic control (80-110 mg/dL) and moderate glycemic control (< 200 mg/dL)	Strict glycemic control lead to higher rates of severe hypoglycemia but lower rates of severe hyperglycemia Surgical site infection rate was higher with moderate glycemic control Rates of other complications were similar in the two groups	Strict glycemic control
Umpierrez *et al*[59] (2015)	Diabetic patients after coronary artery bypass surgery	152	150 non-diabetics	Strict glycemic control (100-140 mg/dL) and moderate glycemic control (141-180 mg/dL)	No significant differences between the two in the rate and severity of complications	Neither
Kar *et al*[9] (2016)	Diabetic ICU patients with HbA1c ⩾ 7.0% admission	83	None	Moderate glycemic control (< 180 mg/dL) and Loose glycemic control (< 250 mg/dL)	Loose glycemic control reduces glycemic variability and moderate to severe hypoglycemia	Loose glycemic control

ICU: Intensive care unit; HbA1c: Glycosylated hemoglobin.

shown that glucose levels correlate well with standard arterial glycemic measurement[62-64].

CONCLUSION

Glycemic control in the ICU continues to be challenging at best. Although the glycemic control strategy does not vary among diabetic individuals without persistent hyperglycemia from non-diabetic individuals (serum glucose goal of 140-180 mg/dL), it is important to note the cases where exceptions should be made. In neurological patients and surgical patients, a stricter glycemic strategy can be maintained (110-140 mg/dL and < 150 mg/dL, respectively) as long as adequate hypoglycemia can be avoided. In patients with a history of persistent hyperglycemia (HbA1c above 7%), liberal glycemic control may be beneficial in reducing the risk of hypoglycemia and glycemic variability, which is known to increase cardiovascular mortality, but further evidence and studies are necessary before a strong recommendation can be given. Further randomized control studies are suggested to further evaluate the variability in the target blood glucose level among different conditions.

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