



## Review Article

# Revisiting tight glycemic control in perioperative and critically ill patients: when one size may not fit all<sup>☆,☆☆</sup>

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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 also may 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.

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## 1. Introduction

In the last decade, glycemic control has been recognized as a crucial aspect in perioperative and critically ill patient

care. Earlier studies suggested that intensive glycemic control improved outcomes in surgical and medical intensive care unit (ICU) patients [1,2]. However, subsequent trials could not confirm the same benefit [3–5]. Moreover, some researchers discovered that increased mortality was associated with intensive targets (80 - 110 mg/dL or 4.4 - 6.1 mmol/L) rather than moderate targets (140 - 180 mg/dL or 7.8 - 10.0 mmol/L) [5]. As a result of these findings, tight glucose control has lost favor [6].

Compounding the problem, tight glycemic control is associated with an incidence of hypoglycemia [3,5–7] and such hypoglycemic episodes may offset some of the potential

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benefits of tight glycemic intervention [6]. Moreover, imposing tight glucose control did not yield robust results when it was applied to all patients regardless of their diabetic status (ie, known diabetes vs no previous diabetes diagnosis) [2,5]. Finally, some studies suggest a differential effect, with a reduction in mortality with tight glucose control in all patients except those with an established diagnosis of diabetes mellitus [6,8]. Nonetheless, despite the record of inconsistent findings, intensive glycemic control continues to be considered beneficial and is still recommended for diabetes care in the outpatient setting [8].

Accordingly, we examined the evidence to ascertain the interaction between diabetic status and outcomes in perioperative and critically ill patients in relation to glucose control strategies. Publications reviewed were limited to the English language and available through PubMed/Medline. The initial search terms used individually or combined were “perioperative”, “tight glucose control”, “intensive insulin therapy”, “intensive care unit”, “critically ill patients”, and “hyperglycemia”. In addition, we reviewed the references cited in the relevant articles to ensure that our search had not missed key papers. The following general themes arose: predominant population type (surgical vs medical); known diabetic and nondiabetic patients; and outcomes studied.

Others have attempted to explain the contradictory results of essentially the same glycemic management strategy. Kavanagh et al [9] proposed a plan for management of a hyperglycemic patient in light of the available literature and attempted to deduce a clinical application from the inconsistent results. Egi et al [10] highlighted the differences among published trials, in particular, those issues related to the differences between diabetics and nondiabetics and the impact of parenteral nutrition and hypoglycemia on outcomes. Van den Berghe [11] discussed the role of nutrition in making tight glycemic control effective; however, that author concluded that moderate hyperglycemia was probably of practical value in patient care.

This review refines existing views so that clinicians will have deeper insight into what appears to be controversial in the effects of tight glycemic management strategies on patients' outcomes.

## 2. Association of diabetes and perioperative hyperglycemia with adverse outcomes

In cardiac surgery, known diabetes and/or hyperglycemia is associated with poor outcomes. In a meta-analysis of 100,217 patients, those with diabetes had a significantly higher risk of mortality than nondiabetic patients from 30 days to 10 years after coronary artery bypass graft (CABG) [12]. In patients who had severe left ventricular dysfunction, diabetic patients were at higher risk than nondiabetics of developing superficial sternal wound infections, renal failure, and rehospitalization [13]. Deep

sternal wound infections and longer hospital length of stay (LOS) also were more common in diabetic than nondiabetic patients [14,15]. A blood glucose level greater than 110 mg/dL (6.1 mmol/L) on the first postoperative day after cardiac surgery increased the patient's risk of developing adverse outcomes such as stroke, myocardial infarction (MI), sepsis, or death [16].

Hyperglycemia also negatively impacts the outcomes of noncardiac surgery. In one study, preoperative blood glucose levels greater than 200 mg/dL (11.1 mmol/L) were associated with a 2.1-fold higher risk in overall 30-day mortality and a 4-fold higher risk of 30-day cardiovascular mortality [17]. Hyperglycemia was associated with a 4-fold increased risk of pulmonary embolism in a small study of patients undergoing total joint replacement [18]. In patients undergoing renal transplantation, admission hyperglycemia rather than a history of diabetes was associated with increased hospital LOS [19].

Findings such as these have prompted clinicians and investigators to devise methods to improve glycemic control for surgical patients. Since not only the diagnosis of diabetes but also the mere presence of hyperglycemia is associated with worse outcomes, glucose control strategies were applied to diabetic patients only or were generalized to include all patients.

## 3. Perioperative and intensive care unit interventional trials

The seminal study by Van den Berghe et al, which was the only investigation conducted in mainly surgical patients in a surgical ICU, showed that controlling blood glucose in the 80 - 110 mg/dL (4.4 - 6.1 mmol/L) range versus 180 - 200 mg/dL (10 - 11.1 mmol/L; actual achieved mean blood glucose levels were 103 vs 153 mg/dL [5.7 vs 8.5 mmol/L]) reduced ICU mortality by 42%, inhospital mortality by 34%, septicemia by 46%, and acute renal failure by 41% [1]. In that trial, only 13% of patients had known diabetes. Furnary et al used a continuous intravenous (IV) insulin infusion postoperatively for diabetic patients who had undergone CABG to maintain blood glucose levels between 150 and 200 mg/dL (8.3 and 11.1 mmol/L) [20]. Over the years, they lowered the glucose goals to 100 - 150 mg/dL (5.6 - 8.3 mmol/L) and started the insulin infusion before incision time. Mortality and mediastinitis were significantly reduced in the continuous IV insulin infusion group in contrast to a historical cohort treated with subcutaneous insulin (2.5% vs 5.3% and 0.6% vs 1.8%, respectively).

Subsequent trials included a mix of surgical and medical ICU patients, and challenged the trend that glucose levels needed to be maintained as low as 80 - 110 mg/dL (4.4 - 6.1 mmol/L). The GluControl trial randomized patients to tight glucose control (80 - 110 mg/dL; 4.4 - 6.1 mmol/L) and conventional glucose control (140 - 180 mg/dL; 7.8 - 10

mmol/L) [3]. Only 18% of their patients had known diabetes. There was no difference between the two groups in mortality, LOS, organ failure, or need for kidney dialysis. The average achieved morning glucose levels were 139 mg/dL (7.7 mmol/L) for the conventional group and 110 mg/dL (6.1 mmol/L) for the tight control group. The VISEP trial (by the SEPNET Group) compared the effects of intensive insulin therapy to achieve a target of 80 - 110 mg/dL (4.4 - 6.1 mmol/L) with conventional insulin therapy to achieve a target of 180 - 200 mg/dL (10 - 11.1 mmol/L) in patients with severe sepsis [4]. Thirty percent had known diabetes. The achieved mean morning blood glucose was 112 mg/dL (6.2 mmol/L) for the intensive insulin therapy group and 151 mg/dL (8.4 mmol/L) for the conventional group. Mechanical ventilation, 28-day mortality incidence, and mean score for organ failure were the same in both groups. The NICE-SUGAR international multicenter trial, the largest randomized trial of glycemic control to date, compared intensive with conventional glucose control (target of 81 - 108 mg/dL vs < 180 mg/dL) in mostly medical (63%) rather than surgical patients (37%) [5]. In that study, a 2.6% higher risk of mortality at 90 days in the intensive arm was noted.

Intraoperatively, a single-center trial by Gandhi et al randomized 400 cardiac surgery patients during surgery to either tight glycemic control (80 - 100 mg/dL or 4.4 - 5.6 mmol/L) or to the usual care (no insulin during surgery unless blood glucose levels were > 200 mg/dL [ $> 11.1$  mmol/L]). The difference in mean glucose concentrations at the end of surgery was about 43 mg/dL (2.4 mmol/L). There was no difference in outcomes between the two groups. In that trial, 20% of patients were diabetic [21]. Moreover, following their cardiac surgery all patients were admitted to the ICU, where they received tight glucose control, the effects of which might have masked any effect of intraoperative glucose control [22]. Abdelmalak et al conducted a randomized trial of tight versus conventional glucose control (DeLiT Trial) to achieve a target of 80 - 110 mg/dL (4.4 - 6.1 mmol/L) versus 180 - 200 mg/dL (10 - 11.1 mmol/L) applied intraoperatively in major noncardiac surgery [23], the results of which were recently published [24]. In our single center trial, 27% were diabetic, and the median intraoperative time weighted average glucose for the intensive glucose control patients was 108 (Q1, Q3:100, 121) mg/dL (6.0 [5.6, 6.7] mmol/L) and for the standard care patients was 139 [124, 165] mg/dL (7.8 [6.9, 9.2] mmol/L). There was no difference in the primary outcome of major in-hospital morbidity and mortality between the two groups.

#### 4. Hyperglycemia and outcomes in patients diagnosed with diabetes versus nondiabetic patients

The studies cited above had varying proportions of patients with diagnosed diabetes and nondiabetic patients; many of the latter were hyperglycemic. Interestingly,

emerging data indicate that the relationship between hyperglycemia and outcomes may differ depending on the presence or absence of a diagnosis of diabetes. In Whitcomb et al's single-center retrospective study of heterogeneous ICU populations, admission hyperglycemia, defined as admission glucose > 200 mg/dL (11.1 mmol/L), was an independent risk factor for inhospital mortality only in patients without diagnosed diabetes and only in the cardiothoracic, cardiac, and neurosurgical units [25]. In the same trial, statistical models were rerun using a threshold of 150 mg/dL (8.3 mmol/L), and the results were remarkably similar. Another retrospective study showed that nondiabetic patients with time-weighted glucose levels of 144 - 180 mg/dL (8 - 10 mmol/L) and 180 - 198 mg/dL (10 - 11 mmol/L) had a 1.7 and 3.3 times, respectively, greater risk of ICU mortality than diabetic patients with the same glucose ranges [26]. In that study, hyperglycemia was independently associated with mortality only in patients without diagnosed diabetes. In a post-hoc analysis of surgical (56%) and medical (44%) ICU patients randomized to intensive insulin treatment (blood glucose target of 80 - 110 mg/dL [4.4 - 6.1 mmol/L]) or conventional treatment (blood glucose target of 180 - 200 mg/dL [10 - 11.1 mmol/L]), reduced mortality with intensive insulin therapy was evident only in patients without a history of diabetes mellitus [27].

Krinsley et al evaluated 5,365 consecutive ICU patients and found that hyperglycemia was associated with higher mortality in nondiabetic patients [28]. However, in contrast to the preceding study [27], strict euglycemia in diabetic patients was associated with a survival benefit in a multivariable model. Graham et al have shown that in the ICU, diabetic survivors had higher glucose concentrations than nondiabetic nonsurvivors. In addition, the unadjusted mortality rates were significantly higher for diabetic than for nondiabetic patients in the subgroup whose maximum glucose was less than 129 mg/dL, but the opposite was true at a blood glucose level greater than 162 mg/dL [29]. Falciglia et al, in their retrospective study of 259,000 multicenter heterogeneous medical and surgical ICU patients, found that mortality was greater for hyperglycemic patients without a diagnosis of diabetes ( $P < 0.01$ ) [30].

Different results are seen in other trials. In Ramos et al's retrospective study of 995 noncardiac surgery patients, the authors concluded that postoperative hyperglycemia increased the risk of postoperative infections regardless of diabetic status [31]. A larger study by Frisch et al [32] retrospectively studied the records of over 3000 noncardiac surgery patients and found that hyperglycemia resulted in worse outcomes (postoperative infections, acute renal failure, acute MI, 30-day mortality), as well as longer ICU and hospital stay for all patients regardless of the presence or absence of a diagnosis of diabetes—thus confirming the findings of Ramos et al. However, in an adjusted multivariate analysis, mortality was significantly proportional to perioperative glucose concentrations only for patients with no history of diabetes ( $P = 0.008$ ).

Overall, these findings suggest that hyperglycemia may bear different clinical and biological implications in patients depending on their chronic metabolic status [26]. In support of this theory, a retrospective study by Egi et al of ICU patients with diabetes, found an interaction between glycosylated hemoglobin (HbA1c) and time-weighted glucose concentrations: a time-weighted glucose level > 180 mg/dL (10 mmol/L) during ICU stay was associated with a lower mortality in patients with a preadmission HbA1c > 7% (indicating chronic hyperglycemia) than in patients whose A1c was < 7% (indicating relatively better chronic glycemic control) [33].

These findings may be important in qualifying the generalization that an association exists between hyperglycemia and poor outcomes in all patients, and in rethinking the claim that tight glucose control is invariably harmful (or beneficial) in all patients; instead they highlight the relative effects of different subgroups. Reassessing the generalization and the claim might lead to the conclusion that for nondiabetic patients with newly detected hyperglycemia, patients with diagnosed diabetes on suboptimal outpatient glycemic control, and patients with diagnosed diabetes on optimal glucose control, glucose targets should be different.

A plausible explanation for the interaction between diabetic status, glycemic status, and outcomes is that diabetic patients may tolerate fluctuations in their blood glucose during periods of extreme hyperglycemia [29]. Moreover, patients who are chronically hyperglycemic may have reset their metabolism in such a way that their body cells cannot tolerate sudden shifts in glycemic concentrations lower than those to which they are accustomed [34].

A somewhat similar paradigm is illustrated in the management of chronic hypertensive patients; during surgery anesthesiologists tend to maintain arterial blood pressure close to baseline in those patients so as to maintain adequate cerebral perfusion. Indeed, in well-controlled type 2 diabetic patients, glucose thresholds for counter-regulatory hormone secretion are altered. Both symptoms and counter-regulatory hormone release can occur in diabetic patients at normal glucose values, and thus such thresholds are at higher glucose concentrations than those in healthy controls [35].

Paradoxically, although it seems feasible to normalize glucose levels in chronically hyperglycemic diabetic patients, this action might actually result in harming the patient [33]. Many theories have been proposed to explain this paradox. For instance, it is likely that diabetic patients with lower blood glucose have an increased risk of hypoglycemia during the ensuing year [36,37]. Moreover, diabetic patients with uncontrolled glucose, who are treated and then reach a normal glucose level, are at increased risk of hypokalemia as well as prolonged QT interval [38,39]. Such aggressive glucose control (tight control) in chronically hyperglycemic diabetic patients may also trigger a hypoglycemic response, and thus increase catecholamines and increase cardiac arrhythmias [35], both of which are risk factors for morbidity and mortality.

## 5. Preoperative hemoglobin A1c and outcomes

Hemoglobin A1c is a good indicator of chronic blood glucose concentrations in the few months preceding surgery. Preoperative HbA1c < 7% in diabetic patients undergoing noncardiac surgery was independently associated with fewer infectious complications [40]. Bishop and colleagues have linked HbA1c > 11.5% to surgical site infections [41], but Wilson et al have refuted that notion [42]. This issue represents yet another area requiring additional investigation in both diabetic and nondiabetic patients.

## 6. Glycemic variability

Glycemic variability is an independent risk factor for mortality in the ICU [28,43]. Glycemic variability, as measured by the glycemic lability index (GLI), is also independently associated with hospital mortality in septic patients [44]. Paradoxically, this relationship is even stronger in the euglycemic range. Fluctuating glucose levels are associated with 8-iso-prostaglandin-F2 $\alpha$ , a marker of oxidative stress and a potential mediator of organ dysfunction [45]. This oxidative stress factor also may be pathophysiologically important, hence its impact on outcomes [43]. In addition, as demonstrated by Monnier et al, acute glucose fluctuations in response to meals may trigger oxidative stress comparable to that of persistent hyperglycemia [45]. This finding may explain why the use of insulin infusions, presumably with better regulation of glucose, results in less all-cause mortality and in fewer poor cardiac outcomes than intermittent bolusing of short-acting insulin [46].

## 7. Glycemic control and various outcomes

Apart from the afore-mentioned diabetic status that might warrant distinct glucose targets, various trials have studied distinct patient outcomes. Tight glycemic control reduces perioperative infections [20,47,48], hospital or ICU LOS [20,47,49], and acute kidney injury [1], and confers myocardial protection in cardiac surgery patients [50]. Moreover, a meta-analysis of tight glucose control trials [51] showed that tight glucose control was associated with a reduction in sepsis (RR 0.58, 95% CI 0.42 - 0.80). These outcomes alone are significant determinants of continued patient health. Therefore, although tight glycemic control strategies have failed to consistently show overall survival benefit [5], perhaps the other intermediate outcomes may benefit patients' quality of life and/or cost of care. Accordingly, such outcomes should be taken into account when patient care protocols are designed, and when future

studies of tight perioperative glycemic control are undertaken. Moreover, other variables also should be considered, such as glucose variability and the correlation (or lack of) between the attempted glucose control target and the patient's chronic glycemic and diabetic state.

## 8. Impact of tight glucose control on outcomes in different settings

The question then arises as to whether tight glucose control is beneficial in some populations and not in others. Van den Berghe et al's [1] randomized trial on tight glucose control published in 2001 was conducted on predominantly postcardiac surgery patients; only 13% of their patients had a history of diabetes (Table 1). Intensive glucose control, defined as a target of 80 - 110 mg/dL, showed a significant difference in decreasing mortality compared with conventional control of 180 - 200 mg/dL. However, other randomized controlled studies, examples of which are included in Table 1 for the purpose of elucidation, had different proportions of medical versus surgical patients, and a different proportion of the surgical procedure. While the definition of tight glycemic control was similar among the studies (mostly 80 - 110 mg/dL), a variety of glucose concentration targets were used to define conventional control (180 - 200 mg/dL in two studies; 129 - 180 mg/dL in one; and < 180 mg/dL in another). The proportion of patients with known diabetes also might have influenced the results.

Attempts at combining these studies and other trials have appeared in the form of meta-analyses [48,49]. However, we contend that results cannot be generalized, and that specific subgroups such as cardiac surgery patients may benefit from tight glucose control whereas others might not.

## 9. Glucose control target versus insulin therapy

The beneficial effects of treating hyperglycemia may result partly from the administration of insulin. Insulin treatment improves protein synthesis, stimulates energy production, and counteracts the detrimental influence of hyperglycemia. Insulin also has additional metabolic effects: it partially reverses dyslipidemia caused by critical illness [52], thereby increasing lipoproteins that can scavenge endotoxins [53] and transport lipid components. Insulin also activates Ca<sup>2+</sup>-independent endothelial nitric-oxide synthase generation in endothelial cells [54], and has anti-apoptotic properties independent of glucose uptake [55-57]. Insulin is also directly anti-inflammatory in that it suppresses intracellular pathways regulated by intranuclear factor kappa-B. This includes pathways responsible for generation of superoxide radicals and the production of inflammatory cytokines such as tumor necrosis factor-alpha (TNF- $\alpha$ ) and macrophage migration inhibitory factor [58,59]. These benefits may help offset some of the inflammatory responses otherwise impaired by poor blood glucose control [60]. Hyperglycemia stimulates the release of inflammatory cytokines and leads to the induction and secretion of acute-

**Table 1** Major published randomized controlled trials of tight glycemic control

Ref. no. and author	Population	Glucose target	Primary endpoint	Results
Van den Berghe et al [1]	Primarily surgical 63% cardiac surgery 37% others (eg, neurologic surgery, thoracic surgery, severe burns) 13% w/history of diabetes	Intensive: 80-110 mg/dL Conventional: 180-200 mg/dL	Mortality	Intensive: 4.6% Conventional: 8.0% <i>P</i> < 0.04
Brunkhorst et al [4] SEPNET glycemic control arm	16% elective surgery 37% emergency surgery 47% medical 30% w/history of diabetes	Intensive: 80-110 mg/dL Conventional: 180-200 mg/dL	28-day mortality and morbidity	No diff. between groups
Preiser et al [3] GluControl study	31% elective surgery 17% emergency surgery 7.5% trauma 41% medical ~32% of all cases cardiac in nature 18.8% w/history of diabetes	Intensive: 79-110 mg/dL Conventional: 129-180 mg/dL	ICU mortality	No diff. between groups
Finfer et al [5] NICE-SUGAR study	37% surgical 67% medical 20% w/history of diabetes	Intensive: 81-108 mg/dL Conventional: < 180 mg/dL	90-day mortality postrandomizn	Intensive: 27.5% Conventional: 24.9% <i>P</i> = 0.02

SEPNET=German Competence Network Sepsis group, diff=difference, NICE-SUGAR=Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation, postrandomizn=postrandomization.

phase reactants by adipocytes. In a population-based, cross-sectional study of 1,000 patients greater than age 50 years, fasting blood glucose level was significantly and independently related to C-reactive protein (CRP) levels (correlation coefficient 0.06; 95% CI 0.014 - 0.11,  $P = 0.011$ ). C-reactive protein levels increased continuously across the spectrum of fasting blood glucose levels, even within the normal range [61].

Few studies have attempted to determine whether insulin itself or tight glucose control confers the benefit. In a post-hoc analysis of patients in the surgical ICU who were randomized to either tight glycemic control or conventional control, the achievement of normoglycemia rather than the dose of insulin infused was associated with improved outcomes [62]. The same team of researchers further investigated this association by manipulating glucose and insulin levels in 4 groups of burn-injured, parenterally fed rabbits: two groups were normoglycemic with either normal or high insulin levels, and two groups were hyperglycemic with either normal or high insulin levels [63]. The researchers found that mortality was significantly lower in the two normoglycemic groups independent of insulin levels, and that normoglycemia prevented endothelial dysfunction and liver and kidney injury. In 2011, Carvalho et al studied the effects of a glucose, insulin, potassium (GIK) regimen while maintaining normoglycemia (so-called GIN therapy) during cardiac surgery and showed that such a strategy confers more cardioprotection than standard care that used the same GIK regimen but did not maintain normoglycemia [50].

Despite these findings, we cannot totally rule out the possibility that insulin infusion, in the presence of hyperglycemia, may also confer greater metabolic improvement than normoglycemia alone.

## 10. Glucose measurement

A serious challenge in implementing any glycemic management strategy is timely and accurate glucose determination. There are many ways to determine glucose level. For instance, central laboratories or arterial blood gas analysis (ABG machines) measure whole arterial or venous blood glucose. Various point-of-care testing (POCT) devices measure capillary blood glucose through direct skin puncture or whole arterial or venous blood sample. Continuous glucometers measure glucose concentrations in the interstitial fluid. Finally, continuous inline glucometers, which measure whole blood glucose concentration through an indwelling arterial or central venous catheter, are in development. Each method has its advantages and disadvantages. While POCT is quick and convenient, the accuracy of these devices has been questioned. These devices appear to overestimate more than underestimate the true glucose concentration in 15% of capillary samples and in 7% of whole blood samples [64]. The continuous

interstitial fluid glucometer, although it is convenient and provides frequent readings, has the disadvantage of a lag period between blood and tissue glucose concentrations. When one methodology is used (such as POCT), sampling site and methodology should remain consistent throughout the procedure. In addition, blood glucose results should be verified using an alternate method; for example, ABG and/or central laboratory analysis when variations in blood glucose results are  $\geq 100$  mg/dL on consecutive blood samples, false laboratory results, or contaminated specimens are suspected, or when the glucose concentration value is nearing "critical values" and/or the POCT device displays a result of "HI" or "LOW" [65].

## 11. Safety of tight glycemic control

While hyperglycemia is detrimental, hypoglycemia is not without risk. Low glucose levels may increase mortality and morbidity and result in neurologic damage. Severe hypoglycemia caused somnolence, unconsciousness, seizures [66], and when persistent, irreversible neurologic sequelae and/or death<sup>1</sup>. It is thus likely that such hypoglycemic episodes may offset some of the potential benefits of tight glucose control intervention [6]. Clinicians thus understandably may be concerned about tightly controlling perioperative blood glucose for fear of the risks associated with inadvertent hypoglycemia.

While hypoglycemia rates as high as 29% have been reported in association with tight glycemic control [7], a meta-analysis of tight glucose trials in the ICU showed that the risk of hypoglycemia was unrelated to the intensity of insulin therapy [67]. Moreover, a well-qualified staff using standard insulin infusion may minimize hypoglycemic events [1]. In fact, in an intensive insulin therapy trial in stroke patients (target blood glucose concentrations between 72 and 126 mg/dL or 4.0 - 7.0 mmol/L), there were no episodes of hypoglycemia (glucose  $< 40$  mg/dL or 2.2 mmol/L) [68]. In 2011, Abdelmalak et al reported no episodes of severe hypoglycemia in their cohort of 364 noncardiac surgery patients randomized to a target intraoperative blood glucose concentration of 80 - 110 mg/dL (4.4 - 6.1 mmol/L, intensive) or 180 - 200 mg/dL (10 - 11.1 mmol/L, conventional) [69].

In addition to vigilance of the clinicians, a proposed approach to prevent hypoglycemia was frequent glucose concentration determinations and the use of dynamic insulin infusion protocols that take into account not only the absolute glucose concentration but also the change from prior readings. Therefore, for the same glucose concentration for the same patient, the insulin infusion rate adjustment may

<sup>1</sup> Ketzler JT, AG, Coursin DB. Perioperative care of the diabetic. In: Ketzler JT, Coursin DB, editors: ASA Refresher courses in Anesthesiology. Park Ridge (IL): American Society of Anesthesiologists; 2001. p. 1-9.

vary depending on the amount of change in relationship to the previous reading.

Only a few studies in this area of glycemic management and outcomes are randomized trials. The majority are observational or retrospective in design. Findings discovered in observational studies are best utilized as hypothesis-generating tools [70]. Such hypotheses generated from retrospective analyses have helped with important discoveries, and in other instances have not been substantiated when a study was performed in a randomized fashion. This limitation is exemplified in Gandhi et al's studies; their prospective trial [21] did not substantiate the results identified in their retrospective study [71] in cardiac surgery patients with regard to the association of intraoperative glucose concentrations and surgical outcomes.

## 12. Summary

The earliest studies using tight glycemic control showed beneficial effects. However, subsequent investigators were unable to reproduce those results. The high incidence of hypoglycemia associated with tight glucose control also might have dampened enthusiasm for such an intervention. Our review highlights the probability that hyperglycemia may impact outcomes differentially, depending on whether patients have diagnosed diabetes, or undiagnosed diabetes but are hyperglycemic; and, if the former, whether or not they are chronically hyperglycemic. Glucose targets therefore have to be different for nondiabetic patients with newly detected hyperglycemia, those with diagnosed diabetes on suboptimal outpatient glycemic control, and those with diagnosed diabetes on optimal glucose control.

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