Perioperative glycemic control: what is worth the effort?

Angelo M. Dell’Aquila and Björn Elger

Purpose of review
Diabetes mellitus and its related comorbidities present a growing challenge in perioperative medicine. And also largely independent from a history of diabetes, dysregulations of glucose homeostasis occur as part of the body’s stress response. Dysregulations of glucose homeostasis, acute or chronic, are closely correlated with impaired prognosis in perioperative medicine. Treatment strategies remain somewhat controversial, as both the affliction and its correction have a blind side.

Recent findings
Anesthesia requires vigilant attention to diabetes-related comorbidities such as neuropathy, angiopathy, cardiopathy and immune dysfunction. Dysregulations of glycemia of any kind, in other words, hypoglycemia and hyperglycemia and fluctuations of blood glucose, should be avoided. Target glycemia remains a matter of discussion: moderate, achievable glycemic target below 180 or 150 mg/dl appears to be reasonable. Modern technical developments like continuous glucose measurement devices and computer-assisted control algorithms are under development, and will hopefully facilitate perioperative glycemic control in the future.

Summary
Literature clearly shows that leaving glycemic control out of focus is dangerous for the patient; efforts to control glycemia to a moderate target improve the patient’s outcome.

Keywords
control algorithms, diabetes, glucose control, perioperative complications

INTRODUCTION
It is commonly accepted that the number of patients suffering from diabetes mellitus who undergo surgical procedures increases. These patients are prone to various specific perioperative complications. However, also nondiabetic patients develop hyperglycemia as a response to stress-like trauma or surgery. Especially in perioperative medicine, an association of hyperglycemia and various adverse events, like surgical side infections, myocardial infarction, stroke and mortality, has been shown in many publications. And also fluctuations of blood glucose and hypoglycemia correlate with impaired prognosis [1], so ‘dysglycemia’ of any kind appears to be the patient’s foe as, among others, concluded from a database analysis including 784,392 patients [2]. However, whether or not to interpret dysglycemia as a marker of severity of the illness or as an independent risk factor itself remains controversial. The latter results in the necessity to treat, an approach that has been the subject of many studies in various afflictions. Unfortunately, most publications report observational findings; evidence from prospective trials powered to address the important outcomes is far from compelling [3**].

This review focuses on perioperative dysglycemia of diabetics and nondiabetics, and gives opinion-based recommendations for the clinician to safely guide patients through the perioperative period.

CAUSE OF STRESS-INDUCED HYPERGLYCEMIA
During and after surgical trauma, both relative insulin deficiency and insulin resistance lead to
hyperglycemia. The latter comprises decreased glucose utilization and increased hepatic gluconeogenesis, using amino acids from muscle catabolism as a substrate. Selected by evolution, it was long deemed an exclusively beneficial adaptation to secure provision of energy to glucose-dependent vital organs such as the brain and immune system. Nowadays, severe medical afflictions can be survived that would have been lethal just a few decades ago. Moreover, medical development allows extending the frontiers of (surgical) treatment. The body’s survival mechanisms have not been selected by evolution in these conditions; hence, adaptations are not necessarily beneficial, but can become detrimental during prolonged illness.

In addition to being associated with increased mortality in critical medical conditions, hyperglycemia causes a number of organ dysfunctions, such as reduction of myocardial performance, glycation of enzymes, endothelial dysfunction and a reduction of cellular and humoral immune defense (see [4] for review).

MECHANISM OF HARM OF HYPERGLYCEMIA

There is abundant literature unravelling the mechanisms behind glucose toxicity in diabetes and stress-induced dysglycemia. Summarizing the data, it is an overload of the cells with glucose that triggers toxic effects in virtually all organ systems. Glucose uptake into the cells is facilitated by different types of glucose transporters; the transport follows the concentration gradient. The number of transporters in the cell wall is the rate-limiting step of cellular glucose uptake as their maximal capacity is below usual blood glucose. In healthy individuals, the number of transporters is downregulated when there is an intracellular glucose overload. During stress, however, this mechanism seems to fail and influx surmounts intracellular glucose utilization. Intracellular and extracellular glucose levels equilibrate on high levels [5]. This resulting intracellular glucose overload triggers detrimental chain reactions that, among others, influence the clearance of toxins. The consequence is (permanent) organ dysfunction [6,7].

Of special importance is the effect of hyperglycemia on host defense against infections. The immunological system is weakened in both defense mechanisms: cellular and humoral. In this setting, a decrease in chemotaxis, phagocytosis, adherence and bactericidal activity of leukocytes has been proven [8]. A recent meta-analysis of high-quality trials in perioperative medicine [3**] showed a trend toward a lower incidence of infectious complications when hyperglycemia in diabetes mellitus patients is avoided, whether the case is equal for nondiabetics is questionable. Anyway, a hyperglycemic environment weakens the body’s response to various microorganisms.

IMPACT OF DYSGLYCEMIA IN THE PERIOPERATIVE SETTING

Patients with a history of diabetes mellitus frequently present with well known comorbidities and typical risk factors [9]. In addition to the vascular complications like myocardial infarction or stroke that occur more frequently in diabetes mellitus, most important for anesthetic management is probably the autonomic neuropathy that is found in about 30% of diabetics. Especially, (cardiac) autonomic neuropathy that can be detected by decreased heart rate variability, orthostatic hypotension or prolonged QT interval must be considered. It further increases the risk of perioperative cardiovascular mortality and morbidity; hence, thorough preoperative assessment (e.g. HbA1c) and vigilant, procedure-adapted perioperative monitoring is required [10]. Special care must be taken when bed- ding the patients with diabetes mellitus as their risk to develop pressure ulcers during surgery is doubled [11].

Dysglycemia frequently occurs perioperatively in both diabetics and nondiabetics. It is associated with complications as shown by an ongoing surge of publications. In general surgery, the risk of complications rises in association with hyperglycemia [12]. Several trials demonstrated that hyperglycemia is an independent risk factor for inferior neurological outcome, for example, in neurosurgery [13] or traumatic brain injury [14]. In trauma patients undergoing orthopedic surgery, hyperglycemia is a risk factor for surgical site infections [15]. Puzzling, there
is not a linear or hyperbolic correlation between blood glucose and outcome. In cardiac surgery, for example, Duncan et al. [16] included more than 4000 patients in a retrospective trial. Patients were categorized in three groups (blood glucose >200, 171–200, 141–170 and <140 mg/dl, respectively). In a logistic regression model, both severe postoperative hyperglycemia (blood glucose >200 mg/dl) and normoglycemia (<140 mg/dl) were associated with worse outcomes compared with moderate hyperglycemia.

So, blood glucose slightly above normal fasting blood glucose is apparently associated with the best prognosis.

**SHOULD WE TREAT PERIOPERATIVE DYSGLYCEMIA?**

Reading the previous paragraphs, it suggests to treat dysglycemia. Early promising single-center trials, especially in myocardial afflictions and in the ICU setting, have initiated a cascade of consecutive clinical trials in different populations. Meanwhile, multicenter trials in the critically ill have not only failed to confirm the promising results, but also raised concern over intervention-associated risks when a tight glucose target is strived for [17]. A recent Cochrane meta-analysis of published trials did not point out a significant benefit of tightly controlling blood glucose in diabetes mellitus in the perioperative setting with respect to mortality [3**]. However, most recent trials showed benefits of treating stress-induced hyperglycemia [18,19]. One explanation for this on first view conflicting data is that patients with diabetes may benefit from higher glucose target ranges than those without diabetes [1]. The reasons for the unequivocal data are complex and extensively discussed in literature [20]. Most likely, different medical conditions require different levels of target glycemia. So what to do?

To guide the reader to our recommendation, we will cite just a few trials. In a prospective, unblinded study in major vascular surgery, Subramaniam et al. [21] randomly assigned patients to continuous insulin infusion with a ‘moderate’ target blood glucose (100–150 mg/dl) or to a standard intermittent insulin bolus scheme (treat blood glucose >150 mg/dl). A significant reduction in perioperative mortality in the intervention group compared with the control group was found. Moreover, patients included in the continuous insulin infusion group experienced significantly less perioperative myocardial infarction and congestive heart failure. Bhamidipati et al. [22] stratified patients undergoing cardiac surgery into three groups: tight (<126 mg/dl), moderate (127–179 mg/dl) and liberal (≥180 mg/dl) glycemic control. The moderate group did best as well as in other trials [18,19]. The same was shown in a large multicenter trial in ICU patients [17].

Surely, in a single-center, prospective, well-controlled study setting, safely achieving euglycemia by well trained staff is reasonable; in everyday life, strict targets might be difficult to reach. The multicenter trials show inferior adherence to glucose control protocols compared with mono-center trials, target populations differed, there were problems to reach and maintain normoglycemia in the intervention group, different nutrition protocols were allowed, faulty blood glucose meters and variable blood sampling sites and subcutaneous insulin injection were approved. This led to insulin-dosing errors with consequently (undetected) hypoglycemia and remarkable blood glucose variability (see [23*] for a meticulous discussion).

Conclusively, clinical associations nowadays recommend ‘reasonable, achievable, and safe’ glycemic goals for in-hospital patients. Targets of 140–180 mg/dl on ICU and 100–180 mg/dl for general medical and surgical wards are advocated [19,24]. Largely, the same is recommended by the current surviving sepsis campaign guidelines for ICU patients [25] and for neuro-ICU [26].

Moderate glucose control avoiding hypoglycemia, fluctuations of blood glucose and hyperglycemia above 180 mg/dl in perioperative medicine appears reasonable, and a good compromise between the risks of blood glucose fluctuations, hyperglycemia and hypoglycemia. Maybe targets should be lower for nondiabetics as it should be for diabetics [1].

**RISK OF HYPOGLYCEMIA**

Treating hyperglycemia with insulin increases the risk of hypoglycemia [27]. Notably, hypoglycemia is as dangerous as hyperglycemia or fluctuations of blood glucose [2], at least in the critically ill [27]. Unfortunately, clinical signs of hypoglycemia are camouflaged in the perioperative setting by sedation or anesthesia. However, as blood glucose can frequently be monitored in the perioperative period, the hypoglycemic episodes should be rather short. Moreover, hypoglycemia might as well be a marker of severity of illness rather than ‘toxic’ itself [27]. And, granted that hypoglycemia does harm [1], maybe the risk is worth it to buy the benefits of avoiding hyperglycemia-induced toxicity. At least, that is what Krinsley et al. [28] pointed out in a database of 6240 patients. When the incidence of hypoglycemia surmounts a certain threshold, benefits of glycemic control are counterbalanced.

In addition to mortality, clinicians fear hypoglycemia-induced deterioration of neurocognitive function. And indeed, we could show in our adult ICU population that even one episode of...
hypoglycemia goes in line with permanently impaired neurocognitive function, using a retrospective case–control design [29]. In contrast, a very recent prospective trial from Belgium did not point out hypoglycemia as an independent risk factor for neurologic dysfunction in a pediatric ICU population [30].

In general, it appears self-evident to avoid hypoglycemia in the perioperative setting if possible.

HOW TO HANDLE PERIOPERATIVE DYSGLYCEMIA IN CLINICAL PRACTICE?

Approaching a patient with a good review of the history is trivial, but necessary. Especially in diabetic patients, it gives information on the risk of autonomous neuropathy, gastroparesis, frequency of hypoglycemia and associated medical conditions.

Usual medical treatment [31] should be continued until the morning of surgery. Then, oral antidiabetics should be withdrawn. If possible, diabetics should be operated early in the schedule to avoid long fasting.

In type 1 diabetes, because of the risk of ketoacidosis, the medication with basal insulin should be continued despite perioperative fasting. If morning blood glucose is low (<100 mg/dl), the dose should be reduced by 25%.

In type 2 diabetes, ketoacidosis is no major hazard. When blood glucose is above 80 mg/dl, patients should get half of their usual morning dose of depot insulin. Patients with low morning fasting blood glucose have a much higher risk to experience profound hypoglycemia in the perioperative setting than those with hyperglycemia and subsequent insulin need [32].

Blood glucose measurements should be performed every 1–2 h and glucose infusion should be started when blood glucose approaches hypoglycemia. Blood glucose measurements in hemodynamically compromised patients should only be done in full blood. Capillary samples carry a high risk of faulty values. If necessary, subcutaneous boli can be applied according to the patient’s dosing scheme. However, continuous intravenous infusion appears to be superior to subcutaneous boli [21]. The onset of action of subcutaneous insulin might be delayed during tissue hypoperfusion.

Normally, 1 IU lowers blood glucose by about 27 mg/dl. Especially in type 2 diabetes mellitus, this can vary remarkably. In insulin-dependent patients, the required dose of insulin can be calculated by the following equation [33]:

\[
\text{Insulin dose} = \frac{(\text{measured BG} - \text{target BG}) \times \text{daily insulin dose}}{1700}
\]

To achieve targets during surgery, glucose–insulin coinfusions (GIK) do not provide convenient glucose control. GIK was originally advocated to improve myocardial function, but was only effective when blood glucose control was established [34]. So, glucose control does the biggest part of the job, GIK alone is defective to reach the blood glucose target. Accordingly, starting a continuous insulin drip during surgery and tapering the drip in the recovery is reasonable and convenient. A standard dosing algorithm facilitates the procedure. In minor or intermediate surgery, intraoperative hyperglycemia will fade away within hours to moderate hyperglycemia when the acute stressor stops. When patients remain severely hyperglycemic, this must be interpreted as a warning signal.

For diabetes mellitus patients, restarting their routine medication as soon as oral nutrition is provided at almost normal level is advocated. If hyperglycemia persists in nondiabetics, the patient should receive follow-up testing in an ambulatory, unstressed state.

THE FUTURE: SAFE GLYCEMIC CONTROL

Obviously, glucose control is not as easy as it seems. Efforts must thus be conducted to facilitate glucose control. Figure 1 gives an overview over the factors that interfere in glucose control. Traditionally, caregivers measure blood glucose and adapt insulin according to an algorithm, for example, a sliding scale. Several algorithms, partly computerized, help to calculate an appropriate insulin dose and recommend a safe control interval (e.g. [35]). However, in real life, algorithms might not be properly followed and many blood glucose-influencing factors, like medication or nutrition, are left out of focus. It is tempting to speculate that poor protocol adherence explains a big part of the conflicting data [23]. (Semi-)automated systems could probably account for influencing factors and help facilitate glucose control (closed-loop control).

Among others, factors that influence blood glucose are glucose intake and insulin dose, both relatively easy to include into an automated system, whereas reflux and vomiting confound any calculation. Almost uncontrollable is the endogenous glucose production and the insulin sensitivity during the course of surgery or illness that makes the patient’s reaction to interventions very individual. The same is true for medical interventions (e.g. glucocorticoids and catecholamines). So, we need algorithms that can detect the individual insulin reactivity. Such reinforced learning algorithms are at least partly commercially available; unfortunately, the costs are not negligible.
Notably, hypoglycemic episodes occur even when glycemic target is not very tight, mostly because of too long intervals between two glucose measures. So ‘online’ measuring devices combined with a reinforced learning algorithm would be the solution. Industry works with high pressure to validate subcutaneous sensors in the critically ill; the published results look promising [36]. First reports from Japan using a control system with glucose measurements via an arterial line in the perioperative setting revealed relevant errors [37]; however, the technique appears to have improved recently [38,39]. By using an online-measuring device combined with proportional integral derivative control, glucose control on a pediatric ICU was improved and the rate of hypoglycemia was reduced [40]\(^\text{1}\). Because of frequent false alarms, the workload for caregivers was not reduced.

So, these are very optimistic results that are worth being confirmed in large outcome trials. Unfortunately, the solutions will probably be quite costly and in times of limited resources we are skeptical whether the devices will survive in practice. The way toward an ‘artificial pancreas’ is stony and needs further research.

CONCLUSION
As dysregulations of glucose homeostasis are associated with adverse outcome in perioperative medicine, controlling the dysregulations and related medical afflictions is worth an effort. Advancing technologies will facilitate safe perioperative glucose control, meanwhile titrating glycemia to a moderate goal can be recommended.

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A very recent meta-analysis of high-quality trials investigating perioperative glycemic control.


