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**ABSTRACT:** Hyperglycemia has long been recognized to have detrimental effects on postoperative outcomes in patients undergoing surgery. The manifestations of uncontrolled diabetes are manifold and can include risk of hyperglycemic crises, postoperative infection, poor wound healing, and increased mortality. There is substantial literature supporting the role of diligent glucose control in the prevention of adverse surgical outcomes, but considerable debate remains as to the optimal glucose targets. Hence, most organizations advocate the avoidance of hypoglycemia while striving for adequate glucose control in the perioperative period. These objectives can be accomplished with careful preoperative evaluation, clear patient instructions the day of surgery, frequent blood glucose monitoring during the perioperative period, and use of effective strategies for insulin initiation and titration. This article highlights the major issues concerning patients with diabetes undergoing surgery and reviews the management recommendations put forth by general consensus guidelines and expert opinion.

**KEYWORDS:** Perioperative, diabetes

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## Introduction

Patients with diabetes requiring surgery can present a challenge to the managing clinician. With the prevalence of diabetes in the United States reaching approximately 8% of the population,<sup>1</sup> it is now commonplace to encounter patients with diabetes presenting for surgery. Suboptimal diabetes control has been associated with adverse perioperative outcomes such as metabolic derangements, infection, poor wound healing, and increased mortality.<sup>2–6</sup> This review article draws from several existing medical and anesthesia guidelines to provide a concise summary of diabetes treatment strategies aimed at reducing perioperative risk.

## Glucose Metabolism

Glucose metabolism is primarily orchestrated by the interplay of insulin and the counter-regulatory hormones glucagon, epinephrine, cortisol, and growth hormone. The major effect of insulin is to stimulate glucose uptake in muscle, adipose, and other tissues. Insulin also inhibits gluconeogenesis and enhances glycogen production in the liver.

Diabetes represents a group of disorders in which glucose metabolism is dysregulated and hyperglycemia dominates. Type 1 diabetes is characterized by the autoimmune destruction of pancreatic beta cells leading to absolute deficiency of insulin: patients with this condition are completely insulin dependent, and the omission of insulin can lead to metabolic decompensation and death. Type 2 diabetes evolves from progressive insulin resistance and a relative deficit in insulin secretion. Patients with type 2 diabetes are typically advised a multifaceted regimen of diet, weight reduction, exercise, and oral and/or injectable medications as appropriate.

## Effects of Surgery and Anesthesia on Glucose Metabolism

Stress related to surgery and anesthesia triggers the release of neuroendocrine hormones such as catecholamines and cortisol that can result in insulin resistance and hyperglycemia. Volume depletion, abrupt discontinuation of outpatient diabetes medications, and administration of steroids are frequent factors that also contribute to hyperglycemia.<sup>7</sup> Even patients without prior history of diabetes can develop hyperglycemia in the setting of acute stress<sup>8</sup>. When observed, an elevated hemoglobin A<sub>1c</sub> can distinguish a previously unrecognized diabetes or prediabetes condition from “de novo” stress hyperglycemia.

## Risk of Hyperglycemic Crises

In the setting of intercurrent stress, patients with type 1 diabetes are at risk for diabetic ketoacidosis (DKA) even in the absence of severe hyperglycemia if adequate insulin is not administered. Although the overall incidence of hyperglycemic crises in the perioperative setting is not widely reported, a recent case series from the Cleveland Clinic cited the incidence of early postoperative DKA in patients with type 1 diabetes undergoing bariatric surgery as high as 25%.<sup>2</sup> The incidence of DKA in patients with type 2 diabetes who underwent the same surgery was far less common at 0.2%.<sup>2</sup> Although DKA in patients with type 2 diabetes is unusual, hyperosmolar nonketotic states can occur with profound elevation of blood glucose and significant dehydration.<sup>9</sup> Patients with type 2 diabetes who are unable to produce a satisfactory compensatory response to surgery-induced stress may be at risk for this complication.



## Complications of Perioperative Hyperglycemia

Hyperglycemia interrupts the stages of normal wound healing by impeding blood flow and tissue oxygenation, causing endothelial dysfunction and prolonging an inflammatory state.<sup>10</sup> Hyperglycemia also impairs neutrophil phagocytic function,<sup>11</sup> which limits bacterial clearance and increases the risk of infection. Many studies have reported the risk of hyperglycemia on postoperative outcomes, although there exists considerable variation among the patient characteristics and study designs.

In observational studies of patients with diabetes undergoing cardiothoracic surgery, perioperative hyperglycemia has been associated with adverse outcomes such as increased risk of sternal wound infections and other infectious complications.<sup>3</sup> Chronic poor glycemic control as indicated by preoperative hemoglobin A<sub>1c</sub> greater than 8.6% was associated with an increase in mortality, myocardial infarction, and sternal wound infection in patients undergoing cardiac bypass grafting.<sup>4</sup> Several studies of post-coronary artery bypass graft (CABG) patients have observed an increased mortality risk in the groups with the highest blood glucose level during surgery.<sup>5,6</sup> Regarding noncardiac surgery, perioperative hyperglycemia has been associated with increased risk of infections, length of stay, and acute renal failure.<sup>12</sup> Chronic suboptimal control as implied by a preoperative hemoglobin A<sub>1c</sub> level higher than 8% was also associated with increased length of stay in noncardiac patients.<sup>13</sup>

## Perioperative Glycemic Targets

Despite the abundance of literature reporting an increased rate of complications and mortality in surgical patients with hyperglycemia, there have been relatively fewer randomized controlled studies testing the role of glucose management in the perioperative setting. An observational study of cardiothoracic intensive care unit (ICU) patients with diabetes reported a decrease in the incidence of sternal wound infection using an insulin infusion protocol compared with conventional sliding scale insulin.<sup>14</sup> Cardiac morbidity and mortality also improved in a randomized study of tight glycemic control compared with standard therapy in post-CABG patients.<sup>15</sup> A rigorous randomized prospective study of surgical ICU patients by van den Berghe et al. demonstrated significant morbidity and mortality benefit with intensive insulin therapy to maintain blood glucose target 80 to 110 mg/dL compared with conventional treatment.<sup>16</sup> However, subsequent studies were not able to replicate these findings. Moreover, a follow-up study to the initial van den Berghe trial generated significant concern about the risks of stringent glycemic control in critically ill patients. Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation (NICE-SUGAR) was a multinational, multicenter study of 6104 medical and surgical ICU patients which demonstrated an increase in 90-day mortality in the intensively treated insulin group compared with the conventionally treated group and a higher incidence of

severe hypoglycemia.<sup>17</sup> Two recent meta-analyses found no significant difference in mortality between intensive insulin therapy and control groups, but a 5 to 6 times greater risk of hypoglycemia with intensive therapy.<sup>18,19</sup> Regarding intraoperative glucose control, a randomized control study of 399 patients undergoing cardiac surgery similarly did not observe any difference in patient outcomes with intensive treatment to an intraoperative target glucose 80 to 100 mg/dL compared with conventional therapy.<sup>20</sup>

Based on the inconsistent data derived from these studies, general consensus guidelines endorse the importance of glycemic control in surgical patients but caution that glucose targets be more conservative than those historically attained with intensive insulin therapy in the critically ill. As such, the American Diabetes Association (ADA) Standards of Medical Care recommends a perioperative glucose target of 80 to 180 mg/dL.<sup>21</sup> The Australian Diabetes Society advises to keep blood glucose levels between 90 and 180 mg/dL (5-10 mmol/L) in their perioperative guidelines.<sup>22</sup> More conservative glucose targets of 106 to 180 mg/dL (6-10 mmol/L) are cited by the Association of Anaesthetists of Great Britain and Ireland<sup>23</sup> in keeping with National Health Service (NHS) perioperative diabetes guidelines.<sup>24</sup> The NHS permits a wider range of acceptable blood glucose 72 to 216 mg/dL (4-12 mmol/L) perioperatively while still aiming for the target levels 106 to 180 mg/dL (6-10 mmol/L) stated above.<sup>24</sup>

## Preoperative Assessment

Clearly then, it is imperative for physicians and multidisciplinary care teams to adopt a comprehensive strategy to optimize patients with diabetes undergoing surgery. Preoperative evaluation for surgical procedures in patients with diabetes should include assessment of glycemic control and any diabetes-associated complications. Comprehensive cardiac evaluation includes resting electrocardiography for intermediate and high-risk surgeries, and if cardiac disease is suspected, stress test or coronary artery angiography as indicated.<sup>25</sup> Baseline laboratory data may include measurement of serum creatinine level to assess for chronic kidney disease, hemoglobin A<sub>1c</sub> if not previously available within the past 3 months, and blood glucose level. Although existing guidelines do not endorse global preoperative A<sub>1c</sub> testing in patients without prior history of diabetes, some experts consider it reasonable to screen those with risk factors for undiagnosed diabetes.<sup>26</sup>

In addition to baseline laboratory investigation, assessment of glycemic control includes a comprehensive history detailing the patient's type and duration of diabetes, medication regimen, home blood glucose measurements, occurrence and frequency of hypoglycemia, and presence of any other diabetes-related symptoms. Ideally glycemic control should be stabilized on an outpatient basis prior to elective surgery. For patients managed with insulin, frequent home glucose monitoring is recommended and insulin doses adjusted in consultation with their outpatient provider or endocrinologist.

### *Patients treated with oral medications and/or noninsulin injectables*

Patients treated with oral medications and/or noninsulin injectable medications (ie, glucagon-like peptide-1 [GLP-1] agonists) are typically instructed to continue their home regimen until the morning of surgery. The morning of surgery, most organizations advise to discontinue oral and noninsulin injectable medications in keeping with current practice guidelines for inpatient diabetes management.<sup>21,27</sup> Sulfonylureas and meglitinides stimulate endogenous insulin secretion independent of glucose levels and have the potential to cause hypoglycemia in the fasting state. Metformin is avoided as perioperative perturbations in renal perfusion or exposure to iodinated contrast may increase the risk of renal insufficiency and lactic acidosis. Thiazolidinediones are avoided due to potential fluid retention, peripheral edema, and congestive heart failure. Dipeptidyl peptidase-4 (DPP-4) inhibitors are generally discontinued before surgery; however, there has been recent interest in using DPP-4 inhibitors in the hospitalized setting due to good tolerability and low risk of hypoglycemia. A recent study establishing the safety and efficacy of sitagliptin alone or sitagliptin in combination with basal insulin in hospitalized medical and surgical patients<sup>28</sup> may expand use of this class in the perioperative setting. To date, only the Association of Anaesthetists of Great Britain and Ireland endorses continued use of DPP-4 inhibitors the day of surgery<sup>23</sup> in view of low risk of hypoglycemia. GLP-1 agonists cause delayed gastric emptying and gastrointestinal side effects that may be exacerbated in the postoperative state and thus are not ideal agents. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors belong to a new class of agents that may increase the risk of volume depletion and DKA and should be withheld the day of surgery.

### *Patients treated with insulin*

Outpatient insulin regimens frequently include a long-acting basal insulin preparation (glargine, detemir, degludec) dosed once or twice daily that provide background insulin coverage in the fasting state. Some patients require more intensive basal/bolus insulin regimens that incorporate both basal and rapid-acting insulin (aspart, lispro, glulisine) or short-acting insulin (regular) injected prior to meals. Basal/bolus insulin regimens are considered to be the most physiologic, as they best mimic normal pancreatic secretory function.

Patients with type 1 diabetes or insulin-treated type 2 diabetes should be instructed to continue their usual meal plan and insulin regimen until the night before surgery. If they are NPO after midnight, the usual dose of long-acting insulin can be maintained; however, if the patient reports a history of nocturnal or fasting hypoglycemia, the basal dose should be reduced by 20% to 30%.<sup>29,30</sup> For type 1 patients who are well-controlled, a mild reduction in the basal insulin dose by 10% to 20% is suggested.<sup>27</sup> Remember that basal insulin is mandatory

to prevent ketoacidosis in patients with type 1 diabetes and should not be withheld even in the fasting state. Once fasting is initiated, prandial boluses should be omitted. Patients should be instructed to perform frequent self-monitoring while NPO and educated on how to treat hypoglycemia if it occurs.

Patients using premixed insulin combinations (70/30, 75/25, 50/50) present more of a challenge in the preoperative period. Premixed insulin formulations consist of intermediate-acting insulin NPH (neutral protamine Hagedorn) combined with rapid or short-acting insulin, and are typically injected twice daily before breakfast and before dinner. These patients should take their usual evening dose the night prior but omit their morning dose the day of surgery. As NPH has only an intermediate duration of action (10-18 hours), one should administer one-half to two-thirds of the NPH component of the patient's usual morning dose during or immediately after the procedure to provide adequate basal coverage.<sup>29,30</sup> Another potential strategy offered by the Cleveland Clinic is to discontinue the patient's premixed insulin and change to a regimen involving long-acting insulin (ie glargine) to be administered the night before surgery.<sup>31</sup> If neither of these options is feasible, one can instruct the patient to halve their usual morning dose of premixed insulin and plan to administer dextrose-containing intravenous fluids and perform frequent blood glucose monitoring perioperatively.<sup>31</sup>

Increasingly, patients with both type 1 and type 2 diabetes are using continuous subcutaneous insulin infusion (CSII) pump therapy as their primary form of treatment. The basal rate on an insulin pump represents the amount of rapid-acting insulin being delivered subcutaneously at a fixed dose per hour, which serves to cover the patient's background insulin needs. Usually the patient will have several different basal rates programmed over a 24-hour period. During mealtimes the patient administers a bolus dose of insulin via their pump based on the calculated amount of carbohydrate to be consumed. It is generally acceptable for patients to continue on their pump for short (<2 hours) or same-day procedures by maintaining their outpatient basal rate.<sup>21,22,29,30,32,33</sup> Data are limited on use of CSII in the perioperative period, but a review of 57 cases confirmed safety of insulin pump use for same-day procedures.<sup>34</sup>

Although expert guidelines endorse the use of insulin pumps in the hospitalized setting, one major caveat is that the patient must demonstrate sufficient mental and physical capacity to operate the pump.<sup>35</sup> Also essential are the input of the patient's outpatient managing physician, the involvement of hospital staff with expertise in pump management, and/or consultation with external specialists.<sup>35</sup> As data and consensus guidelines are limited, the decision of whether to continue insulin pump management during surgery is usually made on an individual basis. Alternatively and especially for longer surgical procedures, patients managed on insulin pumps should be converted to an intravenous insulin infusion on admission to the preoperative unit.



## Perioperative Glucose Monitoring and Insulin Strategies

On the day of surgery, blood sugars should be checked before surgery and subsequently every 1 to 2 hours intraoperatively and in the acute postoperative period.<sup>23,24,29,30</sup> Point-of-care (POC) glucometers are appropriate for blood glucose measurement. If the patient is hemodynamically or metabolically unstable, central laboratory assessment should be performed as POC testing is not as reliable in this scenario.

Most of the patients with diabetes can be managed with subcutaneous insulin perioperatively.<sup>22–24,27,29,30</sup> Hyperglycemia can be corrected with short-acting or rapid-acting insulin based on the patient's insulin sensitivity: regular insulin is dosed every 6 hours or rapid-acting insulin (aspart, lispro, or glulisine) insulin every 4 hours.<sup>27</sup>

Critically ill patients, insulin-treated patients undergoing longer and complicated surgeries or patients with labile type 1 diabetes should be managed with an intravenous insulin infusion.<sup>22,23,27,29</sup> Insulin infusion therapy requires frequent glucose monitoring (at least hourly) and adjustment of the infusion rate according to a protocol-driven algorithm to maintain glucose targets.

## Transition to Ward and Home

When the patient is ready to resume intake of solid food, transition to a subcutaneous basal/bolus insulin regimen should be implemented. In patients switching from an insulin infusion to subcutaneous insulin, the infusion should overlap for at least 1 to 2 hours after administration of the first dose of subcutaneous insulin to prevent a gap in insulin coverage.<sup>27</sup> Patients previously treated with insulin can typically resume their home regimen provided they have good oral intake; otherwise doses should be empirically reduced and titrated accordingly. Remember that patients with type 1 diabetes always require basal insulin as well as prandial insulin with food consumption to prevent DKA.

In patients not previously treated with insulin, a subcutaneous regimen totaling 0.2 to 0.5 units/kg of body weight depending on the patient's insulin sensitivity is calculated.<sup>27</sup> The calculated total daily insulin dose is then divided into a 50% basal component (long-acting insulin) and 50% prandial boluses (rapid-acting insulin) split between breakfast, lunch, and dinner. Scheduled subcutaneous insulin typically includes a correction or supplemental sliding scale administered with mealtime insulin to correct any unexpected glucose excursions. Prolonged therapy with sliding scale insulin should not be used as the sole treatment in patients with insulin-treated diabetes, as this regimen only passively reacts to hyperglycemia but does not abrogate its development.

Some postoperative patients may require enteral or parenteral nutrition. For recommendations on how to navigate these scenarios, it is best to reference the ADA Standards of Medical Care<sup>21</sup> or the Endocrine Society Clinical Practice Guidelines

on inpatient glycemic control in noncritical patients.<sup>27</sup> It is important to monitor blood glucose levels even in previously normoglycemic patients as enteral/parenteral is known to cause hyperglycemia.<sup>27</sup> For enteral feeds, it is recommended to administer basal insulin and use a correctional sliding scale.<sup>21</sup> For parenteral feeds, insulin should be added to the total parenteral nutrition bag and additional correctional insulin administered as needed.<sup>21</sup> If feeds are abruptly discontinued, remember to start a dextrose-containing infusion to avoid potential risk of hypoglycemia.<sup>21</sup>

Hypoglycemia may be detected on blood glucose testing <70 mg/dL or suspected based on patient adrenergic or neuroglycopenic symptoms. Either occurrence should prompt a nursing-driven protocol to administer oral glucose or intravenous dextrose if the patient cannot swallow safely. After resolution of hypoglycemia is verified on repeat testing, vigilant monitoring should continue and the insulin regimen adjusted if indicated.

For patients previously treated with oral and noninsulin injectable agents, their home regimen can be reinstated when medically stable, eating regularly and there are no further plans for procedures or imaging studies. Recall that patients who were exposed to iodinated contrast should not resume metformin for 2 to 3 days due to the potential risk of contrast-induced renal dysfunction. On discharge to home, patients should be provided with diabetes education, specific instructions on their medications and insulin doses, and follow-up with their outpatient providers.

## Conclusions

In conclusion, perioperative diabetes management requires communication and coordination amongst patients, outpatient providers, and surgical and anesthesia staff. Although many areas including the optimal glucose treatment goals require further investigation, it is undeniable that perioperative complications can be reduced in patients with diabetes. Of the utmost importance are diligent preoperative assessment, frequent intraoperative and postoperative monitoring of glucose levels, and the implementation of safe and effective insulin strategies to optimize surgical outcomes.

## Author Contributions

VL & KRT - data gathering, writing and editing.

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