

Perioperative Glycemic Management for Patients with and without Diabetes: A Review for Internists

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ABSTRACT

People with diabetes are at an increased risk for worse postoperative outcomes, compared to people without diabetes. Notably, up to one in 10 people who undergo surgery have unrecognized diabetes and an additional 10% may have postoperative hyperglycemia without meeting the criteria for a diagnosis of diabetes. Management of postoperative hyperglycemia has been demonstrated to reduce the incidence of poor outcomes, but evidence demonstrates that postoperative hyperglycemia remains a quality gap for surgical patients. In this review, we will outline the evidence for preoperative screening for postoperative hyperglycemic risk, review the evidence for perioperative glycemic management, and examine the barriers to these best practices.

RÉSUMÉ

Les personnes atteintes de diabète courent un risque accru de voir leurs résultats postopératoires moins bons que ceux des personnes non atteintes de diabète. En particulier, près d'une personne sur dix qui subit une intervention chirurgicale présente un diabète non diagnostiqué et dix pour cent supplémentaires peuvent présenter une hyperglycémie postopératoire sans pour autant répondre aux critères de diagnostic du diabète. Il a été démontré que le traitement de l'hyperglycémie postopératoire réduit l'incidence des mauvais résultats, mais les données probantes montrent que l'hyperglycémie postopératoire demeure une lacune chez les patients opérés. Dans cette revue, nous présentons les données probantes relatives au dépistage préopératoire du risque d'hyperglycémie postopératoire, nous passons en revue les données probantes relatives à la gestion de la glycémie périopératoire et nous examinons les obstacles à ces meilleures pratiques.

Postoperative Hyperglycemia Is a Modifiable Risk Factor for Worse Postoperative Outcomes

Diabetes affects 20–30% of the surgical patients.¹ People with diabetes who undergo surgery have worse outcomes than people without diabetes, including increased postoperative infection risk,^{2,3} 30-day readmission rates,⁴ length of stay,⁵ and mortality.^{6,7} Recent evidence suggests that these poor

outcomes are more strongly associated with intraoperative and postoperative hyperglycemia rather than a preoperative diagnosis of diabetes.^{6,8} This is especially important, as unrecognized diabetes may account for an additional 4–10% of surgical patients^{8,9} and approximately 10% of people without diabetes will have postoperative hyperglycemia.^{8,10–14} These patients may be less likely to have postoperative hyperglycemia recognized

and appropriately treated, and subsequently may suffer more adverse outcomes than people with recognized diabetes.⁸ The association between intraoperative hyperglycemia and poor patient outcomes is less clear^{15,16}; however, the management of intraoperative hyperglycemia is the responsibility of the anesthesiologist and, therefore, pre- and postoperative diabetes management will be the focus of this review.

Evidence-based glucose management strategies have demonstrated improved glycemic control, reduced length of stay, and reduced incidence of hypoglycemia.^{17,18} Observational studies have found that maintaining blood glucose in-target is associated with lower 30-day readmission rates and shorter length of stay in medical and surgical patients.¹⁹ In gynecologic oncology patients, pre- and post-intervention studies have shown that perioperative glycemic management pathways that are multidisciplinary, comprehensive, and adhere to best practices for glycemic management reduce the incidence of surgical site infections.^{20,21} The RABBIT-2 study was a landmark randomized controlled trial that found that basal bolus insulin therapy (BBIT) to maintain in-target glucose for postoperative patients significantly reduced postoperative complications, compared to subcutaneous sliding-scale insulin regimens.²²

Recommendations for Perioperative Glycemic Management for Patients with and without Diabetes

Preoperative measurement of hemoglobin A1C

There is a considerable variation in perioperative glycemic management recommendations in major society guidelines

(Table 1). Unlike guidelines from Australia, Great Britain, and Ireland that recommend delaying surgery for patients with elevated hemoglobin A1C, Diabetes Canada, the American Society of Anesthesiologists, and the American Diabetes Association do not make recommendations on preoperative hemoglobin A1C measurement or targets for elective surgeries. This is supported by the current evidence that intraoperative and immediate postoperative hyperglycemia is more strongly associated with poor outcomes than preoperative glycemic control.^{6,8,29} However, preoperative hemoglobin A1C measurement can identify patients with unrecognized diabetes and patients without diabetes at risk of postoperative hyperglycemia.^{8,9,29} In addition, preoperative hemoglobin A1C measurement can help guide postoperative glycemic management; patients with elevated hemoglobin A1C will be more likely to require and benefit from insulin than patients with in-target hemoglobin A1C.⁸ As such, it is reasonable to measure hemoglobin A1C in all people with diabetes and those who are at-risk of diabetes within 3 months of a scheduled surgery (Box 1).

Preoperative noninsulin medication management

Similarly, major society guidelines provide differing recommendations for perioperative management of noninsulin medications (Table 2). Diabetes Canada does not make recommendations for holding, continuing, or dose reducing medications for diabetes in the perioperative period. In contrast, guidelines from the Association of Anaesthetists of Great Britain and Ireland, and the American Society of Anesthesiologists make recommendations for each class of diabetes medications.

Table 1. Comparison of major society guideline recommendations for perioperative glycemic management for patients with and without diabetes

Guideline (year)	Preoperative glycemic target	Preoperative glycemic management	Postoperative glycemic target	Postoperative glycemic management
Diabetes Canada (2018) ²³	No recommendations	No recommendations	5.0–10.0 mmol/L	BBIT preferred
American Diabetes Association (2019) ²⁴	No recommendations	Hold metformin on the day of surgery	4.4–10.0 mmol/L	BBIT preferred
American Society of Anesthesiologists (2017) ²⁵	No recommendations	Medication-specific recommendations	<10.0 mmol/L	BBIT preferred
Association of Anaesthetists of Great Britain and Ireland (2015) ²⁶	Delay elective surgery for patients with an HbA1c \geq 8.5%	Medication-specific recommendations	6.0–10.0 mmol/L	Restart noninsulin agents when eating well
Royal Australian College of General Practitioners (2016 & 2012) ^{27,28}	Consider delaying elective surgery for patients with an HbA1c > 9.0%	Hold noninsulin medications on the day of surgery	5.0–10.0 mmol/L	Insulin infusion until eating well, followed by BBIT

BBIT = basal bolus insulin therapy; HbA1C = glycated hemoglobin A1C.

Box 1. Risk factors for diabetes that may prompt preoperative hemoglobin A1c testing.³⁰

- Diagnosis of diabetes
- History of prediabetes
 - Hemoglobin A1C 6.0–6.4%
 - Impaired glucose tolerance
 - Impaired fasting glucose
- Age \geq 40 years
- First-degree relative with type 2 diabetes
- Personal history of gestational diabetes mellitus or delivery of a macrosomic infant
- Body mass index $>$ 25 kg/m²
- Prescription for glucocorticoids, statins, atypical antipsychotics, highly active antiretroviral therapy, and anti-rejection medications
- End organ damage associated with diabetes (retinopathy, neuropathy, nephropathy, cardiovascular disease)
- History of polycystic ovarian disease

Adapted from "Risk factors for type 2 diabetes" in the Diabetes Canada guidelines.³⁰

Alternatively, the Australian Diabetes and American Diabetes Associations suggest holding all noninsulin agents only on the morning of surgery. Recent concerns have arisen about the potential for diabetic ketoacidosis during the fasting period in patients taking sodium-glucose co-transporter 2 (SGLT-2) inhibitors^{31,32}; for this reason, the Canadian Anesthesiologists' Society has recommended holding SGLT-2 inhibitors 3 days prior to scheduled surgery.³³ Diabetes Canada does not make recommendations on how to manage noninsulin diabetes medications in the postoperative period, while other major society guidelines suggest restarting medications when the patient is eating or drinking well.

Preoperative metformin management

Perioperative management of metformin deserves special mention. Guidelines from Great Britain and Ireland, America, and Australia recommend continuing metformin throughout the perioperative period; however, in North America, it is common

Table 2. Recommendations for perioperative diabetes medication management based on contemporary evidence

Medication class	Day before surgery	Day of surgery	Restart
Insulins			
Ultra-long-acting insulin (<i>degludec</i>)	80% of usual dose for 3 days before surgery	80% of usual dose ²⁶	Continue throughout, even if NPO ²⁶
Long-acting insulin (<i>glargine, levemir</i>)	80% of usual dose ^{25,26}	80% of usual dose ^{23–26}	Continue throughout, even if NPO ^{25,26}
Intermediate-acting insulin (<i>NPH</i>)	HS dose—80% of usual ^{25,26}	50% of usual dose ^{24–26}	Continue throughout, even if NPO ^{25,26}
Mealtime doses of short- or rapid-acting insulin	Continue at usual dose ²⁶	Hold when NPO ^{25,26}	Hold when NPO ^{25,26}
Correction doses of short- or rapid-acting insulin	Continue at usual dose ²⁶	Continue at usual dose ²⁶	Continue throughout, even if NPO ²⁶
Noninsulin agents			
Biguanides (<i>metformin</i>)	Continue at usual dose ^{25,26*}	Continue at usual dose ^{25,26}	Continue throughout unless eGFR < 30 mL/min/1.73m ²
SGLT-2 inhibitors (<i>-gliflozins</i>)	Hold 3 days before surgery ³³	Hold ^{24,25,33}	Restart only when eating and drinking well ³³
DPP4 inhibitors (<i>-gliptins</i>)	Continue at usual dose ^{25,26}	Continue at usual dose ^{25,26}	Continue throughout, even if NPO ²⁶
Meglitinides (<i>repaglinide</i>)	Continue at usual dose ^{25,26}	Hold ^{25,26}	Restart only when eating and drinking well ²⁶
Sulfonylureas (<i>gliclazide, glyburide</i>)	Continue at usual dose ^{25,26}	Hold ^{25,26}	Restart only when eating and drinking well ²⁶
GLP-1 analogues (<i>-tides</i>)	Continue at usual dose ²⁶	Continue at usual dose ²⁶	Continue throughout, even if NPO ²⁶

NPO = *nil per os*; NPH = neutral protamine Hagedorn; HS = evening dose; eGFR = estimated glomerular filtration rate (in mL/min/1.73m²).

*Consider holding on day of surgery for patients at risk of developing eGFR < 30 mL/min/1.73.^{25,26}

practice to hold metformin for patients on the day of surgery due to concerns about lactic acidosis in the setting of acute kidney injury (AKI).³⁴ Metformin does not cause hypoglycemia or AKI, and the risk of lactic acidosis is exceptionally low.³⁵ In contrast, withdrawal of metformin in the perioperative period may lead to hyperglycemia. In the absence of contraindications, it would seem reasonable to continue metformin during the perioperative period, including on the day of surgery, aligning with guideline recommendations internationally.

Preoperative insulin management

Recommendations for perioperative management of insulin are variable. While some experts recommend reducing the dose of long-acting insulin formulations by 50% on the day of or the day before surgery,³⁴ Great Britain and Ireland, American, and Australian guidelines recommend a dose reduction by only 20–25%. Diabetes Canada does not make specific recommendations. Basal insulins are intended to maintain glycemic targets during periods of fasting rather than for meals, and so theoretically could be maintained at usual dose. Patients may be at higher risk of hypoglycemia if their basal dose is being used to treat not only fasting hyperglycemia but also to treat mealtime glucose elevations. These patients may be on basal insulin alone or may be on basal and bolus insulin with a basal dose that is 60% or more of their total daily dose. In these cases, patients may require a greater basal dose reduction, particularly if fasting morning blood glucose is routinely 4.0–7.0 mmol/L. Conversely, patients treated with basal insulin with fasting hyperglycemia may not require a dose reduction before surgery. Dose recommendations should be individualized to the patient context.

There is a paucity of evidence on how to manage ultra-long acting insulins (e.g., degludec or glargine 300 U/mL insulin) during the perioperative period. Based on the lack of evidence, and the up to 25-h half-life and duration of action of 42 h of ultra-long acting insulins, it is reasonable to reduce the dose of these insulins by 20–25% for 3 days before scheduled procedures.

Enhanced Recovery after Surgery in patients with diabetes

Carbohydrate-rich drinks have been implemented in the preoperative fasting period to reduce postoperative catabolism.³⁶ Currently, Enhanced Recovery after Surgery (ERAS) guidelines variably address whether patients with diabetes should undergo preoperative carbohydrate loading.^{37–40} There is inconsistent evidence of benefit for preoperative carbohydrate loading; while a few systematic reviews have demonstrated reduced length of stay⁴¹ and improved patient well-being,⁴² most identify no consistent benefits.³⁶ Importantly, many studies examining preoperative carbohydrate loading excluded people with diabetes. Studies that included people with diabetes had small

sample sizes and may be underpowered to identify adverse events.⁴³ Given clear evidence of harm from intraoperative and postoperative hyperglycemia, and a lack of consistent evidence supporting preoperative carbohydrate loading for patients with diabetes, the harm of such a practice may outweigh the benefits. Further work will be necessary to clarify whether preoperative carbohydrate loading with appropriate glycemic management may confer perioperative benefit(s).

Perioperative glycemic targets for patients with and without diabetes

Most major society guidelines recommend maintaining postoperative glucose less than 10.0 mmol/L, and recommend the use of BBIT to achieve this target.²³ The evidence supporting this target is conflicting, primarily observational, and is often extrapolated from medical inpatients. While this range is associated with a reduction in infections,⁴⁴ fewer complications,⁴⁵ lower mortality, and a shorter length of stay⁴⁶ in some publications, many studies demonstrate no benefit or increased harm when maintaining patients less than 10.0 mmol/L.⁴⁴ These targets apply to all patients, regardless of whether or not they have diabetes.

Postoperative glycemic management

Diabetes Canada recommends that patients with and without diabetes who are above the glycemic target postoperatively receive insulin in a BBIT regimen to achieve targets, even if hyperglycemia is expected to be transient.²³ This recommendation is based on the RABBIT-2 trial, a randomized trial which found improved glycemic control and reduced surgical complications in patients who received BBIT compared to subcutaneous sliding-scale insulin.²² Patients with postoperative hyperglycemia who do not have diabetes may need a starting total daily dose of insulin that is less than patients with diabetes, especially for patients with diabetes with hyperglycemia at baseline. Expert consultation with internal medicine or endocrinology services may be required. Patients whose home medications for diabetes are not continued in the perioperative period should restart these medications when they are eating and drinking well, with special consideration for medications that may cause hypoglycemia or are contraindicated in kidney injury (Table 2).

Implementation of best practices for perioperative glycemic management

Implementation of these recommendations has lagged behind supporting evidence. A chart audit study of 119 postoperative patients with known diabetes identified that a quarter of them had an average blood glucose greater than 10.0 mmol/L, and 80% of patients were managed with sliding-scale insulin rather than BBIT.⁴⁷ In our center, an audit of the electronic health record of

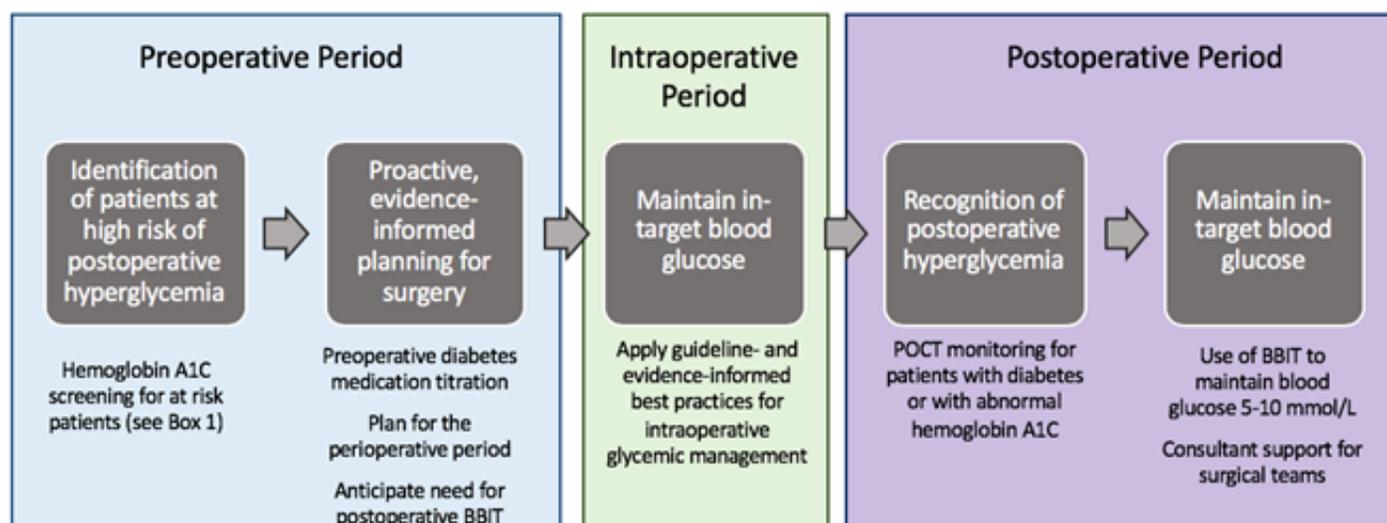


Figure 1. Systems components of a perioperative glycemic management pathway. BBIT = basal bolus insulin therapy; POCT = point of care testing.

197 patients with diabetes demonstrated that 27% had moderate (blood glucose ≥ 14.0 mmol/L) or severe (blood glucose ≥ 18.0 mmol/L) hyperglycemia after surgery (unpublished data). Notably, patients without diabetes who have postoperative hyperglycemia are less likely to receive insulin than patients with diabetes, despite having similar risk of postoperative complications associated with hyperglycemia.⁸

Difficulties in implementing best practices for perioperative glycemic management are multifactorial.⁴⁸ The perioperative period is complex, and implementing recommendations requires coordination between outpatient perioperative physicians and inpatient surgical teams. Even when guideline-based recommendations are made in preoperative assessment, these recommendations may not be followed for up to 13% of the surgical patients.⁴⁹ Previous work in Alberta has identified that physicians find the use of BBIT to be challenging when postoperative patients are not eating well.⁴⁸ Healthcare providers were reluctant to use insulin due to concerns about hypoglycemia.⁴⁸ Clinical inertia by healthcare professionals when managing hyperglycemia may contribute to a lack of intensification of medical therapy in patients with postoperative hyperglycemia.⁴⁷ Furthermore, learning to use BBIT order sets requires training.⁴⁸ Lastly, it is challenging for internists and surgeons to keep up with the rapidly expanding new diabetes medications available and their potential adverse effects.

These challenges speak to the need to develop shared care models of perioperative glycemic management. Involvement of surgical teams, patients, internists, diabetes specialists, endocrinologists, and allied healthcare team members is required to co-develop institution-specific pathways to: (1) identify patients at high-risk

of postoperative hyperglycemia, (2) proactively develop plans for management, (3) adequately monitor blood glucose and recognize hyperglycemia, and (4) apply evidence-informed interventions to maintain glucose targets (Figure 1). Other centers, including the Ottawa Hospital, have seen successful in reducing postoperative complications after implementing similar pathways.^{20,21} Careful attention should be paid to well-described barriers for the implementation of best practices for in-hospital glycemic management, including fear of hypoglycemia, lack of understanding of the rationale for maintaining appropriate glucose targets, and difficulties in managing patients with poor oral intake.⁴⁸ Fortunately, knowledge translation toolkits have been developed to successfully assist teams in overcoming these specific barriers.^{17,50,51}

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