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Perioperative glycemic control: What is the evidence?

ALICE Y.Y. CHENG, MD

Surgery in the patient with diabetes mellitus is relatively common because diabetes predisposes to certain medical conditions that require surgical intervention. The frequency of these interventions will continue to increase as the prevalence of diabetes rises. A number of challenges are faced by the team managing a patient with diabetes in the perioperative period. These include the wide variety of surgical procedures ranging from minor same-day surgeries under local anaesthesia to complicated major cardiothoracic procedures. Control in the patient with diabetes can also vary from one patient to another, with one patient having excellent glycemic control on diet alone, while another may have variable glycemic control on multiple daily injections of insulin. The team must be cognizant of the many patient and surgical factors that play a role in perioperative glycemic control. In addition, the specific target glycemic control needs to be determined. Although it is clear that good glycemic control is beneficial in the period immediately following an acute myocardial infarction,[1] appropriate glycemic control in the perioperative period is less well-defined. In this issue of *Endocrinology Rounds*, the evidence for perioperative glycemic control will be reviewed and recommendations will be provided.

Metabolic effects of surgery and general anaesthesia

The trauma of surgery induces a stress response with multiple hormonal effects including a rise in counter-regulatory hormones, such as catecholamines, ACTH, cortisol, and growth hormone.[2,3] This increase in counter-regulatory hormones leads to the predominantly catabolic state during surgery which contributes to the hyperglycemia seen in the perioperative period. In addition, this can lead to metabolic decompensation and diabetic ketoacidosis in the patient with absolute insulin deficiency or a hyperosmolar nonketotic state in those who are susceptible. The elevated counter-regulatory hormones also play a role in the relative insulin resistance of surgery.[3] This relative insulin resistance, coupled with the impaired insulin response to hyperglycemia seen in surgery with general anesthesia, contributes to the hyperglycemia often seen in the perioperative state.[3]

Metabolic effects of anaesthetic agents and techniques

General anaesthesia produces an alteration of level of consciousness that can mask the usual signs and symptoms of hypoglycemia. This is one of the main concerns of anaesthetists in the perioperative period and may explain some of the permissive hyperglycemia seen in the care of these patients.[2] However, the availability of accurate and easy-to-use glucose monitors facilitates measurement of blood glucose in the operating room and will prevent hypoglycemia.

The choice of anaesthetic agent can affect glucose homeostasis. Benzodiazepines decrease the secretion of ACTH and cortisol when used in high doses during surgery.[2] This may decrease the hyperglycemic response to surgery. High-dose opiates also appear to decrease the hyperglycemic response to surgery by dampening the sympathetic nervous system and the hypothalamic-pituitary axis, thereby decreasing the usual catabolic hormone response to surgery.[4] Halothane, enflurane, and isoflurane appear to exacerbate the hyperglycemic response to surgery by inhibiting the insulin response to glucose in a reversible and dose-dependent manner, in vitro.[2]

The choice of anaesthetic technique will also affect glucose homeostasis. The use of epidural anaesthesia appears to block the perioperative increase in glucose, epinephrine, cortisol, and growth hormone.[5] The use of local anaesthesia for cataract surgery has been shown to have far less effect on blood glucose, cortisol and insulin levels compared to general anaesthesia.[6] The location of anaesthetic block also has an effect. A small study of non-diabetic patients found that

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the usual blunted insulin response to hyperglycemia in surgery is not seen with a low blockade (T9-T12) compared to a high block (T2-T6)[7].

Effects of chronic and acute hyperglycemia on surgery

It is recognized that individuals with diabetes have an increased risk of developing certain bacterial infections including cystitis, cellulitis, and invasive otitis externa.[8] Obese patients with diabetes undergoing coronary artery bypass grafting were found to have more wound infections, more overall complications, increased arrhythmia rates, increased respiratory failure, and more intra-aortic balloon pump use than patients without diabetes.[9,10] A recent study showed that patients with diabetes had an odds ratio of 2.76 (95% CI, 1.64-4.66) for surgical-site infections after cardiothoracic procedure, compared to controls.[11] There are two theories to explain the observed increase in postoperative infections and complications in diabetic patients:

- the long-term effects of chronic hyperglycemia, and
- the acute effects of hyperglycemia.

Chronic hyperglycemia is known to cause significant microvascular and macrovascular disease. Vascular disease can compromise the delivery of nutrients and oxygen that are necessary for appropriate wound healing and host defenses.[8] Continued tissue injury may go undetected with neuropathy, and may disrupt healing, thereby predisposing the patient to infections.[8] If chronic hyperglycemia was the sole explanation, short-term hyperglycemia in the perioperative period should not contribute to increased infections. The improvement of glycemic control in the short perioperative period would not be beneficial and the risk of hypoglycemia would outweigh any benefit. However, this is not the case.

Another explanation for increased infection and poor wound healing is the effect of acute hyperglycemia on the immune system and wound healing. Both in vitro and animal studies have shown that neutrophils exposed to hyperglycemia exhibit decreased chemotaxis,[12] decreased adherence, phagocytic function, and respiratory burst,[13] as well as decreased bactericidal activity.[14] Decreased macrophage activation[15] has also been demonstrated along with increased nonenzymatic glycosylation of immunoglobulins that impair complement fixation and bactericidal effect.[16] The increased glycosylation was demonstrated after only 16 hours of exposure to hyperglycemia of 13.3 mmol/L.[16] Some of the effects have been shown to be reversible with improved glycemic control.[17,18] A prospective study of 26 patients with diabetes undergoing coronary artery bypass grafting determined that improved intraoperative glycemic control with continuous intravenous (IV) insulin attenuated the decrease in neutrophil phagocytic function normally seen in patient with diabetes.[18]

Acute hyperglycemia also has deleterious effects on wound healing.[19,20] Animal studies have shown a significant increase in collagenase and protease activity and wound collagen glycosylation with hyperglycemia.[19] These effects may be reversible. Perioperative glycemic control improved bowel anastomosis healing in rats compared to those exposed to hyperglycemia and reduced the frequency of abscess formation.[20]

The association between perioperative glycemic control and surgical outcomes

Early reports investigating the association between perioperative glycemic control and surgical outcomes were predominantly small, retrospective, and produced conflicting results.[10,21,22] One study demonstrated worsened surgical outcomes with improved glycemic control,[22] whereas others demonstrated no relationship[21] or a trend towards improved outcomes.[10] Most of the early reports did not adjust for relevant co-morbidities. More recent data demonstrate a significant association between glycemic control and surgical outcome.

- A large retrospective analysis of 1585 patients with diabetes undergoing an open-heart procedure between 1987 and 1993 demonstrated that the independent predictors of deep wound infection on multivariate analysis were mean blood glucose level for the first 48 hours postoperatively, obesity, and the use of the internal mammary artery.[23]
- A smaller study of 100 consecutive patients with diabetes undergoing elective surgery with general anaesthesia prospectively monitored glucose control over the first 48 hours postoperatively and postoperative infections that occurred within 14 days after surgery.[24] This study demonstrated that the group with "good" glycemic control, defined *a priori* as all glucose levels ≤12.2 mmol/L, had significantly fewer infections compared to the group with "poor" glycemic control (4.2% vs 24.6%, p=0.03).
- Latham et al prospectively investigated 1044 patients undergoing cardiothoracic surgery.[11] Blood glucose levels were obtained in the first 48 hours after surgery and the outcome of surgical-site infections was assessed blindly. The odds ratio for surgical-site infections for mean postoperative glucose levels of <11.1, 11.1-13.7, 13.8-16.6, and >16.6 mmol/L were 1.00, 2.54, 2.97, and 3.32, respectively, with a statistically significant linear trend.
- Interestingly, recent evidence suggests that peri-operative hyperglycemia is not only associated with post-operative infections, but also with rates of acute allograft rejection after renal transplantation.[25,26] A retrospective review of 50 patients with diabetes receiving their first cadaveric renal transplant and steroid-sparing immunosuppression demonstrated reduced postoperative infections and significantly reduced acute rejection rates from 58% to 11% in those with mean glucose levels < 11.2 mmol/L over the first 100 postoperative hours.[25] The proposed biological explanation for this effect includes the worsened renal ischaemic injury, increased antigen presentation, and co-stimulation and exaggerated inflammatory response to ischemia/reperfusion, that are all seen with hyperglycemia.[26]

All of the previously mentioned studies demonstrate an association between good perioperative glycemic control and fewer postoperative infections and possibly decreased acute allograft rejection rates after renal transplantation. However, cause-and-effect has not been demonstrated. The elevated blood glucose may merely represent an epiphenomenon or a marker of infection or rejection.

The effects of improved perioperative glycemic control on surgical outcomes

To provide further evidence for a cause-and-effect relationship, one must show that intervention with the "cause" will alter the "effect." Surprisingly, only two clinical studies have been published addressing this issue.[27,28]

Furnary *et al* prospectively studied 2467 consecutive patients with diabetes undergoing open-heart surgery in a single Portland, Oregon medical centre between 1987 and 1997.[27] Perioperative blood glucose levels were recorded every 1-2 hours. Those patients enrolled from January 1987

to September 1991 (control group) received sliding scale guided subcutaneous insulin every 4 hours intraoperatively and for 2 days postoperatively to maintain blood glucose around 11.1 mmol/L. The intervention group consisted of patients enrolled between October 1991 and November 1997; they received algorithm-guided variable-rate continuous IV insulin intraoperatively and for 2 days postoperatively to maintain a blood glucose of 8.3-11.1 mmol/L. Of the 2467 patients, the majority (65%) did not require insulin at baseline and were being treated with oral agents or diet alone. At baseline, the intervention group was more obese and used more internal mammary arteries for grafting. As expected, the intervention group achieved lower peri-operative glucose levels. Eighty-five percent of the intervention group maintained blood glucose levels <11.1 mmol/L compared to 47% of the control group. Multivariate analysis revealed that continuous IV insulin provided a 66% relative risk reduction in deep sternal wound infections (p=0.005). This reduction was seen despite the bias against the intervention group with more obesity and higher use of internal mammary arteries. The results of this study suggest that improved glycemic control with continuous IV insulin, aiming for blood glucose of 8.3-11.1 mmol/L, decrease the incidence of deep sternal wound infection. However, the study was not randomized and its sequential nature allows for bias. Subtle changes may have occurred over the 10-year period with respect to surgical technique or nursing care practices. However, the fact that the rates of deep sternal wound infection in non-diabetic patients remained stable over the same period is somewhat reassuring, so the results can be considered in the development of perioperative recommendations.

The only prospective, randomized, controlled study of perioperative glycemic control was recently published by Van den Berghe et al.[28] They included all adults requiring mechanical ventilation admitted to the surgical ICU in a single centre in Belgium between February 2000 and January 2001 (n=1548). Patients were randomized to receive either :

- continuous IV insulin when blood glucose levels were >11.9 mmol/l, adjusted to maintain glucose levels between 10.0 and 11.1 mmol/L (conventional group), or
- continuous IV insulin when blood glucose levels exceeded 6.1 mmol/L, adjusted to maintain glucose levels between 4.4 and 6.1 mmol/L (intensive group).

At baseline, the groups were similar. Sixty-three percent of patients had cardiac surgery and only 13% had known diabetes. The mean glucose level in the intensive group was significantly lower that the conventional group (5.7±1.0 vs 8.5±1.8 mmol/L, p<0.01). It is important to note that the conventional group achieved a mean glucose level of 8.5±1.8 mmol/L, which is better than the current typical glucose level achieved in patients with diabetes in an intensive care setting. Therefore, the benefit seen in this study in the intervention group may, in fact, be greater when compared to typical practice. At 12 months, intensive insulin therapy reduced mortality during intensive care from 8.0% in the conventional group to 4.6% (p<0.04). The benefit was seen mostly in those patients remaining in the ICU for >5 days with a mortality reduction from 20.2% to 10.6% (p=0.005). Intensive treatment also significantly reduced multi-organ failure with a septic focus, overall in-hospital mortality by 34%, bacteremia by 46%, acute renal failure requiring renal replacement therapy by 41%, and critical care polyneuropathy by 44%. This landmark, well-designed, randomized, controlled study demonstrates the importance and feasibility of tight postoperative glycemic control in patients requiring mechanical ventilation and intensive care postoperatively.

Gaps in the literature

There are ample in vitro and animal data showing the adverse effects of hyperglycemia on host defenses and wound healing. An association has been established between impaired perioperative glycemic control and postoperative infections, and perhaps, allograft rejection. There are data supporting the use of variable-rate continuous IV insulin, both intraoperatively and postoperatively, after cardiothoracic surgery, maintaining a glucose level of at most 8.3-11.1 mmol/L. More recently, there are also excellent data supporting the use of variable rate continuous insulin, starting immediately postoperatively, with adjustment to maintain blood glucose between 4.4-6.1 mmol/L to reduce both morbidity and mortality in postoperative patients in a surgical ICU. However, there are still significant gaps in the literature. There are no outcome data available for minor surgical procedures and it remains unclear whether the same glycemic control should be targeted in these procedures. There are still no definitive data on the outcomes of tight intraoperative glycemic control alone, without postoperative glycemic control. Given the compelling results of the study by Van den Berghe et al, should intra-operative glycemic control for those patients also target 4.4-6.1 mmol/L? This is an important question to address, given anaesthetist concern about intraoperative hypoglycemia.

General recommendations

Despite the gaps in the literature, the Division of Endocrinology and Metabolism at St. Michael's Hospital has evaluated the available evidence and devised the following recommendations for perioperative glycemic control for patients with diabetes. Although these recommendations must be tailored to meet the specific needs of the individual patient and should be applied when resources for appropriate monitoring are available, they should be applicable in the vast majority of situations.

Elective surgery in patients with diabetes should be scheduled for the morning when possible, to minimize the disturbance of the usual diabetes treatment regimen. If time permits, glycemic control should be optimized preoperatively to facilitate the achievement of good control on the morning of surgery. Patients on insulin or oral agents should be advised to take their usual treatment the evening before surgery. However, if the patient is experiencing morning or nocturnal hypoglycemia, the evening dose should be reduced or held. In addition, if the patient is on a very long-acting agent (eg, chlorpropamide), one should consider holding the agent for at least 24 hours prior to surgery.[3] Any patient, irrespective of diabetes type or treatment, with evidence of metabolic disturbance, (ie, marked hyperglycemia [arbitrarily, blood glucose >14 mmol/L]), should receive continuous IV insulin to achieve appropriate control, and consideration must be made to postponing non-urgent procedures. If the decision is made to treat perioperatively with insulin, the patient should receive simultaneous IV glucose, typically IV D5W at 50-75 cc/hour. Capillary glucose should be monitored every 1-2 hours before surgery, at least every hour during surgery, and every 2-4 hours after surgery while on IV

Table 1: General recommendations for the perioperative glycemic control of patients with diabetes

- Morning surgery, when possible
- Optimize glycemic control preoperatively when time permits
- Patients on insulin or oral agents should take their usual dose the night before surgery*
- Any patient presenting on the morning of surgery with metabolic disturbances (marked hyperglycemia) should receive continuous IV insulin and consideration should be made to postpone non-urgent procedures
- Patients receiving insulin perioperatively should receive IV glucose simultaneously
- Capillary glucose levels should be monitored every 1-2 hours before surgery, at least every hour during surgery, and every 2-4 hours after surgery while on IV insulin
- In the preoperative and intraoperative period, blood glucose should be maintained at 5.0 to 10.0 mmol/L
- Blood glucose should be maintained at 4.5 to 6.0 mmol/L in the postoperative period for patients in an intensive care setting

* Consider decreasing or holding the dose of evening insulin or oral agent the evening before surgery, if the patient experiences nocturnal hypoglycemia or morning blood glucose levels < 5.0 mmol/L. If patients are on very long-acting agents (eg, chlorpropamide), the agent should be held for at least 24 hours before surgery.

insulin, with appropriate adjustment of infusion rate to maintain adequate control and avoid significant hypoglycemia.

After reviewing the available evidence, it is recommended that preoperative and intraoperative blood glucose be maintained between 5.0 and 10.0 mmol/L. Although Furnary *et al* [27] suggested that a blood glucose of 8.3-11.1 mmol/L is adequate to reduce postoperative infection rates, the study by Van den Berghe *et al*[28] suggests that tighter glycemic control may be better. In addition, studies of perioperative insulin administration have shown that it is safe to achieve blood glucose levels of 5.0-10.0 mmol/L with minimal hypoglycemia. However, it is important to recognize that because data are not available for minor surgeries, this information is being extrapolated for minor procedures as well. In addition, recommendations on specific IV insulin infusion rates are not provided because different studies have used different IV insulin regimens[18,23,27-32] and there have been no comparative studies addressing this issue (Table 1).

Major surgery requiring postoperative intensive care

Irrespective of diabetes type and treatment, all patients undergoing major surgery requiring postoperative intensive care (eg, cardiothoracic, neurological, vascular, abdominal and transplant surgery) should be started on variable rate continuous IV insulin to maintain blood glucose levels, both preoperatively and intraoperatively, between 5.0 and 10.0 mmol/L. Postoperatively, the insulin should be adjusted to maintain blood glucose between 4.5 and 6.0 mmol/L in the ICU. As the study by Van den Berghe et al demonstrated, even patients without a prior diagnosis of diabetes who have a blood glucose value that exceeds 6.1 mmol/L should be placed on intravenous insulin (Figure 1) .

Patients on insulin (Type 1 or type 2 diabetes)

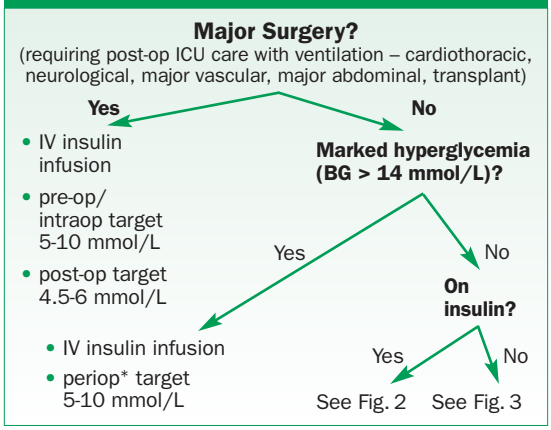
Moderate surgery

Moderate surgery is defined as surgery of >1-2 hours duration, but not requiring intensive care postoperatively. Patients on insulin undergoing any moderate surgery should receive variable-rate continuous IV insulin to maintain perioperative blood glucose between 5.0 and 10.0 mmol/L. A study of 19 children and adolescents with type 1 diabetes undergoing moderate surgical procedures demonstrated that variable-rate continuous IV insulin was superior to subcutaneous insulin for the maintenance of glycemic control and prevention of diabetic ketoacidosis.[29] A study of 30 patients with diabetes undergoing surgery of >2 hours duration, including 17 patients with type 2 diabetes, demonstrated that variable-rate continuous insulin infusion was superior to intermittent subcutaneous insulin for maintenance of adequate glycemic control.[30]

Minor surgery

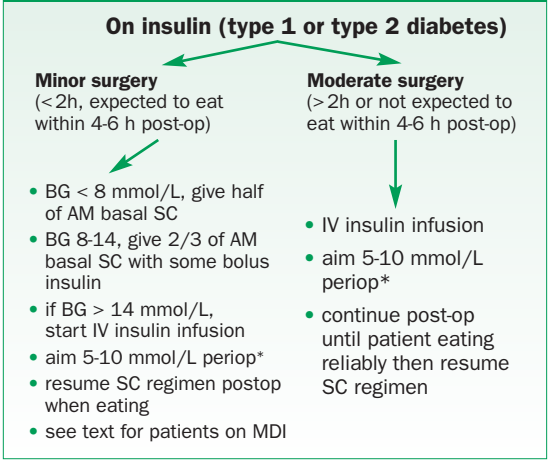
Minor surgery, in this context, is defined as surgery of <1-2 hours duration with the patient expected to eat within 4-6 hours after surgery. The evidence for management in this situation is limited. One small study of 20 patients with insulin-requiring diabetes, undergoing minor hand or eye surgery, showed a statistically non-significant improvement in glycemic control with IV insulin compared to subcutaneous insulin, although the power of the study to demonstrate a difference is questionable.[31] The study did not specify the type of diabetes, but based on the age range of the patients (25-76 years), it is assumed that there was a mixture of patients with type 1 and type 2 diabetes. Given that subcutaneous insulin is easier and less resource-intensive to administer, until more definitive evidence is available favouring IV insulin, subcutaneous insulin can be administered preoperatively as long as blood glucose levels are maintained between 5.0 and 10.0 mmol/L in the perioperative period. Patients can receive half of

Figure 1: Algorithm for perioperative glycemic control for patients with diabetes mellitus



*Periop refers to the preoperative, intraoperative, and postoperative periods.

Figure 2: Algorithm for perioperative glycemic control for patients with diabetes mellitus on insulin



*Periop refers to the preoperative, intraoperative, and postoperative periods.
MDI = multiple daily injections

their usual morning dose of basal insulin subcutaneously before surgery if their blood glucose on arrival on the morning of surgery is <8.0 mmol/L. If it is between 8.0 and 14.0 mmol/L, then the patient should receive two-thirds of the usual morning basal insulin subcutaneously, along with a small dose of bolus insulin such as aspart or lispro. If the blood glucose is >14.0 mmol/L on arrival, then the patient should be placed on variable rate continuous IV insulin. For patients on multiple daily injections of insulin who do not normally receive a morning dose of basal insulin, there are no good data to guide management in this situation. One can either choose an empiric dose of basal insulin to be administered preoperatively, or simply delay (or omit) the usual morning dose of bolus insulin until after the surgery if the delay will be short and assuming that blood glucose levels are maintained between 5.0 and 10.0 mmol/L in the perioperative period. After the procedure, when the patient is able to eat, the patient's usual insulin regimen should be resumed (Figure 2).

Type 2 diabetes (not on insulin)

Moderate surgery

Oral hypoglycemic agents should be held the morning of surgery. The usual dose of evening insulin or oral agent should be taken the night before surgery, unless the patient is experiencing either morning or nocturnal hypoglycemia, in which case, the evening dose should be decreased. If the patient is on a very long-acting oral agent (eg, chlorpropamide), the oral agent should be held for at least 24 hours prior to surgery. A study of 60 patients with type 2 diabetes, not on insulin, undergoing elective surgeries of >2.5 hours duration, showed that continuous IV insulin, intermittent IV insulin boluses, and no insulin with no glucose demonstrated the same glycemic control.[32] However, there was a statistically nonsignificant finding that the blood glucose levels in the group receiving no glucose rose steadily during the surgery. Therefore, it would appear that one treatment option is to simply not administer IV glucose to these patients, to monitor their blood glucose closely, and to administer insulin when their glucose is >10.0 mmol/L to maintain blood glucose levels between 5.0 and 10.0 mmol/L perioperatively. However, if there are concerns about hypoglycemia in a patient on long-acting insulin secretagogues, one can administer some IV glucose. An alternative treatment option is to start immediately on a variable-rate continuous insulin infusion with the same blood glucose targets.

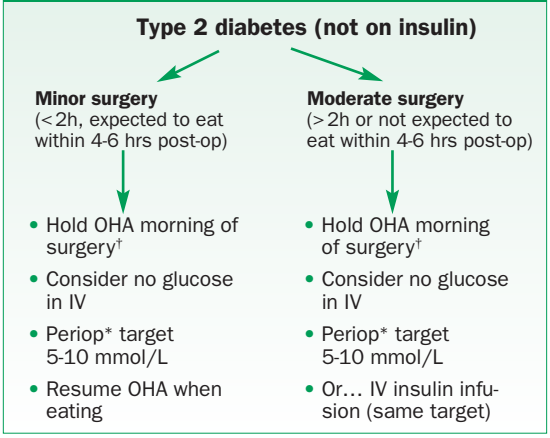
Minor surgery

Oral hypoglycemic agents should be held the morning of surgery or at least 24 hours prior to surgery for those patients on very long-acting agents (eg, chlorpropamide). One can consider not including any glucose in any of the IV fluids administered to the patient unless there are concerns of hypoglycemia in those on long-acting insulin secretagogues. The blood glucose levels should be maintained between 5.0 and 10.0 mmol/L in the perioperative period. If the glucose level exceeds 10.0 mmol/L at any time, insulin should be given. After surgery, their usual oral hypoglycemic agent should be resumed, assuming that renal function is adequate if they are on metformin (Figure 3).

Summary

Perioperative glycemic control in a patient with diabetes can be challenging because of the many different types of surgeries, anaesthesia, and diabetes treatment protocols. There are ample in vitro, animal, and observational data linking perioperative glycemic control and surgical complications such as postoperative infections and perhaps acute allograft rejection. There is some evidence to support the importance of glycemic control intraoperatively and postoperatively in patients undergoing major surgical procedures. However, the evidence for minor procedures is lacking. After reviewing the available evidence, we recommend that all patients undergoing surgical procedures should maintain a blood

Figure 3: Algorithm for perioperative glycemic control for patients with diabetes mellitus who are not on insulin



† If patient is experiencing morning or nocturnal hypoglycemia, then reduce the evening dose prior to surgery. If patient is taking a very-long acting agent (eg, chlorpropamide), then consider holding the agent for at least 24 hours prior to surgery.
*Periop refers to the preoperative, intraoperative, and postoperative periods.

glucose level of 5.0 to 10.0 mmol/L in the preoperative, intraoperative, and postoperative periods for minor and moderate procedures, and 4.5-6.0 mmol/L in the postoperative period for major procedures in the ICU setting.

Alice Y.Y. Cheng, MD, *is a resident in the University of Toronto Endocrine Training Program.*

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