

## In Brief

Diabetes is associated with increased requirement for surgical procedures and increased postoperative morbidity and mortality. The stress response to surgery and the resultant hyperglycemia, osmotic diuresis, and hypoinsulinemia can lead to perioperative ketoacidosis or hyperosmolar syndrome. Hyperglycemia impairs leukocyte function and wound healing. The management goal is to optimize metabolic control through close monitoring, adequate fluid and caloric repletion, and judicious use of insulin.

# Management of Diabetes Mellitus in Surgical Patients

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Patients with diabetes undergo surgical procedures at a higher rate than do nondiabetic people.<sup>1,2</sup> Major surgical operations require a period of fasting during which oral antidiabetic medications cannot be used. The stress of surgery itself results in metabolic perturbations that alter glucose homeostasis, and persistent hyperglycemia is a risk factor for endothelial dysfunction,<sup>3</sup> postoperative sepsis,<sup>4</sup> impaired wound healing,<sup>5,6</sup> and cerebral ischemia.<sup>7</sup> The stress response itself may precipitate diabetic crises (diabetic ketoacidosis [DKA], hyperglycemic hyperosmolar syndrome [HHS]) during surgery or postoperatively, with negative prognostic consequences.<sup>8,9</sup> HHS is a well known postoperative complication following certain procedures, including cardiac bypass surgery, where it is associated with 42% mortality.<sup>9,10</sup>

Furthermore, gastrointestinal instability provoked by anesthesia, medications, and stress-related vagal overlay can lead to nausea, vomiting, and dehydration. This compounds the volume contraction that may already be present from the osmotic diuresis induced by hyperglycemia, thereby increasing the risk for ischemic events and acute renal failure. Subtle to gross deficits in key electrolytes (principally potassium, but also magnesium) may pose an arrhythmogenic risk, which often is superimposed on a milieu of

endemic coronary artery disease in middle-aged or older people with diabetes.

It is therefore imperative that careful attention be paid to the metabolic status of people with diabetes undergoing surgical procedures. Elective surgery in people with uncontrolled diabetes should preferably be scheduled after acceptable glycemic control has been achieved. Admission to the hospital 1–2 days before a scheduled surgery is advisable for such patients. Even emergency surgery should be delayed, whenever feasible, to allow stabilization of patients in diabetic crises.

The actual treatment recommendations for a given patient should be individualized, based on diabetes classification, usual diabetes regimen, state of glycemic control, nature and extent of surgical procedure, and available expertise. Some general rules can be applied, however. Whenever possible, ketoacidosis, hyperosmolar state, and electrolyte derangements should be searched for and corrected preoperatively, and the surgery itself should be scheduled early in the day, to avoid protracted fasting.

## REVIEW OF THE STRESS RESPONSE AND GLUCOREGULATION

Anesthesia and surgery cause a stereotypical metabolic stress response that

could overwhelm homeostatic mechanisms in patients with pre-existing abnormalities of glucose metabolism. The invariant features of the metabolic stress response include release of the catabolic hormones epinephrine, norepinephrine, cortisol, glucagons, and growth hormone<sup>11-16</sup> and inhibition of insulin secretion and action.<sup>17-19</sup>

### **Anti-Insulin Effects of Surgical Stress**

In addition to insulin resistance induced by circulating stress hormones, surgical stress has a deleterious effect on pancreatic  $\beta$ -cell function. Plasma insulin levels fall, and insulin secretory responses to glucose become impaired during surgery.<sup>17-19</sup> The mechanism of the impaired  $\beta$ -cell responsiveness during surgery is unclear, and the defect is poorly correlated with ambient intraoperative catecholamine levels. Postoperatively, however, there is a close inverse correlation between plasma epinephrine and insulin secretion.<sup>17</sup>

These anti-insulin effects of the metabolic stress response essentially reverse the physiological anabolic and anti-catabolic actions of insulin. The important anabolic actions of insulin that may be reversed or attenuated during the stress of surgery include: 1) stimulation of glucose uptake and glycogen storage, 2) stimulation of amino acid uptake and protein synthesis by skeletal muscle, 3) stimulation of fatty acid synthesis in the liver and storage in adipocytes, and 4) renal sodium reabsorption and intravascular volume preservation. The anti-catabolic effects of insulin include: 1) inhibition of hepatic glycogen breakdown, 2) inhibition of gluconeogenesis, 3) inhibition of lipolysis, 4) inhibition of fatty acid oxidation and ketone body formation, and 5) inhibition of proteolysis and amino acid oxidation. Thus, inhibition of insulin secretion and action shifts the perioperative milieu toward hypercatabolism through a variety of mechanisms.

### **Direct Catabolic Effects of Stress Hormones**

The neuroendocrine response to the stress of general anesthesia and surgery leads to activation of potent counterregulatory hormones.<sup>11-16</sup> The catecholamines (norepinephrine is augmented mostly during surgery and epinephrine postoperatively) stimulate gluconeogenesis and glycogenolysis, inhibit glucose utilization by periph-

al tissues, and inhibit insulin secretion.<sup>20</sup> Activation of phosphoproteins by cAMP-dependent protein kinases accounts for the stimulatory effects of catecholamines on liver and muscle glycogen breakdown, whereas phosphorylation of glycogen synthase accounts for the decreased glycogen synthesis.<sup>21</sup>

These effects predispose to severe hyperglycemia, which is further exacerbated by the stimulatory effect of epinephrine and norepinephrine on glucagon secretion. Other catabolic effects of catecholamines include stimulation of lipolysis and ketogenesis. Epinephrine increases adipocyte cAMP levels, leading to phosphorylation and activation of hormone-sensitive lipase. The activated hormone-sensitive lipase promotes lipolysis and release of free fatty acids into the circulation.

Glucagon, whose levels are augmented by catecholamines, exerts catabolic effects similar to those of the catecholamines: stimulation of hepatic glucose production and ketogenesis and inhibition of insulin action in peripheral tissues. Growth hormone and glucocorticoids potentiate the catabolic effects of catecholamines and glucagon. Glucocorticoids increase hepatic glucose production<sup>21,22</sup> and induce lipolysis and negative nitrogen balance by stimulating proteolysis. The products of lipolysis and proteolysis (e.g., free fatty acids, glycerol, alanine, glutamine) provide substrates for increased gluconeogenesis by the liver.

Clearly, the combination of relative hypoinsulinemia, insulin resistance, and excessive catabolism from the action of counterregulatory hormones is a serious threat to glucose homeostasis in all patients with diabetes, particularly those whose preoperative metabolic control is less than perfect. The logical conclusion is that insulin therapy will be needed perioperatively in the majority of patients with diabetes undergoing surgery.

### **APPROACHES TO MANAGEMENT**

Operationally, all patients with type 1 diabetes undergoing minor or major surgery and patients with type 2 diabetes undergoing major surgery are considered appropriate candidates for intensive perioperative diabetes management. The management approach in these categories of patients always includes insulin therapy in combination with dextrose and potassium

infusion. Major surgery is defined as one requiring general anesthesia of  $\geq 1$  h. Type 2 diabetic patients undergoing minor surgery are managed based on their usual diabetes regimen, their state of glycemic control, the nature and extent of the surgical procedure, and available expertise.

### **Patients Managed With Diet Alone**

People whose diabetes is well controlled by a regimen of dietary modification and physical activity may require no special preoperative intervention for diabetes. Fasting blood glucose should be measured on the morning of surgery, and intraoperative blood glucose monitoring is desirable if the surgical procedure is lengthy ( $> 1$  h). If surgery is minor, no specific therapy is required. If surgery is major or if diabetes is poorly controlled (blood glucose  $> 200$  mg/dl), an intravenous infusion of insulin and dextrose should be considered (see below), and hourly intraoperative glucose monitoring is recommended.

### **Patients Treated With Oral Antidiabetic Agents**

Second-generation sulfonylureas should be discontinued 1 day before surgery, with the exception of chlorpropamide, which should be stopped 2-3 days before surgery. Other oral agents can be continued until the operative day. Although metformin has a short half-life of  $\sim 6$  h, it is prudent to temporarily withhold therapy 1-2 days before surgery, especially in sick patients and those undergoing procedures that increase the risks for renal hypoperfusion, tissue hypoxia, and lactate accumulation.

At a minimum, blood glucose should be monitored before and immediately after surgery in all patients. Those undergoing extensive procedures should have hourly glucose monitoring during and immediately following surgery. Bedside capillary blood glucose meters are adequate for these monitoring requirements. However, extremely high or low values should immediately be repeated before instituting remedial action, and a simultaneous blood specimen should be sent for laboratory corroboration.

For minor surgery, perioperative hyperglycemia ( $> 200$  mg/dl) can be managed with small subcutaneous doses (4-10 units) of short-acting insulin. Care must be taken to avoid hypoglycemia. After minor proce-

dures, most usual antidiabetic medications can be restarted once patients start eating. Patients treated with metformin should withhold the drug for ~72 h following surgery or iodinated radiocontrast procedures. Metformin therapy can be restarted after documentation of normal renal function and absence of contrast-induced nephropathy. The recommended treatment for patients undergoing major surgery and for those with poorly controlled type 2 diabetes is intravenous insulin infusion, with glucose, using one of two standard regimens (see below).

### Insulin-Treated Patients

#### Minor surgery

Patients treated with long-acting insulin (e.g., ultralente, glargine, protamine zinc insulin) should be switched to intermediate-acting forms 1–2 days before elective surgery. Close perioperative blood glucose monitoring is crucial to avoid extremes of glycemia. Intravenous insulin/glucose/potassium should be commenced before surgery. Blood glucose levels should be monitored hourly intraoperatively and immediately after surgery. The infusion should be stopped and usual insulin treatment resumed once oral intake is established. There should be a 1-h overlap between stopping intravenous insulin and re-instituting subcutaneous insulin.

#### Major surgery

Insulin-treated patients undergoing major elective surgery should preferably be admitted 2–3 days before surgery, if glycemic control is suboptimal (hemoglobin A<sub>1c</sub> >8%). If admission is not feasible, a physician or diabetes nurse practitioner should work with the patient to optimize self-monitoring of blood glucose (SMBG) values in the days preceding the planned surgery. In such circumstances, SMBG should be performed at least before each meal and at bedtime, with target preprandial values of 80–120 mg/dl and bedtime values of 100–140 mg/dl.<sup>23</sup>

The preoperative evaluation should include a thorough physical examination (with particular focus on autonomic neuropathy and cardiac status), measurement of serum electrolytes and creatinine, and urine ketones. The presence of autonomic neuropathy mandates increased surveillance for hypotension, respiratory arrest, and hemodynamic instability during

surgery.<sup>24</sup> Gross metabolic and electrolyte abnormalities (e.g., hyponatremia, dyskalemia, acidosis) should be corrected before surgery.

#### Intravenous Insulin, Glucose, Potassium, and Fluids

Intravenous infusion of insulin, glucose, and potassium is now standard therapy and has replaced subcutaneous insulin therapy for the perioperative management of diabetes, especially in type 1 diabetic patients and patients with type 2 diabetes undergoing major procedures. Several reports have emphasized the advantages of the insulin infusion regimen over subcutaneous delivery.<sup>25–27</sup>

It is not necessary to add albumin to the insulin infusion to prevent non-specific adsorption of insulin to the infusion apparatus; flushing ~50 ml of the insulin infusion mixture through the tubing will accomplish the same purpose.

Adequate fluids must be administered to maintain intravascular volume. Fluid deficits from osmotic diuresis in poorly controlled diabetes can be considerable. The preferred fluids are normal saline and dextrose in water. Fluids containing lactate (i.e., Ringer's lactate, Hartmann's solution) cause exacerbation of hyperglycemia.<sup>28</sup>

#### Insulin

Two main methods of insulin delivery have been used: either combining insulin with glucose and potassium in

the same bag (the GIK regimen) or giving insulin separately with an infusion pump.

The combined GIK infusion is efficient, safe, and effective in many patients but does not permit selective adjustment of insulin delivery without changing the bag. The glucose component can be either 5 or 10% dextrose. The latter provides more calories.

Regardless of whether separate or combined infusions are given, close monitoring is required to avoid catastrophe during these infusion regimens. A sample regimen for separate insulin infusion is indicated in Table 1. These recommendations must be interpreted flexibly, given the individual variability in insulin requirements and metabolic profiles. In the absence of strict evidence-based guidelines, the consensus approach is to avoid extremes of glycemia (aiming for 120–180 mg/dl) and to tailor therapies to individual patients based on feedback from glucose monitoring.

The initial insulin infusion rate can be estimated as between one-half and three-fourths of the patient's total daily insulin dose expressed as units/h. Regular insulin, 0.5–1 unit/h, is an appropriate starting dose for most type 1 diabetic patients. Patients treated with oral antidiabetic agents who require perioperative insulin infusion, as well as insulin-treated type 2 diabetic patients, can be given an initial infusion rate of 1–2 units/h.

An infusion rate of 1 unit/h is obtained by mixing 25 units of regu-

**Table 1. Regimen for Separate Intravenous Insulin Infusion for Perioperative Diabetes Management**

- Prepare a 0.1 unit/ml solution by adding 25 units regular insulin to 250 ml normal saline.
- Flush 50 ml of insulin solution through infusion tubing to saturate nonspecific binding sites.
- Set initial infusion rate (generally, 0.5 unit/h [5 ml/h] for thin women; 1.0 unit/h [10 ml/h] for others)
- Adjust infusion rate according to bedside blood glucose measurement as follows:

Blood Glucose (mg/dl)	Insulin Infusion Rate
<80	Check glucose after 15 min*
80–140	Decrease infusion by 0.4 unit/h (4 ml/h)
141–180	No change
181–220	Increase infusion by 0.4 unit/h (4 ml/h)
221–250	Increase infusion by 0.6 unit/h (6 ml/h)
251–300	Increase infusion by 0.8 unit/h (8 ml/h)
>300	Increase infusion by 1 unit/h (10 ml/h)

\*Regimen assumes separate infusion of glucose at ~5–10 g/h and hourly blood glucose monitoring. Extremely high or low glucose values should be confirmed with an immediate repeat measurement. Intravenous boluses of dextrose (50%) or supplemental regular insulin can be used for rapid correction but are rarely necessary.

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lar insulin in 250 ml of normal saline (0.1 unit/ml) and infusing 10 ml/h. Alternatively, 50 units of regular insulin is made up to 50 ml with saline and given by syringe pump at 1–2 ml/h. Adjustments to the insulin infusion rate are made to maintain blood glucose between 120 and 180 mg/dl. (See Table 1.)

The duration of insulin (and dextrose) infusions depends on the clinical status of the patient. The infusions should be continued postoperatively until oral intake is established, after which the usual diabetes treatment can be resumed. It is prudent to give the first subcutaneous dose of insulin 30–60 min before disconnecting the intravenous line.

### Glucose

Adequate glucose should be provided to prevent catabolism, starvation ketosis, and insulin-induced hypoglycemia. The physiological amount of glucose required to prevent catabolism in an average nondiabetic adult is ~120 g/day (or 5 g/h). With preoperative fasting, surgical stress, and ongoing insulin therapy, the caloric requirement in most diabetic patients averages 5–10 g/h glucose. This can be given as 5 or 10% dextrose. An infusion rate of 100 ml/h with 5% dextrose delivers 5 g/h glucose. If fluid restriction is necessary, the more concentrated 10% dextrose can be used. Many now prefer to give 10% dextrose at a starting rate of ~100 ml/h.

The usual range of perioperative blood glucose that clinicians are comfortable with is ~120–180 mg/dl. The insulin and glucose infusion rates should be adjusted accordingly if blood glucose monitoring shows marked deviation from the acceptable range. The convention is to administer ~0.3 units of insulin/g glucose in most otherwise stable patients. However, insulin requirements are higher in septic, obese, or unstable patients and in those treated with steroids or undergoing cardiopulmonary bypass surgery. If the GIK regimen is to be used, then 15 units of insulin in 500 ml 10% dextrose containing 10 mEq potassium is the usual starting solution given at 100 ml/h. Table 2 shows such a regimen based on a 1-liter volume of infusate.

### Potassium

The infusion of insulin and glucose induces an intracellular translocation of potassium, resulting in a risk for

hypokalemia. In patients with initially normal serum potassium, potassium chloride, 10 mEq, should be added routinely to each 500 ml of dextrose to maintain normokalemia if renal function is normal. Hyperkalemia (confirmed with repeat measurement and electrocardiogram) and renal insufficiency are contraindications to potassium infusion.

### Emergency Surgery

Approximately 5% of people with diabetes will require emergency surgery over their lifetime.<sup>1</sup> The commonly performed surgeries include general procedures (laparotomy, appendectomy, cholecystectomy, and so forth) and diabetes-related procedures, such as abscess drainage, ulcer care, and lower-extremity amputation.

By definition, the time of occurrence of these emergencies cannot be predicted, and appropriate surgical care must not be unduly delayed. Nonetheless, particular care must be taken to exclude DKA and other conditions that are likely to be mistaken for surgical emergencies. Many patients with DKA and prominent abdominal symptoms have undergone needless surgical exploration for a nonexistent acute abdominal emergency.<sup>29</sup> Functional syndromes due to diabetic autonomic neuropathy of the gastrointestinal tract (gastroparesis, gastroenteropathy, intractable or cyclical vomiting) may mimic anatomical surgical emergencies.<sup>30</sup> Similarly, the rare diabetic pseudotabes syndrome, characterized by sharp neuropathic pain along thoracolumbar dermatomes, can be confused with visceral disorders. Patients with pseudotabes typically have pupillary and gait

abnormalities from associated cranial and peripheral neuropathy. The initial evaluation of a diabetic patient with a suspected surgical emergency must, therefore, include a thorough medical history and physical examination directed at excluding the aforementioned diagnostic pitfalls.

Unfortunately, many patients who require emergency surgery will have suboptimal glycemic control. However, this is not necessarily a contraindication to the timely performance of potentially life-saving surgery. An intravenous access should be secured and immediate blood specimens should be sent for glucose, electrolyte, and acid-base assessment. Gross derangements of volume and electrolytes (e.g. hypokalemia, hypernatremia) should be corrected.

Surgery should be delayed, whenever feasible, in patients with DKA, so that the underlying acid-base disorder can be corrected or, at least, ameliorated. Patients with HHS are markedly dehydrated and should be restored quickly to good volume and improved metabolic status before surgery. Blood glucose should be monitored hourly at the bedside, and insulin, glucose, and potassium infusion should be administered, as appropriate, to maintain blood glucose in the 120–180 mg/dl range. Serum potassium should be checked frequently (every 2–4 h), and potassium supplementation should be adjusted to ensure that the patient remains eukalemic throughout surgery and postoperatively.

### CONCLUSION

Therapeutic surgery is a frequent requirement for diabetic patients and in the past has been associated with

**Table 2. Regimen for Glucose-Insulin-Potassium (GIK) Combined Infusion\***

Blood Glucose (mg/dl)	Glucose-Insulin-Potassium Infusion Rate	
	5% Dextrose	10% Dextrose
<80	↓ 5 units	↓ 10 units
<120	↓ 3 units	↓ 5 units
120–180	No change	No change
181–270	↑ 3 units	↑ 5 units
>270	↑ 5 units	↑ 10 units

5% dextrose: 1,000 ml containing 20 mEq KCl + 15 units regular insulin

10% dextrose: 1,000 ml containing 20 mEq KCl + 30 units regular insulin

Arrows indicate amount by which insulin in each 1,000-ml bag of infusate is to be decreased or increased.

\*Adapted from reference 31.



increased morbidity and mortality. Recent outcomes data are lacking, but it is likely that advances in surgical science, anesthesiology, and intensive care medicine, together with increased awareness and appropriate metabolic intervention, may have improved the perioperative fate of diabetic patients in recent times. Clinicians are encouraged to continue to give careful attention to metabolic control in surgical patients with diabetes.

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