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Perioperative management of type 1 diabetes mellitus

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There are approximately 1 million patients with type 1 diabetes mellitus in the United States today. It is estimated that 50% of diabetic patients will require surgery of some kind during their lifetime [1]. Therefore, perioperative management of these patients is not by any means a rare event. As a group, diabetic patients represent a larger portion of the surgical population annually than nondiabetic individuals. Many of the surgical procedures done in patients with diabetes are necessitated by the classic complications of diabetes—retinopathy, neuropathy, nephropathy, and vasculopathy. For instance, in 1980 11.3% of all surgeries in diabetic patients were cardiovascular whereas 5.5% were ophthalmologic. This is compared with only 4.3% and 3.3% of surgeries, respectively, in nondiabetic patients [2]. Procedures specific to diabetic complications include ophthalmologic procedures (cataract extraction and vitrectomy), limb amputation, renal transplantation, and coronary artery bypass grafting (CABG) [3]. Whether the surgery is being performed for a diabetic complication or is unrelated to diabetes, the presence of one or more of the complications of diabetes increases the perioperative risk and prolongs hospitalization. The average diabetic patient will spend 30% to 50% more time in the hospital postoperatively than a nondiabetic patient undergoing the same procedure, regardless of the surgical outcome [4].

Therefore, patients with diabetes mellitus need careful preoperative assessment to identify previously unknown complications or stabilize those

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that are known before undergoing the stress of surgery. This assessment includes detecting occult coronary artery disease, peripheral vascular disease, renal insufficiency or autonomic insufficiency. Naturally, diabetic patients must then undergo appropriately aggressive glycemic management perioperatively.

The pathophysiology of type 1 diabetes mellitus and the endocrine stress response

Type 1 diabetes is believed to be mediated by progressive T-cell mediated immune destruction of the β cells of the endocrine pancreas. Cytotoxic T cells and T-cell products, such as interferon-α and tumor necrosis factor-α (TNFα) are believed to induce this destruction. Islet cell antibodies and antibodies directed against insulin and GAD65 (an antibody to a specific β cell protein product) are present in 70% or more of type 1 diabetics. The frequent coexistence of other autoimmune endocrine phenomena within the same patient, most commonly thyroid disease, is further evidence of an autoimmune diathesis [5]. The destruction is characterized clinically by the complete cessation of insulin production.

Patients with type 1 diabetes mellitus usually require physiologic amounts of insulin in the unstressed state. A major surgical procedure, however, causes the release of catecholamines, glucagon, cortisol, and growth hormone. These counterregulatory and stress hormones induce insulin resistance, glycogenolysis, and gluconeogenesis causing hyperglycemia within the first 2 to 4 hours after the surgical incision [6]. Often this results in higher doses of insulin than usually required as an outpatient. Furthermore, in the absence of sufficient insulin and especially in the presence of increased glucagon and catecholamines, there is a tendency toward ketone production. Ketones substitute for glucose as a metabolic substrate for cerebral function.

Each of the counterregulatory hormones contributes to hyperglycemia in a diabetic patient undergoing surgery through overlapping mechanisms. Glucagon causes direct suppression of insulin secretion along with hepatic glycogenolysis and gluconeogenesis. It is also considered the primary inducer of ketogenesis among the catabolic hormones. Epinephrine stimulates glucagon production but also directly increases glycogenolysis and gluconeogenesis in the short-term, and impairs glucose tissue use in the long run. Cortisol impairs insulin binding to its receptors thus decreasing glucose use, and increases gluconeogenesis, proteolysis, and lipolysis—the latter contributing to ketone formation. Finally, growth hormone increases insulin resistance with the resultant impairment of glucose use and stimulates hepatic gluconeogenesis [7]. These effects may be compounded by metabolic acidosis (from either ketosis or lactic acid generation in a septic or

hypotensive patient) that produces further decreases in peripheral tissue sensitivity.

Preoperative evaluation and the effects of diabetic comorbidities

Because all diabetic patients undergoing surgery fall into a higher risk category than comparable patients without diabetes, they should be assessed thoroughly for presence or stability of cardiovascular, renal, and neurologic disease. In addition, routine laboratory screening studies should be done to exclude electrolyte, renal, hepatic or hematologic abnormalities.

Most importantly, it should be remembered that coronary artery disease can manifest at a young age or atypically in the patient with type 1 diabetes mellitus. There should be a low threshold for evaluating symptoms, such as dyspnea or chest discomfort at rest, or unilateral extremity, and neck or jaw discomfort (with or without exertion). Asymptomatic diabetic patients who are sedentary, especially if other cardiac risk factors are present such as hypertension, hyperlipidemia, tobacco use, or family history of cardiac disease, should undergo cardiac imaging/stress testing to exclude potential occult coronary artery disease before general anesthesia because a routine EKG is insufficient to detect silent coronary artery disease. Should significant disease be discovered, it may be necessary to perform angioplasty or coronary artery bypass surgery before an elective surgical procedure. Even if stress testing is negative, a patient who has had diabetes for more than 15 years (especially if control has been suboptimal) or other cardiac risk factors should be strongly advised to consider β-blockade perioperatively for its known cardioprotective benefits [8].

Particular attention should be paid if renal insufficiency is present because these patients may have increased sensitivity to IV fluids and a prolonged half-life of insulin, raising the risk for hypoglycemia. This mandates closer monitoring of glucose levels (hourly) than in patients without this diabetic complication.

Finally, evidence of peripheral and autonomic neuropathy should be sought. The presence of peripheral neuropathy within the desired operative field may make local anesthesia (which would otherwise be a desirable alternative to general anesthesia) less attractive due to increased risk for vascular damage and poor healing perioperatively [9]. Peripheral neuropathies also make decubitus ulcerations more likely in a patient who requires a prolonged bed rest. Intraoperative hypotension and perioperative cardiac arrhythmias are more frequent in patients with autonomic neuropathy and, thus, patients should be monitored closely for these potential complications in the operating room, followed by observation in a telemetry-monitored bed postoperatively for 24 to 48 hours. Hypoglycemic unawareness, another manifestation of autonomic neuropathy, can make insulin management challenging especially if the patient also has gastroparesis.

Detrimental effects of hyperglycemia

That chronic hyperglycemia causes serious long-term complications is a commonly accepted principle of outpatient diabetes management. In the in-patient setting, morbidity and mortality are also significantly increased in diabetic versus nondiabetic patients due to increased incidences of perioperative myocardial infarction, stroke, and renal insufficiency. In addition, serious infections (both at the surgical wound site and elsewhere from nosocomial sources) related to reduced wound healing and leukocyte function are common in postoperative diabetic patients. Hyperglycemia, particularly at the time it exceeds 200 to 250 mg/dL, seems to be causally related to these deleterious consequences. This is supported by studies that show that comparable postoperative complication rates between diabetic and nondiabetic surgical patients are achieved after near-normalization of blood glucose levels with intensive insulin regimens in patients undergoing cardiovascular surgery [10]. There is a growing body of evidence that acute hyperglycemia associated with critical illness is also detrimental, thus substantiating similar observations seen in the surgical patient. In-hospital mortality was noted to be significantly increased in a recent meta-analysis of hyperglycemia in nonsurgical patients (postmyocardial infarction) whether or not they had a known diagnosis of diabetes mellitus before the admission [11]. In fact, those who had "occult diabetes" (not previously known to be diabetic but with documented in-patient hyperglycemia) had a higher risk for death (nearly fourfold) compared with those with known diabetes, which carried a twofold risk compared with their nondiabetic counterparts. The reasons for this are unclear. Perhaps the patients with "occult diabetes" were inherently sicker or less likely to be treated as aggressively with insulin. Potentially damaging cytokines such as TNFα, may play a pathophysiologic role in this effect [12]. The study of Umpierrez et al [13] confirms these findings. They retrospectively evaluated over 2000 general medicine in-patients and found that 12% had new hyperglycemia and 26% had known diabetes. The in-hospital mortality after multivariate analysis for those with "new" hyperglycemia was increased over 18-fold compared with an almost threefold increase in the known diabetic group. Those with hyperglycemia but no previous diagnosis of diabetes were much less likely to be on insulin therapy (42%), whereas 77% of the known diabetics were on some type of insulin regimen though the type, route, and schedule were not reported.

There is no agreement on exactly how, and to what degree, to achieve glycemic control in the in-patient setting because of concerns over hypoglycemia. Large outpatient trials involving insulin-requiring patients with diabetes mellitus such as the Diabetes Control and Complications Trial demonstrate that the tighter the glycemic control, the higher the incidence of significant hypoglycemic episodes [14]. Avoidance of postoperative hypoglycemia is critical because surgical patients are exposed to general anesthetic agents and narcotic analgesics that by virtue of their sedative properties can

mask hypoglycemia and lead to significant strain on the cardiovascular or neurologic systems. Those patients on β-blocking agents have added risk because of suppression of classic hypoglycemic symptoms. Due to ethical issues, no studies have been done clearly defining the lower safe limit of glycemic control. A lower limit goal of 120 to 150 mg/dL seems reasonable, whereas a level as low as 100 mg/dL in otherwise healthy type 1 diabetics may be even more beneficial. The upper limit of glycemic control is better defined by studies looking at "intensive" versus "standard" management (ie, sliding scale subcutaneous insulin regimens given in response to high blood sugars) and suggests that levels above 200 mg/dL are likely to be detrimental in the perioperative patient [3,7,15–19]. Recently, Van Den Berghe et al [20] evaluated over 1500 surgical intensive care unit (ICU)admissions, 13% of whom had pre-existing diabetes mellitus. All patients were randomized to treatment of hyperglycemia with either intensive insulin therapy geared toward normalization of blood glucose (average glucose was 103 +/− 19 mg/dL or approximately 5.7 mmol/L), or with conventional insulin therapy given only at the time glucose levels exceeded 215 mg/dL and then with a target blood sugar of 180 to 200 mg/dL (10–11.1 mmol/L). Even though the conventional treatment group achieved a range of glycemic control of 120 to 186 mg/dL, their ICU mortality rate was 42% higher, in-hospital mortality 34% higher, and morbidity from sepsis, renal failure and anemia was also significantly increased compared with the intensive group.

The reasons for improved outcomes may be, in part, related to improved wound healing and reduced infection rates. Laboratory studies of wound healing rates and strength have been performed on rodents with alloxan-induced diabetes whose blood sugar ranged between 200 to 500 mg/dL. These studies have repeatedly shown numerous defects in wound healing in addition to decreased neutrophil number and function [21–24]. Decreased capillary volume, fibroblast numbers, collagen synthesis, and tensile wound strength and increased edema were found and these effects were reversible to some degree with insulin therapy [25].

There are conflicting reports, however, over how tightly glucose control needs to be to improve collagen synthesis or whether it is the early use of insulin at all, rather than the amount, that improves results [25]. When applied to human forearm abrasion studies in type 1 diabetics, leukocyte migration, collagen synthesis, and overall cellularity of the inflammatory response are reduced compared with nondiabetic controls. Only one study of leukocyte migration clearly monitored blood glucose, with a level of 160 to 240 mg/dL, making it difficult to assume that hyperglycemia played a primary role in all the defects outlined [26]. Large studies of postoperative diabetic patients have established that overall wound infection rates were significantly higher (approximately 10-fold in one study of 23,000 patients) than in their nondiabetic counterparts [27,28]. Though few of these earlier studies documented degree of glycemic control, J.A. Galloway and Shuman [24] found that one-third of their diabetic patients had a random blood

glucose measured at over 200 mg/dL. Hjortrup et al [29] found in a study which matched the control group to the diabetic group for confounding risk factors of poor wound healing (ie, age, weight, and other comorbidities) that there was no difference in risk for postoperative wound infections. The blood glucose range for their diabetic group was between 122 and 168 mg/dL and might have biased their study against finding positive results. Many studies have also been done on neutrophil function in vitro. Most of those neutrophil studies done in type 1 diabetics suggest that either phagocytosis or intracellular killing are impaired by hyperglycemia, though to variable degrees, and are significantly improved with tightening of glycemic control [30–33]. Other factors may impair neutrophil function in these patients. For example, their function cannot be normalized entirely even with complete normalization of blood glucose levels [31,33]. Furthermore, early leukocyte apoptosis has been demonstrated in diabetic patients and their nondiabetic relatives, suggesting that a potential underlying genetic defect plays a role [34,35].

As far as how to achieve this in-patient glycemic "hot spot" of 100 to 200 mg/dL, the common practices that have been tried include: (1) reduced dosing of subcutaneous intermediate-acting and short-acting insulin combinations with a background of IV dextrose infusion that can be titrated; (2) continuous IV insulin infusion with a separate IV dextrose infusion; or (3) using the glucose–insulin–potassium (GIK) combined infusion [36–41]. Each has its own set of advantages and limitations, as discussed later.

Preoperative preparation—making the transition to in-patient status

Ideally, the type 1 diabetic patient undergoing elective surgery should always have excellent glycemic control (an hemoglobin A1c of less than 7% or fructosamine of less than 310 uU/mL) before undergoing the procedure. Even if prior control has been sub-optimal, a renewed, more aggressive effort should be made by modifying the outpatient regimen in the days to weeks before the surgery.

Although unusual in today's cost-containing medical care environment, occasionally it may be best to admit a patient 24 to 48 hours before the planned surgery to improve glycemic control. Lum et al [42] reported that in 529 type 1 diabetic patients who received a renal transplant, the recipient and graft survival rates were equivalent to nondiabetic patients over the first two years post-transplantion. They attributed this, in part, to excellent perioperative management that resulted from their ability to tighten glycemic control as an in-patient before the day of surgery. Extrapolating to other elective surgeries, it may be argued that preoperative admission could be cost effective in other selected cases.

Whether the patient's preoperative glycemic control is achieved as an in-patient or outpatient, prevention of hypoglycemia and minimization of hyperglycemia are the two major postoperative goals. The authors

recommend that, if possible, continuous IV insulin be used perioperatively and that an internist or endocrinologist be consulted to co-manage all patients with type 1 diabetes undergoing surgery because many surgeons are either not trained or are disinterested in this form of management. One of the key additional considerations is determining whether or not the nursing and other support staff are capable of intensive management. Many medical facilities lack a sufficient number of properly trained personnel to support a continuous insulin infusion outside of an intensive care or postoperative unit. Thus, the age-old and ineffective practice of "sliding scale" short-acting subcutaneous insulin used reactively to blood glucose values over 200 to 250 mg/dL is still the most common regimen encountered [43,44].

If conditions do not allow a continuous insulin infusion to be used perioperatively, a few options arise. In 1979, Alberti and Thomas [45] recommended the use of an infusion combining glucose, insulin, and potassium (known as a "GIK infusion") based on their prospective study demonstrating its superiority to subcutaneous insulin injections in surgical patients. Some have noted that the GIK infusion can be cumbersome to modify if only one variable requires adjustment, whereas others find that the advantage to having insulin and glucose in the same infusion is that it minimizes the risk for either iatrogenic hyper- or hypoglycemia [46–48]. More recently, variable-rate insulin infusions with separate glucose infusions have shown similar superiority to subcutaneous insulin regimens. In one study however, this advantage seems most evident intraoperatively because comparable control was achieved pre- and postoperatively with either subcutaneous or IV insulin [47].

The type of anesthesia used is also a consideration when choosing the modality of insulin therapy. If the surgery is to be a minor one, of short duration, or requiring local anesthesia, epidural anesthesia or splanchnic blockade, there is no need for IV insulin infusion. For example, one study comparing intraoperative splanchnic nerve blockade, epidural anesthesia, and general anesthesia in patients undergoing gastrectomy demonstrated significant attenuation of elevations in the stress factors cortisol, glucose, free fatty acid, and norepinephrine in the splanchnic blockade and epidural groups [49]. This supports previous studies that have documented that unlike general anesthesia, epidural anesthesia does not cause an increase in counterregulatory hormones, precursors of gluconeogenesis, or ketones [50]. In all other cases, including minor surgeries that do require general anesthesia, most studies indicate that continuous IV insulin infusion is superior to the subcutaneous route [51,52].

The actual anesthetic agent used may also be a factor in perioperative insulin resistance. Isoflurane causes significant elevations in growth hormone and glucose, whereas enflurane anesthesia has no effect on insulin, cortisol, or growth hormone levels. It has also been reported that halothane is associated with mild hyperglycemia intraoperatively though the true clinical significance of this is not known [53].

Perioperative insulin and glucose dosing algorithms

There are multiple insulin algorithms that have been proposed by a variety of well-respected diabetologists, internists, and anesthesiologists. Their success has in common the consideration of the basic principles of management in a patient with type 1 diabetes.

The first principle is that type 1 diabetes patients always need a basal amount of insulin to prevent ketoacidosis. If the plan is to continue with subcutaneous insulin therapy throughout the perioperative period and the patient is taking NPH, Lente, Ultralente, or glargine at bedtime, then two-thirds or more of their bedtime dose should be given the night before surgery. On the morning of surgery, one half of their usual morning dose of NPH, Lente, (or glargine/ultralente if they take these long-acting insulins in the morning) should be administered (Table 1). On the other hand, if the patient uses an insulin pump as an outpatient, then the usual overnight basal insulin should be reduced by about 30% of the usual rate. No bolus insulin from bedtime until the morning of surgery should be given unless the blood sugar is over 200 mg/dL. On the morning of surgery, one of two options are available: (1) the patient continues insulin delivery through the insulin pump at the basal rate until it can be transitioned to the same starting rate in an IV insulin infusion; or (2) the insulin pump is discontinued 90 to 120 minutes after a subcutaneous injection of long-acting glargine insulin to cover the basal requirement over the ensuing 24 hours. The glargine dose is determined by multiplying the patient's average hourly basal rate by 24 (Table 1). Alternatively, if a continuous infusion of regular insulin is to be used perioperatively, the initial rate should be based on either the patient's total outpatient insulin requirement daily divided by 24 hours, or approximately 0.02 U/kg/h. A rough estimate of the starting insulin dose would be 1.4 U/h for a 70 kg individual. The insulin concentration in the IV fluids is typically 1 U/10mL (ie, 50 U of regular insulin in 500 mL of normal saline) or if the individual patient's insulin or fluid requirements dictate, a more concentrated solution can be used, (ie, 100 U in 200 mL to give 0.5 U/mL fluid). The insulin infusion in the subset of patients undergoing cardiovascular surgery differs from that of other elective procedures because the insulin requirements are usually two to six times higher (Box 1) [16,54].

This is based in part on a study by Thomas et al [6] in which insulin-dependent diabetic patients undergoing either a major general surgical procedure or CABG were compared with each other and to a control group of nondiabetic CABG patients. Perioperative blood glucose ranges and insulin/glucose ratios required to adequately control each of the two study populations were assessed. They found that peak insulin/glucose ratios were significantly higher in the CABG patients than the general surgery or control patients at 1 and 4 hours intraoperatively and were persistently elevated compared with the two other groups for at least the first 72 hours postoperatively.

Table 1
Transition from outpatient regimen to preoperative inpatient management

Outpatient regimen	Evening prior to surgery	Morning of surgery	Immediate preoperative period (at time of hospital admission)
SQ NPH + regular insulin	Give two-thirds of PM or HS N and two-thirds of PM R	Give half of AM N; hold all R	Start IV D5W at 100 mL/h and titrate according to the IV glucose alogorithm (Table 4). Monitor capillary blood glucose and give additional SQ R, LP, or A at Q 4 h as needed based on the nomogram in Box 2.
SQ Glargine + lispro or aspart insulin	Give two-thirds of G HS and 100% of PM L or A	Hold all insulin	Start IV D5W at 100 mL/h and titrate according to the IV glucose algorithm (Table 4). Monitor capillary blood glucose and give additional SQ lispro or aspart at Q 4 h as needed based on the nomogram in Box 2.
Insulin pump option # 1	Give 70% of basal insulin rate, two-thirds of PM bolus rate	Give 70% basal insulin rate; hold all boluses	Start IV D5W at 100 mL/h Give a Glargine SQ dose Q 24 h equivalent to the outpatient insulin pump basal rate × 24 h (should be close to 50% of total daily insulin requirement) Discontinue the SQ insulin pump 1–2 h after giving the Glargine dose.
Insulin pump option # 2	Same as above	Same as above	Start IV D5W at 100 mL/h. Disconnect outpatient subcutaneous insulin pump. Start IV insulin infusion at the same hourly rate as the SQ pump basal rate.

Abbreviations: A, aspart insulin; AM, prebreakfast; G, glargine insulin; HS, at bedtime; IV D5W, intravenous 5% dextrose in water; LP, lispro insulin; N, NPH insulin; PM, predinner; Q, every; R, regular insulin; SQ, subcutaneous.

Table 2 compares the glucose to insulin ratios in a classic study of IV insulin and glucose infusions used in noncardiac surgery patients versus a protocol that has been used successfully in acute myocardial infarction patients and CABG patients perioperatively [48,55,56]. Both types of infusions are efficacious in the appropriate setting. They report rapid

Box 1. IV insulin protocol

Preparing the infusions

Start IV 5% dextrose in 0.45% sodium chloride at 100–150 mL/h to provide a minimum of 5–7.5 g of glucose/h with 20 mEq/L KCl added to each liter or given by separate infusion as needed based on every 2–4 hours serum potassium levels.

The standard insulin concentration used is 0.1 U/mL or 50 U in 500 mL of saline. A more concentrated solution of 100 U in 200 mL, giving a concentration of 0.5 U/mL (5 U/10 mL) may be used.

Flush the IV tubing with 25–30 mL of solution before each infusion.

Monitoring

Capillary blood glucose monitoring should be done every hour from initiation of the insulin infusion until postoperative stability of glucose levels has been maintained within the target range of 120–180 mg/dL for at least 4–6 hours.

Note: Frequency of testing should be increased to every 30 minutes during cardiopulmonary bypass or during titration of vasopressor agents.

Once stable, the monitoring can be reduced to every 2–4 hours until transition back to a subcutaneous regimen is appropriate.

Initiating the insulin infusion

Start the insulin infusion at either 0.02 U/kg/h (1.4 U/h in a 70-kg patient 2 or 14 mL/h of 0.1 U/mL) or based on the patient's total daily insulin (TDI) requirement divided by 24 hours to get the hourly rate. Increased starting infusion rates are needed in the following situations:

CABG. . . . . 0.06 U/kg/h
Steroid-dependence (high-dose). . . . . 0.04 U/kg/h
Severe infection. . . . . 0.04 U/kg/h

achievement of target blood glucose between 120 to 180 mg/dL within hours of starting, and no clinically significant hypoglycemia or other adverse outcomes [48,55,56]. For cardiovascular surgery, the authors recommend starting the insulin infusion at 0.04 to 0.05 U/kg/h (~2.5–4 U/h) and then adjusting as indicated in Table 3 [36].

The second component of management is the provision of carbohydrate in the form of glucose to protect against hypoglycemia and to provide caloric substrate to prevent ketone formation. Dextrose is given as a 5% solution in 0.45% saline and run at 100 to 150 mL/h or approximately 5 to

Table 2
Insulin/glucose recommendations in noncardiac versus cardiac patients

	WATTS PROTOCOL (separate insulin and glucose infusions) Infusion #1: 5% dextrose solution at 100 mL/hr 0.45% saline (fixed) Infusion #2: insulin at 1.5 U/h starting rate	DIGAMI PROTOCOL (GIK) GIK Infusion: 5% dextrose + 80 U insulin + 40 mEq/L KCI in 500 mL water run at 30 mL/h starting rate
Blood glucose values	Hourly rate	Hourly rate
> 240 mg/dL	5 g glucose/2.5 U insulin (2 g/U)	1.8 g glucose/6.0 U insulin (0.3 g/U)
181–240 mg/dL	5 g glucose/2.0 U insulin (2.5 g/U)	1.65 g glucose/5.5 U insulin (0.3 g/U)
121–180 kg/dL	5 g glucose/1.5 U insulin (3.3 g/U)	1.5 g glucose/5.0 U insulin (0.3 g/U)
80–120 mg/dL	5 g glucose/1.0 U insulin (5 g/U)	1.2 g glucose/4.0 U insulin (0.3 g/U)
< 80 mg/dL	Hold insulin	Hold infusion

Data from Refs. [48,55,56].

7.5 g of glucose per hour. The average postabsorptive steady-state hepatic glucose production in an adult on a regular diet is 8 g/h, and the average insulin dose required to dispose of 8 g of glucose is 1 U of insulin [16]. This can then be titrated downward based on the patient's inherent balance of hepatic glucose production versus glucose disposal. An example of this is given in Table 4. Higher concentrations of dextrose can also be used at lower infusion volumes to accomplish the same goal if a patient is volume sensitive as a result of renal failure or congestive heart failure.

Supplemental insulin may be required and can be administered in a variety of ways depending on the basal mode of insulin delivery chosen from earlier information. For those on subcutaneous intermediate or long-acting insulin, ultra-short acting lispro insulin or insulin aspart may be given subcutaneously on a sliding scale targeted to a blood glucose goal of 120 to 200 mg/dL. For those on a continuous insulin infusion system, the infusion can be adjusted upward or downward based on the desired blood glucose goal (Table 3).

Supplemental potassium is often needed during insulin and glucose infusions, because insulin drives potassium intracellularly. Therefore, 20 mEq/L of potassium chloride can be added to the IV infusion of glucose or insulin (as in the "GIK" infusion) or separate supplementation can be given by IV as needed.

Monitoring glucose in the perioperative type 1 diabetic patient

Bedside blood glucose monitoring up to hourly pre- and intraoperatively is essential to using these insulin algorithms safely and effectively. Blood

Table 3
Intravenous insulin protocol—ongoing infusion management

	Infusion rate					
Glucose level	1–3 U/h	4–6 U/h	7–9 U/h	10–12 U/h	13–16 U/h	>16 U/h
Below desired range (< 120 mg/dL)						
< 60 mg/dL (< 3.3 mmol/L)	Hold insulin infusion and give 25 mL of 50% dextrose IV push; then recheck blood glucose level in 30 min. When glucose >120 mg/dL restart infusion 50% lower.					
60–80 mg/dL (3.3–4.5 mmol/L)	Hold insulin infusion and give 25 mL of 50% of dextrose IV push; then recheck blood glucose level in 30 min.					
	When glucose > 120 mg/dL, restart infusion 50% lower.	When glucose > 120 mg/dL, restart infusion 2 U/h lower.	When glucose > 120 mg/dL, restart infusion 3 U/h lower.	When glucose > 120 mg/dL, restart infusion 4 U/h lower.	When glucose > 120 mg/dL, restart infusion 5 U/h lower.	When glucose > 120 mg/dL, restart infusion 6 U/h lower.
81–120 mg/dL (4.6–6.7 mmol/L)	Hold insulin infusion. When glucose > 120 mg/dL, restart infusion 50% lower.	Decrease infusion by 2 U/h	Decrease infusion by 3 U/h	Decrease infusion by 4 U/h	Decrease infusion by 5 U/h	Decrease infusion by 6 U/h
Within the desired range (120–180 mg/dL)						
121–180 mg/dL (6.8–10 mmol/L)	No change unless glucose level continues to decrease over 3 consecutive measurements.					
	If decrease occurs, lower insulin infusion by 1 U/h. (0.5 U/h if starting at 1 U/h)			If decrease occurs, lower insulin infusion by 2 U/h.		

	1–1.5 U/h	2.0–9.0 U/h	10.0–20.0 U/h	> 20 U/h
Above the desired range (> 180 mg/dL)				
181–200 mg/dL (10.1–11.1 mmol/L)	Increase infusion by 0.5 U/h	Increase infusion by 1 U/h	Increase infusion by 1.5 U/h	Increase infusion by 2 U/h
201–240 mg/dL (11.2–13.3 mmol/L)	Increase infusion by 0.5 U/h	Increase infusion by 1 U/h	Increase infusion by 2 U/h	Increase infusion by 3 U/h
241–300 mg/dL (13.4–16.7 mmol/L)	Increase infusion by 1 U/h	Increase infusion by 2 U/h	Increase infusion by 3 U/h	Increase infusion by 4 U/h
> 300 mg/dL	Increase infusion by 2 U/h	Increase infusion by 3 U/h	Increase infusion by 4 U/h	Increase infusion by 5 U/h

Adapted from Brown G, Dodek P. Intravenous insulin nomogram improves blood glucose control in the critically ill. Critical Care Medicine 2001;29(9):1714–9; with permission.

Table 4
IV glucose (5% dextrose) algorithm

Capillary blood glucose measurement (every hour intraoperatively, every 1–2 hours in immediate pre-/postoperative period)	IV 5% dextrose rate
< 100 mg/dL	150 mL/h
101–150 mg/dL	75 mL/h
151–200 mg/dL	50 mL/h
> 200 mg/dL	Keep vein open

glucose should be monitored at least every 2 to 4 hours overnight and then every 1 to 2 hours preoperatively. The continuous insulin infusion should be started at least 2 hours before surgery, if not earlier, to allow titration and stabilization before entering the operating room. As soon as the insulin infusion is begun, blood glucose values should be measured hourly. Intraoperatively, the blood glucose should be checked hourly (or every 30 minutes in patients undergoing cardiovascular procedures) regardless of the mode of delivery of the insulin, because the IV dextrose can be titrated as needed to prevent hypoglycemia in either situation. Postoperatively, initial monitoring should continue every 1 to 2 hours, but once stabilized both modalities can be monitored every 1 to 4 hours until transition back to an outpatient regimen is appropriate. Spot urine glucose monitoring, which formed the basis of the insulin sliding scales of the past, is not a reliable indicator of true blood levels and is not recommended [57]. Urine ketone measurement is indicated in a patient with type 1 diabetes if hyperglycemia persists at greater than 250 mg/dL—usually an issue in more critically ill patients. Routine screening of ketones is not necessary otherwise.

We anticipate that now that the technology for a portable subcutaneous continuous blood glucose monitoring (CBGM) device is available, it will be adapted for use in the operative and postoperative setting. This should revolutionize perioperative management in providing the basis for a user-friendly artificial endocrine pancreas or "closed-loop system" of insulin and glucose management. Such systems (eg, Biostator ®, Miles Science Instruments, Elkhart, Indiana) are not a new concept but have up until now been invasive, temperamental, labor intensive, and cumbersome and as a result rarely used except in the research setting [58,59].

Postoperative care and discharge planning

Theoretically, postoperative care for a type 1 diabetic patient may consist of simply advancing the diet slowly from clear liquids to full liquids and on to a solid food diabetic meal plan (hopefully somewhat similar to that prescribed as an outpatient), then beginning a subcutaneous or insulin pump

dose based on the outpatient regimen to complement what is being eaten. These assumptions typically prove to be incorrect for several reasons. First, the typical hospital diet usually underestimates the individual's caloric needs either due to poor appetite during surgical recovery or to the failure to provide comparable calories to that consumed at home. Second, if the patient has had suboptimal glycemic control as an outpatient, the outpatient insulin regimen is unlikely to be a good estimate of the true requirement even in the normal unstressed state. Finally, the stressors of the surgery may only have gradually resolved requiring a larger insulin dose at the time of discharge compared with the usual. Under these circumstances, using the in-patient daily dose requirement to calculate a new insulin regimen for discharge may be the most appropriate solution. Alternatively, the patient's insulin requirement may be almost identical to the outpatient dose and schedule. The preoperative outpatient dose can be checked against the patient's most recent 24-hour insulin requirement as an in-patient (with stable dietary intake) to confirm adequate dosing postoperatively and at discharge.

The discharge insulin dose can be determined by totaling all the insulin (long, intermediate, and short/rapid-acting) given over the last 24 hours (or an average 24-hour dose over several stable postoperative days). The total long or intermediate-acting insulin dose the patient requires per day will be half of this total and the rest will be the short/rapid-acting dose requirement. If the patient is on a twice-daily intermediate-acting insulin (NPH or Lente), two-thirds of this is given in the morning and one-third at bedtime. Insulin glargine, the newest long-acting formulation of subcutaneous insulin, can be used instead of the intermediate-acting insulin to provide for basal insulin needs. Glargine is preferred to ultralente insulin because of its flatter insulin delivery profile [60]. Glargine is usually given once daily at bedtime but at 80% of the calculated basal insulin requirement. Glargine occasionally must be split into two doses (about 12 hours apart) but it should be noted that it cannot be mixed in the same syringe with short/rapid-acting insulins.

If the patient had been on an insulin pump before surgery, the pattern of basal rate delivery should be reconstituted although the total amount delivered as basal insulin may differ in the immediate postoperative days for reasons noted earlier. Similarly, the bolus doses, which should total the remaining one-half of the daily insulin use, may differ in amount from the preoperative boluses but should reflect the preoperative pattern of distribution. If the patient had been bolusing because of carbohydrate counting plus a high blood sugar correction dose, this may be resumed at the time the patient has stabilized postoperatively (Box 2) [61]. The guidelines for a correction bolus may change based on the total daily insulin dose using the ''rule of 1500'' (Box 3) [61].

A follow-up visit with an internist or endocrinologist should be scheduled within two weeks of discharge (or sooner if the blood glucose levels are routinely exceeding 200 mg/dL).

Patients that require intensive care immediately postoperatively or after complications that develop later in the hospital course should always be placed on IV insulin with titration similar to that outlined above in the perioperative setting. This allows the greatest flexibility and safety in a potentially unstable scenario. Confounding factors in these circumstances may include the introduction of enteral or parenteral nutrition or the addition of pressor agents that can severely worsen hyperglycemia. The infusion of norepinephrine, for instance, can raise the insulin requirement 10-fold or more depending on the dose used. Subcutaneous delivery of

Box 2. Regular, lispro, or aspart insulin nomogram: the rule of 1500

Calculate the patient's
ISF[a] by compiling their total daily insulin requirement (TDIR) and dividing this total into 1500:

1500 ÷ TDIR = ISF

Use the ISF to construct a tailored sliding scale for the patient beginning above 200 mg/dL (since below this value the IV glucose algorithm will be in effect).

Example

Patient A has a current total daily insulin requirement of 50 Us. The patient's ISF would be calculated as follows:

1500 ÷ 50 = 30 mg/dL

The patient's sliding scale would then be constructed in 30 mg/dL increments per 1 U of insulin, starting at capillary blood glucose (CBM) value above 200 mg/dL:

CBM	Insulin dose
201–230 mg/dL	1 U
231–260 mg/dL	2 U
261–290 mg/dL	3 U
291–320 mg/dL	4 U
321–350 mg/dL	5 U
351–380 mg/dL	6 U
381–410 mg/dL	7 U

[a] The insulin sensitivity factor (ISF) is the incremental fall in blood sugar that can be expected from each U of insulin in an individual patient.

Data from Davidson PC. Bolus and supplemental insulin. In: Fredrickson L, editor. The insulin pump therapy book. Los Angeles: Minimed Inc.; 1995. p. 65–8.

Box 3. Calculating a meal bolus of insulin for the subcutaneous insulin pump

Meal bolus dose = carbohydrate dose + correction factor dose
Carbohydrate dose = total carbohydrate (g) × insulin/carbohydrate ratio[a]
Correction factor insulin dose = (actual blood glucose measurement−goal blood glucose) ÷ ISF (defined in Table 5)

[a] Insulin/carbohydrate ratio usually 10–20 g/U of insulin, tailored to individual patient and individual meal requirements.

Data from Davidson PC. Bolus and supplemental insulin. In: Fredrickson L, editor. The insulin pump therapy book. Los Angeles: Minimed Inc.; 1995. p. 65–8.

insulin in the hypotensive patient receiving pressors is unreliable because of variable tissue perfusion. This further exposes an already insulinopenic patient to the development of ketoacidosis. Alternatively, patients in an ICU setting have a greater chance of acute hepatic or renal failure, which can impair glycogenolysis and gluconeogenesis or prolong the half-life of insulin, respectively, leading to life-threatening hypoglycemia.

At the time the patient on a continuous IV insulin infusion is ready to be transitioned to a subcutaneous regimen, it is critical to be aware of the need to begin the subcutaneous insulin before discontinuing the infusion. One of the most frequent errors in postoperative insulin management is the premature discontinuation of IV insulin infusions leading to severe hyperglycemia over the subsequent 4 to 24 hours. The amount of overlap of subcutaneous and IV insulin depends on whether an intermediate or long-acting insulin will be used alone (ie, in the setting of continuous enteral nutrition) or in combination with a short-acting insulin. If regular insulin plus a longer-acting insulin are be given together, then the infusion can be discontinued approximately 30 to 45 minutes later. If insulin lispro or insulin aspart is to be used as the short-acting agent, then the infusion can be turned off after approximately 15 to 30 minutes. If NPH, lente, or glargine is given without a rapid- or short-acting insulin, the infusion should not be stopped for 90 to 120 minutes to allow for onset of the subcutaneous insulin. If short or rapid-acting subcutaneous insulin is used, of course, a meal should also be given within the same timeframe as discontinuation of the insulin infusion.

Special scenarios

Urgent and emergent surgery

Fortunately, few conditions require emergent surgery and most, such as acute appendicitis or gangrene requiring amputation of an infected limb,

can be delayed for 4 to 6 hours to allow the patient to be hydrated, have an IV insulin infusion begun and titrated, and electrolytes stabilized. If significant hyperglycemia is present (> 250 mg/dL), diabetic ketoacidosis (DKA) should be excluded by anion gap calculation, arterial blood gases, and testing the urine and serum for the presence of ketones. If present, DKA should be reversed using large volumes of normal saline infusion and initiation of the IV insulin infusion at 0.1 mg/kg/h after an initial 0.1 mg/kg bolus. Potassium, magnesium, and phosphate should be monitored at least every two hours and replaced aggressively as indicated. At the time the acidosis is corrected and glucose levels fall below 250 mg/dL, then 5% dextrose infusion should be started as described earlier for elective procedures. The patient is then ready to proceed to the operating room with continued hourly glucose monitoring and every 2-hour serum electrolyte evaluation and replacement as required.

Cardiopulmonary bypass surgery

Diabetic patients have a significantly higher incidence of coronary artery disease than those without diabetes and better survival with CABG compared with angioplasty [62,63]. Therefore, it is reasonable to expect that this type of surgery will be encountered within the lifetime of many patients with type 1 diabetes. This type of surgery may produce severe hyperglycemia for several reasons. First, the cardiopulmonary bypass (CPB) technique uses large volumes of dextrose containing solutions (such as Hartmann's solution) to prime and perfuse the pump. Second, the hypothermia achieved during the procedure causes hyperglycemia itself. This is postulated to be due to an increased ratio of hepatic glucose production to glucose use during the hypometabolic state and in the acute warming phase [64,65]. Third, hyperglycemia is exacerbated by the frequent use of pressor agents required to stabilize the patient perioperatively. Finally, hemodilution of circulating insulin may also make the patient insulinopenic [6,64]. The result may be marked hyperglycemia in nondiabetic and diabetic patients into the 400 to 500 mg/dL range.

The complications of hyperglycemia in this population of surgical patients can be severe. In a retrospective review of 60 patients with diabetes mellitus, Kuntschen et al [64] found significantly increased rates of supraventricular arrhythmias and low cardiac output states in the terminal "weaning phase" of CPB and postoperatively compared with 467 nondiabetics undergoing the same procedure. This was regardless of the severity of the diabetes. Kuntschen et al also prospectively studied 30 diabetic patients (10 of whom were insulin-dependent) and compared them to 10 nondiabetic controls undergoing CBP. They found that tight glycemic control in the patients with diabetes mellitus reduced the complication rate, including a decreased supraventricular arrhythmia rate, to the range of the control groups (or lower).

Kalin et al [10] prospectively evaluated 400 patients with type 1 and 2 diabetes undergoing cardiovascular surgery and compared their outcomes with 876 nondiabetic controls. Tight glycemic control with an IV insulin infusion throughout the perioperative period was achieved. The results showed that the hospital mortality was equivalent between the tightly controlled diabetic group and the nondiabetic controls. The contemporaneous records of the National Cardiac Surgery Database (NCSD) of perioperative hospital mortality in diabetic patients undergoing bypass surgery found a 46% higher mortality in diabetic patients undergoing bypass surgery compared with their counterparts without diabetes [38].

Enteral or parenteral nutrition

Enteral or parenteral feeding is often used in the postoperative period. Recent clinical experience suggests that at the time of choosing a formulation for a diabetic patient, a higher fat, lower carbohydrate, calorically-dense product may be beneficial in controlling hyperglycemia [66]. The comparable contents of a variety of commonly-used enteral formulations are shown in Table 5. Enteral feeding can be administered by bolus or continuous infusion (either throughout the day or only during the night). Subcutaneous insulin can be used in either case but the regimen must be tailored to the enteral feeding schedule. Those patients receiving bolus dosing should have a basal insulin, such as glargine provide about 50% of their insulin requirements and the remainder given as either short- or rapidly-acting insulin before each bolus. If an insulin bolus is given at night however, (after 9 PM) it should be initially begun at about 50% of the daytime bolus doses to reduce the possibility of nocturnal hypoglycemia. We recommend that blood sugar testing be performed at 3 AM if a bedtime dose of insulin is given simultaneously with an enteral feeding. Those patients receiving continuous enteral feeding may receive most of their insulin as intermediate-acting insulin divided into three or four equal doses or glargine as a single dose (or a half dose every 12 hours). In the circumstance of continuous enteral feeding, additional short- or rapidly-acting insulin given every 4 to 6 hours may be required if the blood sugar exceeds the target range. In those receiving bolus enteral feeding, this supplemental insulin dose should be added to that calculated as necessary to prevent the feeding-induced hyperglycemia. If a patient is on IV insulin, the infusion rate can be calculated based on the amount of carbohydrate to be delivered in the tube feeds per hour (approximately 12 to 22g/h based on 100 mL of solution, but may vary based on the liquid formula selected and the infusion rate desired) plus the basal expected hepatic glucose production. For every 7.5 to 10 g of carbohydrate, approximately 1 U of regular insulin is required to allow adequate glucose use and disposal in the nonstressed individual. The basal expected hepatic glucose production is about 8 g of glucose per hour, which, is covered by approximately 1 U of insulin [4]. ''Stress factors'' may increase

Table 5
Enteral formulations

Formulation	Osmolarity	Kcal/mL	Protein gm/L	Protein % Kcal	Carb gm/L	Carb % Kcal	Fat gm/L	Fat % Kcal	Na mEq/L	K mEq/L	Phos mM/L	Mg mEq/L
Alitraq (semi-elemental)	410	1	53	21	165	66	16	13	44	30	26	11
Nepro (renal)	635	2	70	14	223	43	96	43	37	27	22	9
Promote (high protein/fiber)	380	1	63	25	138	50	28	25	57	51	39	17
Osmolite HN (standard)	300	1.06	44	17	143	53	37	30	40	40	24	13
Ultracal (standard with fiber)	310	1.06	44	17	122	46	45	37	40	41	27	14
Sustacal (oral supplement)	650	1.01	61	24	140	55	23	21	40	54	30	16
Impact (immune-modulating)	375	1	56	22	132	53	28	25	46	36	26	11

Abbreviation: HN, high nitrogen.

the insulin needs by 3- to 5-fold due to increased hepatic glucose production, insulin resistance, and decreased glucose disposal brought on by the physiologic effects of postoperative complications ranging from mild (ie, urinary tract infection) to severe (ie, stroke, myocardial infarction, or sepsis). The insulin is titrated to reach a blood glucose goal of 120 to 200 mg/dL. If the patient is on enteral feeding for a more prolonged period of time and is not at significant risk for hypoglycemia based on prior history or continued medical instability, tighter control in the range of 100 to 150 mg/dL may be attempted.

When a patient requires total parenteral nutrition (TPN), significant hyperglycemia is likely because it avoids first-pass metabolism through the liver. This has been demonstrated by Park et al [67] in patients with type 1 and type 2 diabetes. The patients with type 1 diabetes required a substantial increase of 55 ± 18 U/day (up to 225% of their usual outpatient regimen). We recommend a separate continuous IV insulin infusion for maximum flexibility in controlling potentially severe hyperglycemia while avoiding hypoglycemia. Although it is convenient to add the insulin to the TPN bag, this should be reserved for later in the hospital course. Woolfson [68] demonstrated that a separate IV insulin infusion achieved good glycemic control (125–200 mg/dL) within 24 hours in 32 of 34 diabetic patients without a single episode of symptomatic hypoglycemia. Sajbel et al [69] also used a separate insulin infusion initially for patients on TPN with hyperglycemia, then switched to adding insulin to the TPN bag once control within the desired range of 100 to 250 mg/dL was achieved. With this method, he reported success on the separate insulin infusion 73% of the time with only two isolated episodes of mild hypoglycemia in a single patient. He also noted a significant cost savings by separating the insulin titration from the TPN and thus decreasing the total required TPN by an average of 7.3 L per patient.

The calculation of insulin doses in patients receiving TPN is similar to that used in enteral feeding. A basal rate of 1 U of regular insulin per hour is necessary for hepatic glucose output. In addition, insulin to cover the carbohydrate infused through the TPN per hour must be added. Standard TPN typically uses 25% dextrose solution, which at 100 mL/h would provide 25 g of carbohydrate per hour. Based on a need of 1 U of insulin for each 7.5 to 10 g of infused carbohydrate, an additional 2.5 to 3.5 U per hour would be needed. Thus, the total dose per hour would then be 3.5 to 4.5 U of regular insulin, or a total daily dose of 84 to 108 U of insulin [4]. If this proves adequate to stabilize the patient's glycemic control for greater than 24 to 48 hours, 35 to 45 U of insulin can be added to each 1000 mL of the TPN infusion instead of using a separate insulin infusion.

Glucocorticoids and management of hyperglycemia

Glucocorticoids are frequently used in the perioperative setting and patients with type 1 diabetes mellitus are particularly vulnerable to their

complications. Perioperative conditions for which these drugs are used in particularly high doses include neurologic conditions, such as head trauma, intercranial malignancy, or recovery from neurosurgical procedures. Patients who have received a renal or other organ transplant almost always require high dose short-term corticosteroid treatment in conjunction with other potent immunosuppressive agents. In addition, patients with type 1 diabetes mellitus who may be on chronic corticosteroid treatment for pulmonary or rheumatologic diseases (in doses of prednisone greater than 7.5 mg/day, dexamethasone greater than 0.75 mg/day, or hydrocortisone greater than 30 mg/day) and who require surgical intervention need to be placed on stress doses of corticosteroids perioperatively to prevent adrenal insufficiency. Usually this is about 2 to 3 times the outpatient dose.

Glucocorticoids have a myriad of direct and indirect effects on the actions of insulin. Steroids directly inhibit peripheral adipose and muscle tissue binding and uptake of insulin. They alter insulin receptor and postreceptor functions on hepatocytes and adipocytes, especially soon after initial exposure to corticosteroids. Hepatic function is also modified by stimulating gluconeogenesis. The net effect is worsening insulin resistance.

Management of a steroid-dependent in-patient, especially one on high or tapering doses, is ideally done through the use of a continuous variable-rate IV insulin infusion. If this is not possible or the patient is already on a stable dose of corticosteroid, subcutaneous insulin may be used safely with close medical supervision to allow fine-tuning. The dynamics of the steroid effect on plasma glucose should be kept in mind when dosing insulin in these patients. The most significant hyperglycemia associated with steroids occurs postprandially and can be severe [70].

If the steroids are dosed once daily in the morning, the peak of hyperglycemia usually occurs 4 to 12 hours later with return to baseline overnight. Thus, fasting and postbreakfast hyperglycemia tends to be much less remarkable. Therefore, an insulin regimen based on prebreakfast blood sugars will often underestimate the requirement in a steroid-dependent patient. Twice-daily regular and NPH insulin (so-called ''split-mixed'' dosing) may be hazardous in the patient receiving a single dose of corticosteroid in the morning because the predinner NPH/Lente will be peaking just at the time the steroid effects are waning. Similarly, the pre-dinner dose of regular insulin, which is likely to be substantial because of the hyperglycemia induced by the morning steroid dose, will carry over into the early morning hours and put the patient at further risk for nocturnal hypoglycemia. Therefore, we prefer rapid-acting insulin (lispro or aspart) for the predinner injection and small doses of NPH/Lente at dinner (or bedtime [71]). On the other hand, regular insulin is preferable to lispro/aspart for the prebreakfast dose because the hyperglycemic effects of the morning corticosteroids do not occur for a few hours and using rapid-acting insulin at this time may cause midmorning hypoglycemia. Most importantly, NPH/Lente must be given in sufficient doses in the morning to

prevent afternoon and predinner hyperglycemia. This often requires large doses (often 90% of the total "basal" insulin dose) combined with regular insulin. In addition, it is usually necessary to use the regular insulin aggressively in the morning to prevent prelunch hyperglycemia.

Summary

Clearly, perioperative management of diabetic patients requires thorough preoperative evaluation and planning whenever possible. A firm understanding of the pathophysiology of type 1 diabetes mellitus, the metabolic stress response, and the interactions between various forms of insulin and other variables such as supplemental nutrition and glucocorticoids can greatly assist in achieving a positive outcome. Consultation with an endocrinologist, internist, or other primary care provider comfortable with managing type 1 diabetes patients is strongly recommended to assist in the details of in-patient care and overseeing of proper ancillary support. It may also be helpful to allow the patient to function as an active decision-maker in the coordination of care, especially because a large percentage of type 1 diabetes patients (particularly those who are on insulin pumps) are well-educated about their disease process and their own physiologic idiosyncrasies. This knowledge can save valuable time and effort toward achieving the ultimate united goal of avoiding perioperative morbidity and mortality by maximizing glycemic control.

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