Perioperative management of ambulatory surgical patients with diabetes mellitus

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Purpose of review

Patients with diabetes frequently present for ambulatory surgery concomitant with the rise in incidence of the disease. This review will examine recent evidence on glucose control, the harmful effects of hyperglycemia, fluctuations of blood glucose, and hypoglycemia, as well as treatments and medications utilized for type 1 and type 2 diabetes mellitus. Based on this evidence, a strategy for perioperative decision making for the diabetic patient undergoing ambulatory surgery will be presented.

Recent findings

New studies question the practice of intensive control of blood glucose in critically ill patients. Also, tight control of HbA1c levels in patients with type 2 diabetes may have associated cardiovascular risks. Glucose fluctuations and hypoglycemia may pose greater risks to patients than elevated glucose itself. New medications and insulin regimens make perioperative blood glucose control easier now than in the past.

Summary

The ambulatory anesthesiologist, with a dedication to low-impact practices and emphasis on rapid recovery, provides an ideal environment of care for the patient with diabetes. This review will examine issues and concerns with management of the patient with diabetes undergoing ambulatory surgery and address them in a step-wise strategy for care, including recommendations for perioperative insulin administration.

Keywords

ambulatory anesthesia, ambulatory surgery, diabetes, hyperglycemia, perioperative insulin

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Introduction

As the prevalence of diabetes mellitus surges in the world, more patients with diabetes present for ambulatory surgery. In the United States, 1.6 million new cases of diabetes are diagnosed each year and almost 8% of the population or 24 million patients carry a diagnosis of diabetes mellitus [1•]. Currently, 21% of adults 60 years of age or older have diabetes, and this number is expected to double by 2025 [2••]. This article will review the current literature and incorporate new concepts, regimens, and medications into a step-wise strategy for the care of the patient with diabetes undergoing ambulatory surgery.

Type 1 vs. type 2 diabetes mellitus

Although both type 1 and type 2 diabetes significantly alter glucose control, the underlying mechanisms are distinct. Type 1 diabetes arises from the auto-immune destruction of beta cells resulting in an absolute insulin deficiency [3••,4••]. Type 2 diabetes results from a progressive insulin secretory deficit in the setting of high insulin resistance and altered nutrient metabolism [3••,5•]. Prediabetes is a complex of impaired fasting glucose and impaired glucose tolerance [3••]. Type 1 patients are truly insulin-dependent, and this term should be reserved only for insulinopenic patients [6]. Type 1 patients experience more fluctuations in blood glucose and more episodes of hypoglycemia, and may develop diabetic ketoacidosis (DKA) with insulin deficiency. In contrast, patients with type 2 diabetes experience fewer blood glucose fluctuations and may reach a hyperosmolar state at very high blood glucose levels. Treatment of type 2 patients is multifaceted, beginning with diet control, progressing to one or more oral hypoglycemics, and/or combination with insulin.

Outpatient glucose control

Three recent trials examining cardiovascular events in type 2 diabetes outpatients treated with oral medications and/or insulin have questioned the benefits of tight glucose control [7•–10•]. In the ACCORD trial, patients receiving intensive therapy, to reduce HbA1c less than 6.0%, suffered a high mortality rate, halting the study [8•]. For veterans, intensive therapy (median HbA1c = 6.9%) did not lessen cardiovascular complications and increased the risk of sudden death three-fold [9•]. The occurrence of severe hypoglycemia appeared to correlate with mortality in all three studies [10•].

In a study of patients with diabetes undergoing cardiac surgery, it was found that patients with poor glucose control, that is HbA1c more than 8.6%, had a four-fold increase in mortality and, for each 1% elevation of HbA1c, there was a significant increase in rates of perioperative myocardial infarction (MI) and sternal wound infection [11•].

Fluctuations in blood glucose

Recent data suggest that glycemic variability may be as important as absolute glucose values [12,13]. Acute changes in blood glucose levels have been proven to 'have detrimental biochemical effects' [14]. Oxidative stress, a major cause of macrovascular disease, is triggered by swings in blood glucose more than by sustained hyperglycemia. A minimization of the degree of glucose variability may be cardio-protective, and mortality may correlate more closely with blood glucose variability than mean blood glucose itself [4••,13,15••,16]. Similarly, the rapid decline in HbA1c achieved in type 2 outpatients in the ACCORD trial possibly contributed to the increased mortality noted in the study [17•]. Thus, it may be important to maintain stable control and avoid fluctuations in blood glucose perioperatively.

Perioperative hyperglycemia

Blood glucose increases significantly over the course of surgery and recovery [18] and may lead to more perioperative complications [4••,11•,19]. Stress is the primary source of perioperative hyperglycemia, followed by iatrogenic causes such as the discontinuation of hypoglycemic medications and insulin. Stress and fasting both increase insulin resistance and decrease insulin secretion [20]. The release of stress-related hormones inhibits glucose utilization and promotes gluconeogenesis [4••]. Hyperglycemia hinders immune function leading to increased risk of infection [3••,20,21•,22], promotes a pro-thrombotic state due to increased platelet aggregation and adhesiveness in the setting of endothelial dysfunction [2••,20,23] and impairs wound healing [6]. Glycosuria begins at a blood glucose of 180 mg/dl causing fluid shifts, dehydration, and electrolyte abnormalities [6,20,22]. Pre-existing diabetic complications such as gastroparesis and pulmonary dysfunction are worsened by hyperglycemia [24•]. Pulmonary complications are more frequent in patients with type 1 diabetes, especially those who are poorly controlled [19,25•]. Overall, the stress of surgery makes glycemic control challenging and places patients at risk of DKA or hyperosmolar state and other complications [2••–4••,21•,23,24•,25•].

Perioperative hypoglycemia

Fear of hypoglycemia under anesthesia has led many anesthesiologists to take a reactive approach to blood glucose control, leading to discontinuation of insulin and hypoglycemic medications. Hypoglycemia is a common event in patients with type 1 diabetes. Patients aiming for good control average two episodes of asymptomatic hypoglycemia each week and spend 10% of their time with blood glucose levels 50–60 mg/dl [26]. The Diabetes Control and Complications Trial showed an 18% increase in the risk of hypoglycemia with each 10% reduction in HbA1c [21•]. The threshold at which a patient experiences hypoglycemia is dynamic and varies with recent glucose targets [3••]. Hypoglycemia is normally corrected by reduction in insulin secretion and increased release of glucagon, epinephrine, growth hormone, and cortisol [3••,26]. Type 1 patients have an impaired release of counter-regulatory hormones, whereas type 2 patients do not, which explains why type 2 patients rarely encounter hypoglycemia, even when using insulin. Neurogenic symptoms of hypoglycemia, due to the perception of sympatho-adrenal activation, include sweating, elevated heart rate, and hunger. When the brain encounters low glucose levels, serious neuroglycopenic symptoms occur. Weakness, fatigue, confusion, and behavioral changes mimicking inebriation may lead to seizure, loss of consciousness, brain damage or death. Interestingly, geriatric patients experience fewer hypoglycemic symptoms [2••], and women respond less strongly to hypoglycemia than men [26]. Patients with poorly controlled type 2 diabetes may experience hypoglycemic symptoms at normal blood glucose levels [26], so one must be cautious with glucose correction in these patients.

Treatment of diabetes and implications for perioperative care

The overall goal of outpatient treatment is to control blood glucose in order to prevent diabetic complications. Maintenance therapies for type 1 and type 2 diabetes are discussed here in relation to their potential impact on perioperative care.

Oral and injectable hypoglycemics

Oral agents are the first step in the treatment of type 2 diabetes. Many patients are on multiple drugs with different modes of action to both effectively reduce blood glucose and minimize side effects [5•]. Insulin may be added to the regimen, although often delivered solely as basal insulin or in fixed-combination [21•]. Hypoglycemia in the perioperative period is possible with the insulin secretagogues, which promote endogenous insulin release, mainly the sulfonylureas and less so with glinides [2••,3••,27•]. Oral agents that do not cause hypoglycemia as sole therapy may do so in combination [5•].

The newest agents for type 2 diabetes are incretins, meant to mimic naturally occurring peptides released in response to carbohydrate or fat intake. These drugs are unlikely to cause hypoglycemia, unless combined with other drugs such as a sulfonylurea [21•,27•,28•]. This group includes the oral DPP-4 inhibitor (Januvia) and the injectables exenatide (Byetta) and pramlinitide (Symlim). Gastrointestinal side effects including nausea, vomiting, and delayed gastric emptying occur soon after initiation of therapy and usually resolve after 4–8 weeks of treatment.

Insulin

Basal–bolus maintenance regimens are commonplace and closely replicate physiologic insulin delivery [23]. Basal insulin replaces a diabetic patient's baseline insulin that would be produced during a fasting state [2••]. Skipping a meal while on basal insulin will not cause hypoglycemia [12], as all food including snacks must be covered with insulin boluses. The total daily insulin dose is divided approximately into a 50% basal component and 50% prandial boluses [12,23]. The basal–bolus regimen is delivered in two ways: by an insulin pump in a continuous subcutaneous insulin infusion or by injections of both a long-acting peakless insulin once or twice daily and ultra-rapid (usually) or regular boluses (rarely) with food intake. The basal insulin glargine is usually administered once daily, and detemir is administered once or twice daily. Both insulins have reliable prolonged absorption due to formation of microprecipitates and detemir also binds to albumin [21•]. When these insulins are utilized by patients with type 2 diabetes as a sole insulin, this is not basal dosing, and doses should be decreased perioperatively. If basal insulin exceeds 40–60% of the patient's total daily dose, hypoglycemia for a long period may be seen with fasting [2••,12].

The intermediate-acting neutral protamine Hagedorn (NPH), protamine, and Lente insulins are still commonly used. These insulins display a peak in activity, which can cause hypoglycemia in a fasting patient [2••]. Premixed insulins, primarily used for type 2 patients, combine both intermediate-acting and nutritional insulins in a convenient pen [21•]. None of these intermediate-acting insulins are considered as basal insulins, and require dosage adjustments for the perioperative period. An original insulin management table for ambulatory surgery patients is provided in Table 1 and described below. Alternatively, the algorithms that served as resource material for this table are also applicable to outpatient surgery patients [6,22].

Insulin pumps usually deliver an ultra-rapid-acting insulin. Modern pumps have multiple basal rates based on the time of day and activity level, variable bolus capability, and numerous safety features to prevent malfunction and excessive insulin delivery [12]. Although the decision to continue use of a pump intraoperatively is practitioner and institution specific [21•] and an off-label use, it is well tolerated when maintained at a basal rate and when secured away from the surgical field [29]. Recommendations to limit pump use to cases less than 2 h [12,21•,22] allows the patient to remain in reasonable control even if the pump is stopped inadvertently during the surgery.

Table 1 Maintenance insulin management for surgical outpatients: day of surgery dosing[a]

Insulin regimen	Dosing for early case	Dose adjustments for later case	During case in OR	Dosing in PACU	Instructions for home
Insulin pump (basal–bolus)	Maintain basal rate	Maintain basal rate	Maintain basal rate if possible	Maintain basal rate if possible; bolus without food	Resume usual rate + boluses without food
(Basal–bolus) Peakless basal dosing plus rapid acting without food (e.g. glargine, detemir)	No change in basal doses	No change	No change	No need	Back to usual dosing with rapid-acting boluses with meals
Intermediate-acting: single or multiple dose (e.g. NPH)	Hold morning dose until after case, or give percentage of dose[b]	Give percentage of dose based on time to first meal and next dose (Fig. 2)	No change	Give calculated percentage of insulin if necessary	Resume schedule if eating, careful with overlapping times
Peakless single or multiple dosing as sole insulin (e.g. glargine, detemir)	Same as intermediate-acting above	Same as above	No change	Give calculated percentage of insulin if necessary	Resume schedule if eating, careful with overlapping times
Fixed combination long and short acting (e.g. 70/30)	Hold morning dose or give percentage[b] [calculate amount of long-acting insulin (70%) as dose for multiple dose above]	Calculate amount of long-acting insulin (70%) as dose for multiple dose above and adjust	No change	Give calculated percentage of insulin if necessary	Resume schedule if eating, careful with overlapping times

OR, operating room; PACU, postanesthesia care unit.
[a] Correction of elevated glucose may be done with a subcutaneous dose of ultra-rapid-acting insulin as needed at any point in care.
[b] Calculated percentage insulin refers to dosing formula in Fig. 2.

Three ultra-rapid insulins are available: lispro (Humalog), aspart (Novalog), and glulisine (Apidra). These insulins are suitable for subcutaneous dosing during outpatient surgeries due to their fast, reproducible effects. Onset time is less than 15 min [30], the peak is at 30–90 min, and total duration is 3–4 h. The risk of hypoglycemia subsides at 90 min [22], a reasonable time frame to observe a patient in an ambulatory facility. Intravenous regular insulin acts in minutes and is gone in 30–40 min, resulting in rapid swings in blood glucose which may be undesirable [23,31]. Modern insulin analogs as well as highly knowledgeable and involved patients make perioperative glucose management easier now than in the past.

Intraoperative glucose control

Despite large numbers of diabetic surgical patients, there are scarce data on the impact of glucose control on routine ambulatory surgeries. Recent studies have focused on intensive control of blood glucose in critically ill patients. The NICE-SUGAR study [32••] of ICU patients found a reduction in mortality in the group whose blood glucose targets were less strict (blood glucose <180) than those tightly controlled (blood glucose 81–108), as well as fewer incidents of severe hypoglycemia. Two meta-analyses [15••,33] found no benefit in 90-day mortality or septicemia with intensive blood glucose control, but a five to six times greater risk of hypoglycemia. These publications have led to the current opinion that recommendations for intensive glucose control in critically ill patients are 'unjustifiably strong' [10•] and are not supported by the evidence [4••,15••].

Two recent studies investigated patients undergoing noncardiac surgery. In neurosurgical patients, perioperative glucose control decreased infection rates and ICU stays [34]. Glucose control with an insulin infusion was found to be superior to insulin boluses in reducing myocardial infarctions for patients undergoing vascular surgery [16].

A step-wise strategy for management of the ambulatory surgery patient with diabetes

Perioperative management of the diabetic patient is directed towards minimizing fluctuations in blood glucose level while avoiding hypoglycemia, hyperglycemia, and complications that hinder a return to a normal routine. A step-wise strategy for perioperative management of the ambulatory surgery patient with diabetes is presented in Fig. 1.

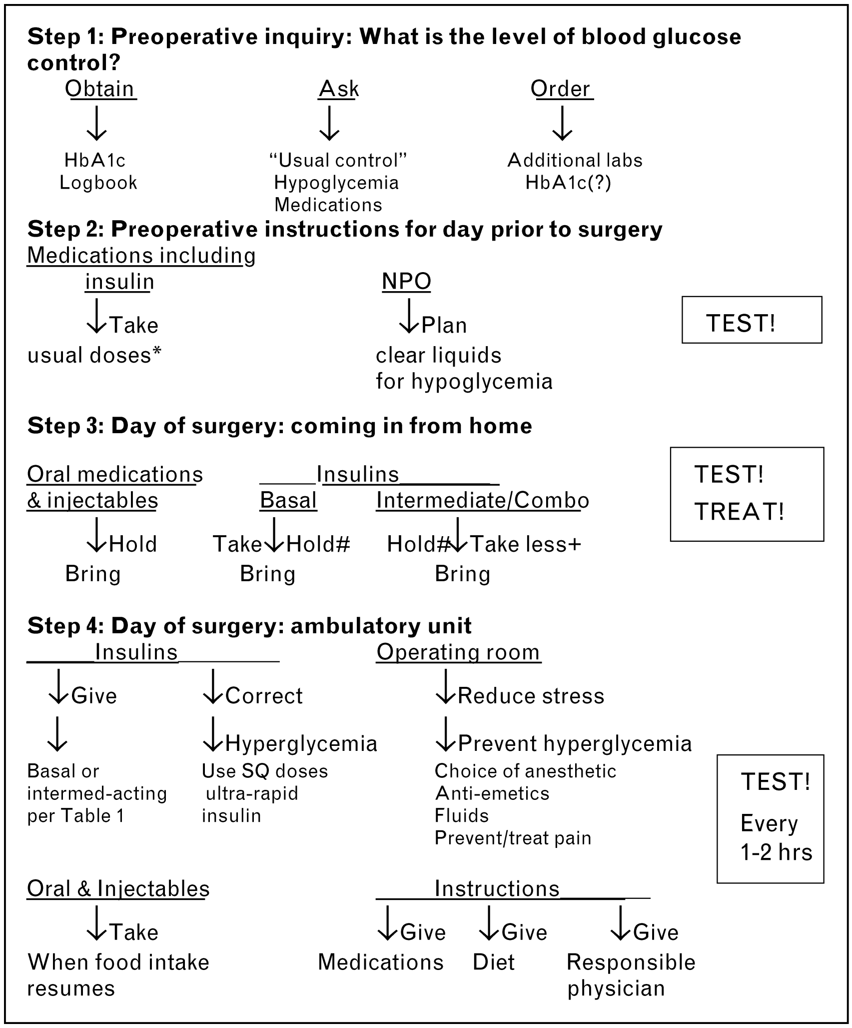
The first step is assessment of the patient's diabetes: type, medications, and usual level of blood glucose control. The patient's ability to understand and manage their diabetes, reliably test their blood glucose, as well as their motivation to maintain good control should guide perioperative treatment goals [1•]. The history should include the occurrence and frequency of hypoglycemia, the symptoms and blood glucose level where it arises, and presence of hypoglycemia unawareness [6]. Patients should be asked to what extent they are concerned about actual or possible hypoglycemia [26]. A recent HbA1c level can provide an indication of adequacy of glucose control [35] and is useful to obtain preoperatively. A look at a logbook or a spot glucose, however, provides limited information.

Step 2 involves instructions for the patient. Oral medications are usually dosed normally on the day prior to surgery. Likewise, long-acting or intermediate-acting insulin may be taken in usual doses while normal diet continues, or decreased by 20–30% in the setting of frequent nocturnal or morning hypoglycemia [6,29]. Planning for the treatment of hypoglycemia while NPO is important. The preferred method is consumption of 15–20 g of glucose [3••,26], which is repeated until blood glucose rises and symptoms resolve. Clear liquids suitable to treat hypoglycemia include sugary drinks, sodas or electrolyte solutions, and fruit juices. Glucose tablets or gels are usually particulate and should be avoided. Patients should be instructed to check blood glucose levels frequently while NPO, and carry hypoglycemia treatments while traveling to the facility.

On the day of surgery (step 3), type 2 patients should hold oral medications and injectables [2••,28•]. Basal insulin (as part of a basal–bolus regimen) may be given in full, and insulin pumps maintained at basal rates. Intermediate-acting and combination insulins may be held and brought with the patient, or dosed at home according to Table 1. Doses of long-acting insulins, such as glargine or detemir, taken as sole insulin, should be reduced to avoid hypoglycemia (Table 1).

At the facility (step 4), blood sugars should be checked every 1–2 h. Point-of-care glucometers are suitable for this purpose. When possible, patients with diabetes should be scheduled first in the day, to minimize disruption to their routine. For early morning cases, the full daily dose of insulin may be given after completion of the surgery [6], approximating a late awakening. Otherwise, intermediate-acting insulin is reduced by a fraction relating the period of fasting to the time to next dose, similar to that proposed by Jacober and Sowers [6]. Figure 2 describes the application of this new dosing formula for a sample patient. This insulin can be given prior to surgery if the time to the next meal is predictable, or on arrival in the postanesthesia care unit, as intermediate-acting insulins take several hours to lower blood glucose levels. For

Figure 1 Step-wise strategy for perioperative care of diabetic patients undergoing ambulatory surgery



Test!, May be done with point of care glucometer, by patient or hospital staff. Treat!, Hypoglycemia with clear liquids containing glucose 15-20gm. $*$, Usual doses of insulins may be taken if patient does not suffer from hypoglycemia while sleeping or in the morning. #, Morning insulins may be held on day of surgery and administered in ambulatory unit, either before or after surgery. $+$, The patient may be instructed to take less insulin at home prior to surgery based on guidelines in Table 1.

fixed-combination insulins, the amount of intermediate-acting insulin is calculated (e.g. 70% of 70/30 total dose) and is adjusted in the method illustrated in Fig. 2. However, one may need to substitute NPH for the protamine insulins only available in combination (e.g. lispro-protamine or aspart-protamine).

Correction of hyperglycemia in the perioperative period can be done safely and easily with subcutaneous doses of ultra-rapid-acting insulin, which has been proven as effective as intravenous regular insulin for treatment of DKA [30]. The patient is often the best source for the amount of bolus insulin needed to treat a particular blood glucose. Correction doses of 1–4 U of ultra-rapid-acting insulin per 50 mg/dl decrement of blood glucose have been suggested based on a patient's insulin sensitivity [23]. The 'rule of 1800' formula (Fig. 3) calculates the drop in blood glucose expected after 1 U of ultra-rapid-acting insulin [22] based on the patient's current total daily insulin dose. Caution, however, should be taken when administering multiple subcutaneous correction boluses, as 'stacking' the doses can cause hypoglycemia [12]. Subcutaneous doses of insulin can be administered by nurses or physicians, cause less severe swings in blood glucose, and provide good and safe control in the perioperative period approximating a patient's usual routine.

Anesthetic management should aim for a stress-free environment and a prompt return to normal life. One must consider diabetic complications in anesthetic care, such as gastroparesis or delayed gastric emptying, possibly due to injectable incretins [28•]. The prevention of pain and nausea and vomiting is paramount. Dexamethasone causes an elevation in blood sugars in diabetic

Figure 2 Adjustment of intermediate-acting insulin

Taking into account the time of fasting and time interval until next dose of insulin.

$$\frac{[\text{Dosing interval (hrs)} - \text{Hours of fast during interval}]}{\text{Dosing interval (hrs)}} = \text{fraction of intermediate-acting insulin to give}$$

Scenario 1: A patient undergoing knee arthroscopy. He will be eating normally by 10am after a minimally disruptive anesthesia technique. (He will miss three hours of normal food intake)

A. If the patient usually takes one dose of 24U of NPH at 7am daily:
(24–3)/24 = 21/24
He would receive 7/8 of his morning dose or 21U.

B.If this patient usually takes 24U twice daily at 7am and 7pm:
(12–3)/12 = 9/12
He would receive 3/4 of his usual morning dose or 18U.

Scenario 2: Pt B above is scheduled later in the day and is expected to eat at 1pm. He will miss 6 hours of food intake during dosing interval.
(12–6)/12 = 6/12
He would receive ½ of his usual morning dose or 12U, which should be given prior to surgery and BG checked frequently until eating normally.

Figure 3 'Rule of 1800'

1800 ÷ TDD = the mg/dl decrease in BS with each unit ultra-rapid acting insulin given

Scenario: patient takes total daily dose(TDD) of 60U of insulin:
glargine 30U qday, 7-8U of Lispro 4x daily with meals= 60U

How much will this patient's BG decrease with 1 U of Lispro?

1800 ÷ 60 = 30mg/dl decrease with each unit of insulin

patients and nondiabetic people [18]. The peak blood glucose occurs 120 min after dosing and correlates with HbA1c levels. Fluid replacement with isotonic solution should account for maintenance and insensible losses as well as fluid shifts due to glycosuria. Caution in patients with type 2 diabetes taking oral thiazolidinediones, as there is a risk of fluid retention and heart failure [3••,23,27•].

In the recovery room, the patient should receive any remaining insulin doses, as described in Table 1. Oral medications and injectables can resume with food intake. At discharge, patients need to be given specific instructions on medications and insulin, including treatment options for diet disruption, encouragement of blood glucose testing, and a responsible physician to contact with questions about their glucose management.

Conclusion

Ambulatory anesthesiologists provide the ideal environment of care for patients with diabetes, as usual practices are low impact and minimize stress. Despite seemingly complicated treatment strategies, remember that many patients with diabetes can provide valuable information about, and assistance with, their glucose management. This author agrees with Jacober and Sowers [6] that perioperative care of the patient with diabetes is 'more art than clinical science', but 'minimal disruption of the regimen tends to be the easiest course of management'.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 822).

1 • American Association of Clinical Endocrinologists and American Diabetes Association. Consensus statement on inpatient glycemic control. Diabetes Care 2009; 32:1119–1131.
This consensus document asks and answers specific questions about glycemic control in hospitalized patients. The authors cover recent evidence on glycemic control, including recommended glucose targets, methods of treatment, safety concerns and the transition to outpatient treatment, much of which is applicable to the outpatient surgery setting as well. The authors advocate the use of subcutaneous insulin for correction of hyperglycemia outside of the ICU.

2 •• Maynard G, O'Malley CW, Kirsh SR. Perioperative care of the geriatric patient with diabetes or hyperglycemia. Clin Geriatr Med 2008; 24:649–665.
An excellent review of perioperative care of the diabetic patient covers pathophysiology and medications as well as preoperative and intraoperative concerns, not solely applicable to the elderly patient. However, ambulatory surgery is not the focus of this article.

3 •• American Diabetes Association. Standards of medical care in diabetes – 2008. Diabetes Care 2008; 31 (Suppl 1):s12–s54.
These ADA standards of care provide a good review of the issues with patients with diabetes and current treatment options. Topics of interest to anesthesiologists in this article include the stress response to illness, hypoglycemia, diabetic complications, insulin regimens and oral medications.

4 •• Lipshutz AKM, Gropper MA. Perioperative glycemic control. Anesthesiology 2009; 110:408–421.
This excellent review includes a good description of stress and hyperglycemia due to surgery. It covers issues of intensive control in the operating room and ICU as well as risks due to glucose variability. The authors recommend that maintenance of blood glucose less than 150 mg/dl and reduction of variability is safe and effective in settings where intensive therapy is warranted.

5 • Bailey CJ, Day C. Fixed-dose single tablet antidiabetic combinations. Diabetes Obesity Metabolism 2009; 11:527–533.
A good review of oral medications concentrating on fixed combination preparations.

6 Jacober SJ, Sowers JR. An update on perioperative management of diabetes. Arch Intern Med 1999; 159:2405–2411.

7 • The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; 358:2560–2572.
Patients with type 2 diabetes in the ADVANCE collaborative study who were intensively controlled (HbA1c reduced to 6.5%) had a decreased incidence of nephropathy or microvascular disease, but did not experience fewer macrovascular events.

8 • The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group. Effect of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358:2545–2559.
The ACCORD study randomized over 10 000 patients with type 2 diabetes to either intensive therapy (target HbA1c <6%) or standard therapy (target HbA1c 7–7.9%). The intensive therapy group showed an increased risk of mortality and no decrease in cardiovascular events.

9 The Veterans Affairs Diabetes Trial. Glucose control and vascular complica-
• tions in veterans with type 2 diabetes. N Engl J Med 2009; 360:129–139.
In this large study of veterans with poorly controlled type 2 diabetes, intensive therapy (median HbA1c = 6.9%) was compared with standard therapy (median HbA1c = 8.4%) with oral medications and/or insulin. There were no significant benefits of intensive therapy on the incidence of major cardiac events, death or microvascular complications, but a higher incidence of hypoglycemia. The authors note that it may require 10 years of intensive treatment before a beneficial effect is detected for cardiac events in these patients with preexisting disease.

10 Skyler JS, Bergenstal R, Bonow RO, *et al.* Intensive glycemic control and the
• prevention of cardiovascular events: implications of the ACCORD, ADVANCE and VA diabetes trials: a position statement of the American Diabetes Association and a Scientific Statement of the American College of Cardiology Foundation and the American Heart Association. Circulation 2009; 119:351–357.
This position statement addresses the cardiovascular risks of tight control of HbA1c seen in recent studies of patients with type 2 diabetes such as the ACCORD and ADVANCE trials, and the implications of these findings on clinical care.

11 Halkos ME, Puskas JD, Lattoug OM, *et al.* Elevated preoperative hemoglobin
• A1c level is predictive of adverse events after coronary bypass surgery. J Thorac Cardiovasc Surg 2008; 136:631–640.
This prospective study found that patients presenting for coronary artery bypass graft (CABG) surgery with elevated HbA1c levels (>8.6%) had an increased mortality as well as a progressively greater risk of myocardial infarction and deep sternal wound infections that correlated with elevations in HbA1c. The authors recommend that an attempt should be made to try to improve blood glucose control and reduce HbA1c prior to elective CABG. They note that HbA1c is a useful prognostic tool for assessing risk of morbidity and mortality after CABG.

12 Phillip M, Danne T, Battelino T, *et al.* Use of insulin pump therapy in the pediatric age-group. (Consensus statement from the European Society for Paediatric Endrocrinology *et al.* ... endorsed by the American Diabetes Association and the European Association for the Study of Diabetes). Diabetes Care 2007; 30:1653–1662.

13 Egi M, Bellomo R, Stachowski E, *et al.* Variability of blood glucose concentration and mortality in critically ill patients. Anesthesiology 2006; 105:244–252.

14 Monnier L, Mas E, Ginet C, *et al.* Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA 2006; 295:1681–1687.

15 Griesdale DEG, deSouza RJ, vanDam RM, *et al.* Intensive insulin therapy and
•• mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ 2009; 180:821–827.
In this recent meta-analysis of intensive glucose control in critically ill patients, the authors found there was no overall benefit in mortality, but increased risk of hypoglycemia in the intensively treated group.

16 Subramanian B, Panzica PJ, Novack V, *et al.* Continuous perioperative insulin infusion decreases major cardiovascular events in patients undergoing vascular surgery. Anesthesiology 2009; 110:970–977.

17 Cefalu WT. Glycemic targets and cardiovascular disease [editorial]. N Engl J
• Med 2008; 358:2633–2635.
In this editorial accompanying the ACCORD and ADVANCE studies, it is postulated that the increased risk of cardiovascular events seen in the ACCORD study may have been related to the rapid reduction of HbA1c levels in the intensive therapy group.

18 Hans P, Vanthuyne A, Dewandre PY, *et al.* Blood glucose concentration profile after 10 mg dexamethasone in nondiabetic and type 2 diabetic patients undergoing abdominal surgery. Br J Anaesth 2006; 97:164–170.

19 Schmeltz LR, Henske J, DeSantis AJ, *et al.* Reduction of surgical mortality and morbidity in diabetic patients undergoing cardiac surgery with a combined intravenous and subcutaneous insulin glucose management strategy. Diabetes Care 2007; 30:823–828.

20 Gandhi GY, Murad MH, Flynn DN, *et al.* Effect of perioperative insulin infusion on surgical morbidity and mortality: systematic review and meta-analysis of randomized trials. Mayo Clin Proc 2008; 83:418–430.

21 Ferrari LR. New insulin analogues and insulin delivery devices for the peri-
• operative management of diabetic patients. Curr Opin Anaesthesiol 2008; 21:401–405.
A review of newer medications and insulin including novel methods of administration and glucose monitoring devices.

22 Rhodes ET, Ferrari LR, Wolfsdorf JI. Perioperative management of pediatric surgical patients with diabetes mellitus. Anesth Analg 2005; 101:986–989.

23 Inzucchi SE. Management of hyperglycemia in the hospital setting. N Engl J Med 2006; 355:1903–1911.

24 Albacker T, Carvalho G, Schricker T, Lachapelle K. High-dose insulin therapy
• attenuates systemic inflammatory response in coronary artery bypass grafting patients. Ann Thorac Surg 2008; 86:20–28.
The beneficial effects of control of blood glucose with insulin during CABG are described in this study. The authors note that the anti-inflammatory actions of insulin during cardiac surgery exceed that of simple glucose control.

25 Lauruschkat AH, Arnrich B, Albert AA, *et al.* Diabetes mellitus as a risk factor
• for pulmonary complications after coronary bypass surgery. J Thorac Cardiovasc Surg 2008; 135:1047–1053.
A retrospective analysis found increased pulmonary complications after CABG surgery in patients with type 1 or undiagnosed diabetes. This article also reviews the pathophysiology of lung changes in patients with diabetes.

26 Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. Diabetes Care 2003; 26:1902–1912.

27 Nathan DM, Holman RR, Buse JB, *et al.* Medical management of hypergly-
• cemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. Diabetes Care 2009; 32:193–203.
The treatment of patients with type 2 diabetes with oral medications, injectables, and insulin are all described along with issues with therapy including insulin resistance.

28 Chen D, Lee SL, Peterfreund RA. New therapeutic agents for diabetes
• mellitus: implications for anesthetic management. Anesth Analg 2009; 108:1803–1810.
This anesthesia-focused article on new agents for the treatment of type 2 diabetes provides a detailed review of mechanisms of action and potential side effects or interactions of these medications in the perioperative period.

29 Betts P, Brink SJ, Swift PGF, *et al.* Management of children with diabetes requiring surgery. Pediatr Diabetes 2007; 8:242–247.

30 Umpierrez GE, Latif K, Stoever J, *et al.* Efficacy of subcutaneous insulin Lispro versus continuous intravenous regular insulin for the treatment of patients with diabetic ketoacidosis. Am J Med 2004; 117:291–296.

31 Ahmed Z, Lockhart CH, Weiner M, Klingensmith G. Advances in diabetic management: implications for anesthesia. Anesth Analg 2005; 100:666–669.

32 The NICE-SUGAR Study Investigators. Intensive versus conventional glucose
•• control in critically ill patients. N Engl J Med 2009; 360:1283–1297.
In this large, multicenter study of 6100 ICU patients, the group with a blood glucose target of 180 mg/dl or less experienced less mortality than the group with a lower blood glucose target of 81–108 mg/dl.

33 Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. JAMA 2008; 300:933–944.

34 Bilotta F, Caramia R, Paoloni FP, *et al.* Safety and efficacy of intensive insulin therapy in critical neurosurgical patients. Anesthesiology 2009; 110:611–619.

35 Rohlgin CL, Wiedmeyer HM, Little RR, *et al.* Defining the relationship between plasma glucose and HbA1c: analysis of glucose profiles and HbA1c in the Diabetes Control and Complications Trial. Diabetes Care 2002; 25:275–278.