



## Perioperative evaluation and management of the patient with endocrine dysfunction

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Over the past two decades the worldwide prevalence of diabetes mellitus has steadily risen. In the United States, an estimated 16 million people have diabetes mellitus [1]. Factors contributing to the increased prevalence of diabetes include the proliferation of obesity, lower levels of physical activity, and the aging of the population. Individuals with diabetes mellitus often require surgery sometime during their life [2]. Physicians in many specialties are involved in the perioperative care of patients with diabetes mellitus including internists, surgeons, anesthesiologists, and endocrinologists.

### Diabetes mellitus and surgery

Patients with diabetes mellitus who undergo surgery have an increased risk of developing perioperative complications [2,3]. They are particularly at greater risk for infectious, metabolic, electrolyte, renal, and cardiac complications during and after surgery [4-6]. The primary goal of perioperative care for the diabetic patient undergoing surgery is a safe and effective outcome without complications. Steps involved in achieving that outcome include the preoperative evaluation, a plan for managing diabetes during surgery, and postoperative diabetic care. The timing of the surgery is also important, particularly when other medical conditions coexist with diabetes (eg, cardiac, renal, or infectious problems). Communication and coordination of care between the internist or endocrinologist and the surgical team (surgeon and anesthesiologist) are often important for achieving a safe outcome.

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### *Perioperative metabolic changes*

Many metabolic changes occur during surgery that have an effect on diabetes mellitus. With the onset of anesthesia and surgery, there is an increase in the secretion of epinephrine, norepinephrine, cortisol, and growth hormone [2,7]. The extent of the metabolic changes is related to the type of surgery, the length of surgery, and the stress of surgery. Whether the surgery is an elective or emergent procedure also affects the extent of metabolic changes. Epinephrine, norepinephrine, cortisol, and growth hormone are all insulin antagonists and cause insulin resistance at the tissue level. In addition, epinephrine causes a decrease in insulin secretion [2,6]. All of these metabolic changes contribute to hyperglycemia during and after surgery.

The stresses of anesthesia and surgery also cause an increase in gluconeogenesis. There is mobilization of gluconeogenesis precursors, including amino acids, free fatty acids, and glycerol [7,8], and an increase in the metabolic rate during surgery. There is also a net protein catabolism during and after surgery [6]. These perioperative changes can result in poor control of blood glucose, ketosis, and acidosis [2,7]. Factors that affect the extent of the endocrine and metabolic changes during and after surgery include the type of diabetes, preoperative diabetic control, the magnitude of the surgery, and perioperative complications.

Patients with diabetes mellitus are also at risk for hypoglycemia in the perioperative period. Hypoglycemia in the anaesthetized or sedated diabetic patient may be unrecognized if appropriate glucose monitoring is not done. Factors that may contribute to perioperative hypoglycemia in patients with diabetes mellitus include prolonged fasting, hypoglycemic medications, inadequate nutritional therapy, sedation, and postoperative gastrointestinal problems (eg, vomiting, gastroparesis, and ileus).

### *Ramifications of perioperative hyperglycemia*

One of the most important consequences of perioperative hyperglycemia is impaired wound healing. Phagocytic function of granulocytes is adversely affected by hyperglycemia, particularly when blood glucoses are greater than 250 [9]. Collagen synthesis is suppressed by hyperglycemia when glucose levels are higher than 200mg/dL. Granulocyte chemotaxis is also decreased by hyperglycemia. The higher prevalence of vascular disease and renal disease in patients with diabetes mellitus also contributes to the greater frequency of postoperative wound infections [6]. Impaired wound healing contributes to the increased rate of postoperative infections in patients with diabetes mellitus. These infections, including wound infections, skin infections, pneumonia, and urinary tract infections, are a major cause of morbidity, accounting for about two thirds of all postoperative complications [10] and 20% of all postoperative deaths [11] in patients with diabetes.

There is evidence from *in vitro* studies that hyperglycemia impairs wound healing. The best method for tightly controlling diabetes mellitus during

major surgery is with a continuous IV insulin and glucose infusion [7,12,13]. Is there evidence that better control of diabetes in the perioperative period decreases morbidity or mortality? At this time, there are no prospective studies that document better perioperative outcomes from tighter control of diabetes mellitus. Some retrospective studies show that higher glucose levels perioperatively are associated with an increased risk of infection in patients with diabetes mellitus [5,14].

A recent prospective study randomly assigned 1548 critically ill patients admitted to a surgical intensive care unit to intensive insulin therapy or conventional insulin therapy [15]. Only 13% of these patients had a history of diabetes mellitus. Two thirds of the patients had undergone cardiothoracic surgery. In the intensive insulin therapy group, an insulin infusion was started if the blood glucose level exceeded 110 mg/dL, and, in the conventional insulin therapy group, it was started if the blood glucose exceeded 215 mg/dL. Patients in the intensive insulin group had a mean A.M. blood glucose of 103 mg/dL, and in the conventional insulin group it was 153 mg/dL [15], but hypoglycemia occurred in 5% of the intensive insulin group compared with 1% in the conventional group. The 12-month mortality rate for the intensive insulin therapy group was 4.6% which was significantly lower than the 8.0% mortality rate for the conventional insulin group. The intensive insulin therapy group had 46% fewer episodes of septicemia and a 34% lower in-hospital mortality rate [15].

A retrospective study of 411 adults with diabetes mellitus who had coronary artery bypass surgery divided these patients into four quartiles based on their mean postoperative blood glucose levels [14]. Mean postoperative blood glucose levels ranged from 121–206 mg/dL in quartile 1 to 253–352 mg/dL in quartile 4. One hundred patients (24.3%) developed one or more postoperative infections. In adjusted risk models (adjusting for confounding variables such as age and comorbid conditions), those patients in the higher postoperative glucose quartiles had an increased risk for postoperative infections [14].

Another retrospective study examined the incidence of deep sternal wound infections in diabetic patients undergoing open heart surgery before and after instituting a continuous intravenous insulin infusion protocol [4]. Their control group included 968 patients who received sliding scale subcutaneous insulin and had a mean glucose of 206 on postoperative day 1. The study group of 1499 patients received a continuous intravenous insulin infusion and had a mean glucose of 176 on postoperative day 1. Institution of the continuous intravenous insulin infusion protocol resulted in a significant decrease in the incidence of deep sternal wound infections to 0.8%, compared with the rate of 1.9% in the subcutaneous insulin therapy group [4].

### *Preoperative evaluation*

The objectives for the preoperative assessment of patients with diabetes mellitus include evaluation of the status of their diabetes, identifying other

medical problems, consideration of the type of surgery planned to assess the surgical risk, and measures to minimize the risk of surgery. It is important to identify both the type and duration of diabetes mellitus. Patients with diabetes for more than 10 years are more likely to have complications from diabetes. The patient's current therapy for diabetes should be ascertained including diet, oral medication(s) and doses, and any insulin therapy including the type and dose. The status of diabetes control should be assessed by evaluating recent blood glucoses and hemoglobin A1C. The patient should be queried about any complications from diabetes. Because patients with diabetes mellitus are at increased risk for coronary artery disease, a cardiac history should be obtained prior to surgery. The preoperative physical exam should include an evaluation of cardiovascular status including blood pressure, heart rate and rhythm, and a cardiac exam. An abdominal exam and neurologic exam should also be undertaken.

Certain preoperative tests should be done for all patients with diabetes mellitus before surgery. A chemistry panel to evaluate electrolytes and renal function should be ordered before surgery. An electrocardiogram should be taken before any major surgery for patients with diabetes mellitus. Whether any additional tests are indicated would depend on the patient's medical problems and the type of surgery planned.

#### *Management of diabetes during surgery*

How a patient's diabetes will be managed during surgery is dependent on several patient specific issues and several surgical factors. Patient issues to consider include whether the patient is being treated with diet alone, with oral hypoglycemic agent(s), or with insulin as well as the degree of glycemic control. Surgery-specific factors to consider are the type of anesthesia (local, regional, or general) and whether major or minor surgery is scheduled. How long the patient is expected to be nil per os (NPO) should also be considered. For example, an early morning knee arthroscopy may enable the patient to eat lunch, whereas an early morning laparoscopic cholecystectomy may preclude a normal lunch.

For patients who undergo minor surgery (eg, cystoscopy, dilation and curttage, laparoscopic hernia repair) therapy for diabetes mellitus should be modified (Table 1). Patients undergoing minor surgery whose diabetes mellitus is controlled with diet alone or with oral hypoglycemic agents usually do not need insulin during surgery. For all patients with diabetes mellitus, a bedside blood glucose should be checked preoperatively and every 1–2 hours during minor surgery. Patients who are taking oral hypoglycemic agents should omit these on the morning of surgery or 24–48 hours preoperatively if on metformin or chlorpropamide. These patients can restart their usual oral hypoglycemic medication when they are able to resume their usual diet. Diabetic patients controlled with oral hypoglycemic medications who undergo major surgery usually do not need insulin during surgery. Patients on oral

Table 1  
Management of diabetes mellitus during surgery

	Minor surgery	Major surgery
DM controlled with diet alone:	No insulin during surgery	No insulin during surgery
DM controlled with oral meds:	No insulin during surgery	Insulin may be required during surgery
DM poorly controlled with oral meds:	Insulin may be required	IV insulin infusion during surgery
DM on insulin therapy:	1/2–2/3 of usual AM insulin SQ	IV insulin infusion during surgery

*Abbreviations:* DM, diabetes mellitus; SQ, subcutaneous.

hypoglycemic medications with poorly controlled diabetes should receive an insulin and glucose infusion during major surgery (Table 1).

Insulin-treated patients should have their insulin dose modified before minor surgery. One half to two thirds of their usual morning insulin can be given. Less insulin should be given (eg, one half their usual dose) if it is anticipated that they will be NPO past their noon meal. Their IV fluids during surgery should be D5W/0.45NS at 100cc/hr to prevent hypoglycemia. When they are able to resume their usual diet, they can restart their preoperative insulin treatment.

Patients with diabetes mellitus on insulin who undergo major surgery should receive a continuous IV insulin and glucose infusion during surgery [7]. An insulin infusion is the best method to control glucose levels and can be easily adjusted depending on the stress of surgery, the length of surgery, and the patient's insulin requirements [7,11]. There is a wide variation in how much insulin is needed during surgery for these patients ranging from 0.7–4.2 units of regular insulin/hr [11]. A continuous IV glucose infusion should also be given to prevent hypoglycemia and to provide a source of carbohydrate to minimize the risk for ketosis and acidosis during fasting and the stress of surgery. Potassium chloride should be included in the insulin and glucose infusion (Table 2) unless the patient has hyperkalemia or chronic renal failure. It is inappropriate to use only IV push insulin to manage diabetes perioperatively, because IV push insulin has a half-life of only 5–10 minutes [7].

#### *IV insulin and glucose infusion*

When a patient is started on a continuous IV insulin and glucose infusion for surgery, the usual insulin and oral hypoglycemic medication(s) should be held on the morning of surgery. Prior to starting the infusion, a bedside blood glucose should be checked. One IV line should be used for the insulin and glucose infusion, and a second IV line for any other fluids, medications, and/or blood products that are needed during surgery. The IV insulin infusion should be started at 1.0 units/hr of regular insulin by infusion pump.

Table 2  
Protocol for perioperative IV insulin infusion

- 
- Check bedside blood glucose.
  - Hold usual morning diabetes medications.
  - Begin insulin and glucose infusion:
    1. Discard first 50 mL of insulin infusion
    2. Start insulin infusion at 1.0 units/hr of regular insulin by infusion pump
    3. Start D5W/0.45NS with 20 meq of KCL at 100 cc/hr
  - Maintain one IV line for insulin and glucose infusion, and a separate IV access for any fluids, blood products, or medications.
  - Monitor bedside blood glucose every 1–2 hs before surgery and every 1 hr during surgery.
  - Aim for glucose of 100–200 mg/dL by adjusting insulin infusion rate in 0.5 unit/hr increments.
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The first 50–60 mL of the insulin infusion should be flushed through the plastic tubing and discarded because insulin binds to plastic tubing, and this will saturate the insulin binding sites on the plastic tubing. When the insulin infusion is started, the glucose infusion should also be started with 1000 cc of D5W/0.45NS with 20 mEq of KCL to run at 100cc/hr. The bedside blood glucose should be checked every 1–2 hours (every 1 hour during surgery) and adjusted to maintain a glucose of 100–200 mg/DL. The insulin infusion can be adjusted in 0.5 unit/hr increments. For example, if at 1 hour the glucose is 250 mg/dL, then the infusion rate should be increased to 1.5 units/hr. If at 1 hour the glucose is 70 mg/dL, the infusion rate should be decreased to 0.5 units/hr. The IV glucose infusion should be maintained during these adjustments at 100cc/hr. For a very low glucose (eg, 50mg/dL) 1 ampule of D50 should be given IV push and the insulin infusion rate should be decreased by 0.5units/hr. For patients undergoing open-heart procedures, the metabolic changes that cause hyperglycemia are accentuated [13]. Diabetic patients undergoing open-heart procedures will usually require higher hourly infusion rates of IV insulin.

What are the advantages of continuous IV insulin infusion compared with giving subcutaneous insulin during surgery? The absorption of subcutaneous insulin may be erratic and highly variable during surgery. Continuous IV insulin has the flexibility to control diabetes better, whether the surgery and its peak stresses occur early in the morning, late in the morning, or later in the day. The IV insulin infusion can be easily adjusted in response to complications that occur during or after surgery and can be individualized to meet the insulin requirements of each patient.

### *Diabetes therapy after surgery*

The metabolic and hormonal stresses of surgery persist during the early postoperative period after major surgery. These metabolic changes can continue for up to 4 days after major surgery [8,17] but are most pronounced on the day of surgery and the first postoperative day. While the patient remains NPO, the insulin and glucose infusion can be continued. The insulin

and glucose infusion can usually be stopped when the patient begins eating, although they are often unable to initially tolerate their usual diet. Until their usual diet is tolerated, subcutaneous regular insulin can be given every 6 hours based on bedside blood glucoses. When a patient's dietary intake improves, their usual insulin dosing (or a reduced long-acting insulin dose) can be resumed. Patients on oral hypoglycemic agents who require an insulin and glucose infusion can restart their oral hypoglycemic medications when they resume their usual diet.

### **Surgery in the hypothyroid patient**

Hypothyroidism affects many bodily systems that can influence perioperative outcome, including myocardial function, pulmonary ventilation, hemostasis, gastrointestinal (GI) motility, and free water balance. There are no randomized, prospective studies looking at surgical outcomes in hypothyroid patients versus controls. Older case studies reported intraoperative hypotension, cardiovascular collapse, and extreme sensitivity to narcotics, sedatives, and anesthesia in undiagnosed hypothyroid patients [18,19]. There are also case reports of myxedema coma developing after surgery [20–22]. Thus for many years, expert opinion encouraged clinical and chemical euthyroidism prior to any surgery.

Two retrospective case-matched control studies from the 1980s evaluated the hypothyroid patient undergoing surgery. Weinberg et al [23] reviewed anesthetic and surgical outcomes in 59 hypothyroid patients and 59 paired euthyroid controls. There were no differences between the groups in surgical outcome, perioperative complications, or hospital length of stay. There were also no differences in outcome among subsets of hypothyroidism determined by level of thyroxine, though only a few were severely hypothyroid. The authors concluded that there was no evidence to justify deferring needed surgery in patients with mild to moderate hypothyroidism, and insufficient evidence to make recommendations for patients with severe hypothyroidism. Another retrospective study by Ladenson et al [24] looked at perioperative complications in 40 hypothyroid patients compared with 80 matched controls. Hypothyroid patients had more intraoperative hypotension in noncardiac surgery and more heart failure in cardiac surgery. They also had more postoperative GI and neuropsychiatric complications and were less likely to mount a fever with infection. There were no differences between the groups in duration of hospitalization, perioperative arrhythmias, delayed anesthetic recovery, pulmonary complications, or death, however.

Patients with mild to moderate hypothyroidism may undergo urgent or emergent surgery without delay. Elective surgery in patients with mild hypothyroidism is probably safe, though minor complications such as ileus, postoperative delirium, or infection without fever may occur. Elective surgery should be postponed for patients with moderate and severe hypothyroidism.

Patients with severe hypothyroidism who require urgent or emergent surgery should be treated perioperatively with intravenous T3 or T4 and glucocorticoids. Definitions of mild, moderate, and severe hypothyroidism are often vague and vary between studies. A useful definition of a severely hypothyroid patient includes one with myxedema coma; one with severe complications of the disease such as delayed mentation, pericardial effusions, or heart failure; or one with very low levels of thyroxine [25].

Thyroid replacement can be started or continued in the patient with mild to moderate disease going to surgery, with the same schedule as therapy in the outpatient setting. Levothyroxine has a half-life of 5–9 days, and so doses can be missed for several days if the patient is not eating. Initiation of thyroid replacement in the patient undergoing cardiovascular surgery or catheterization has been controversial. The risk of precipitating or worsening unstable coronary syndromes with thyroid hormone conflicts with the concern that untreated hypothyroidism might worsen heart failure or hypotension in the cardiac surgery patient. Studies of cardiac patients found no adverse outcomes in cardiac patients going to surgery or catheterization without thyroid replacement [26,27]. The need for thyroid hormone replacement should be assessed in each patient on an individual basis, with the knowledge that most patients can begin their replacement after the cardiac intervention.

Myxedema coma is a rare complication of surgery and should be considered in any patient who develops seizures, coma, unexplained heart failure, or hypothermia perioperatively. Undiagnosed hypothyroidism should be suspected in any postoperative patient with difficulty weaning from ventilatory support, unexplained heart failure, prolonged ileus, or postoperative delirium.

### **Surgery in the patient with hyperthyroidism**

The effect of thyrotoxicosis on the heart carries perioperative risk for the hyperthyroid patient. T3 and T4 exert direct inotropic and chronotropic effects on cardiac muscle. Left ventricular ejection fraction may not increase normally during exercise, and increased cardiac output may limit cardiac reserves during surgery in the hyperthyroid patient. Atrial fibrillation is present in 10–20% of patients [28–31]. The greatest risk to the perioperative thyrotoxic patient is thyroid storm, a rare but life-threatening complication that presents with fever, tachycardia, and confusion and may quickly lead to cardiovascular collapse and death. It can occur in the inadequately treated or undiagnosed hyperthyroid patient during or soon after surgery [16,32].

Patients with mild hyperthyroidism can go to surgery with preoperative beta blockade [33], but elective surgery should be postponed in those with moderate to severe disease until they are euthyroid. Propranolol has been the beta-blocker of choice at doses of 10–40 mg q.i.d., though cardioselective beta-blockers can also be used. The latter may be better tolerated in

patients with asthma. Longer acting beta-blockers such as atenolol taken before surgery may maintain adequate heart rate control until the patient is able to take oral medication postoperatively [34].

The thyrotoxic patient undergoing urgent or emergent surgery needs premedication with antithyroid agents, beta blockade, and possibly corticosteroids. Close perioperative assessment and management of cardiac function is essential. Antithyroid medications include thionamides, iodine, and iopanoic acid. The thionamides, methimazole, and propylthiouracil (PTU) block thyroid hormone synthesis. Iodine blocks release of T4 and T3 from the thyroid, and iopanoic acid blocks T4 to T3 conversion. Iopanoic acid contains iodine and thus also blocks release of thyroid hormone. Euthyroidism can be achieved in 3–8 weeks with thionamides alone. Methimazole reverses hyperthyroidism sooner than PTU. There are other published combination regimens that can prepare a patient more rapidly for urgent surgery in 10 days or less [35,36].

Adrenal reserve may be low in the thyrotoxic patient. If time does not allow for completely adequate preparation prior to emergent surgery in the patient with severe hyperthyroidism or if thyroid storm occurs, hydrocortisone can be given 100 mg every 8 hours. This will not only treat possible adrenal insufficiency but may block peripheral conversion of T4 to T3 as well. One study showed improved outcomes in patients with thyroid storm treated with corticosteroids [37].

Thyroid storm should be considered in any patient who develops fever, tachycardia, and confusion in the postoperative period. Laboratory values do not differ between thyrotoxicosis and decompensated hyperthyroid crisis, and treatment may need to start before results of thyroid function tests are available. Burch devised a point system based on cardiac, neuropsychiatric, and other physical findings to help with diagnosis [38]. Treatment of thyroid storm includes beta blockade, thioamides, iodinated contrast agents, iodine, and corticosteroids. Thioamides should be given at least 1 hour prior to iodine to prevent uptake of iodine by the thyroid as substrate for more hormone production. Methimazole and PTU are available rectally, and PTU can be given intravenously [39–41]. Supportive care in the intensive care unit (ICU) setting is essential and should include hydration, nutrition with glucose and vitamins, antipyretics, cooling blankets, and treatment of cardiac complications such as heart failure and atrial fibrillation that may develop. Acetaminophen is the antipyretic of choice, as aspirin may increase thyroid hormone concentrations by interfering with protein binding of T4 and T3.

### **Perioperative management of the patient with pheochromocytoma**

Rarely is communication between surgeon, anesthesiologist, and internist more vital than in the preoperative preparation and perioperative management of the patient with a pheochromocytoma. In case series before 1961,

surgical mortality ranged from 24–45% [42]. Introduction of alpha adreno-receptor blockade in the 1950s, improved anesthetic drugs and management, and better localization techniques from the 1970s onward are the probable reasons for significantly improved surgical outcome [43]. With appropriate medical preparation and an experienced anesthesiologist and surgical team, survival of excision of a pheochromocytoma is 93.3–100% [44,45].

Pheochromocytoma is an uncommon neuroendocrine tumor of the chromaffin cell that is a cause of less than 0.2% of hypertension [46]. The most common sign of the tumor is hypertension, which can be paroxysmal. The tumor's intermittent catecholamine surges can cause a variety of symptoms, including headache, chest pain, palpitations, diaphoresis, dyspnea, anxiety, and dizziness. Surgical excision can prevent the life-threatening complications of hypertensive crises, stroke, arrhythmias, and myocardial infarction.

### *Preoperative preparation*

Catecholamine excess causes vasoconstriction that leads to both hypertension and hypovolemia. Pheochromocytoma patients can die intraoperatively from severe hypertensive crisis or hypotension that leads to cardiovascular collapse. When tumor veins are ligated during surgery, the sudden drop in circulating catecholamines can lead to vasodilatation. The catecholamine output of the contralateral adrenal may be suppressed from previous catecholamine excess. In the hypovolemic patient, this can lead to hypotension, shock, and death. Alpha adrenergic blockade has been the cornerstone of preoperative preparation in the past, as it treats both hypertension and vasoconstriction and improves circulating plasma volume prior to surgery. After alpha-blockers are initiated, beta-blockers are added if not contraindicated by heart failure or asthma to prevent the reflex tachycardia associated with nonselective alpha-receptor blockade. Beta-blockers may also prevent perioperative arrhythmias and cardiac complications. Beta blockade should not be given alone in a patient with pheochromocytoma, as it augments effects of catecholamines at the alpha adrenoreceptors, blocks beta receptor-mediated vasodilatation in skeletal muscle, and can cause higher blood pressure.

Particular attention should be paid to preoperative evaluation of myocardial function. Not only can long-standing hypertension cause left ventricular hypertrophy and dysfunction, but chronic catecholamine excess can cause cardiomyopathy. The intraoperative hypotension that often occurs after excision of the tumor can be refractory in the patient with low cardiac output [47].

Regimens vary among centers, but usually alpha blockade for at least 10–14 days prior to surgery is recommended. Normotension (140/90) is a preoperative goal, and one anesthesia review recommended no blood pressure greater than 160/90 in the 24 hours prior to surgery [54]. A recent retrospective case-series review showed a correlation that approached statistical sig-

nificance between the level of preoperative hypertension and perioperative complications [45]. The long-acting, nonselective alpha blocker phenoxybenzamine has been the past drug of choice. Doses are initiated at 5–10 mg by mouth b.i.d. and increased by 10 mg every few days to a dose of 0.5–1 mg/kg/day or until blood pressure is controlled. The average dose is 40–80 mg per day. It has significant side effects including somnolence, orthostasis, and stuffy nose. If phenoxybenzamine is not tolerated, the selective alpha 1 receptor blockers prazosin, doxazosin, or terazosin can be used. One study showed that doxazosin did not cause the prolonged duration of postoperative hypotension that can occur with phenoxybenzamine [48].

Some authors recommend metyrosine (alpha-methyl-p-tyrosine) at doses of 1–4 mg per day in addition to alpha blockade. It competitively inhibits tyrosine hydroxylase, the rate-limiting step in catecholamine biosynthesis. Patients who received it in combination with alpha blockade had better blood pressure control, as well as less need for intraoperative antihypertensives and pressors compared with patients who were on alpha blockade alone [49,50].

Propranolol, metoprolol, and atenolol have all been recommended for beta blockade. They should be begun several days after alpha blockade and at least a few days prior to surgery. Liberalization of salt in the diet along with alpha blockade should expand plasma volume. Though some centers admit patients preoperatively for blood pressure management, at least one retrospective study has documented the safety of outpatient preoperative preparation [51].

A few authors have argued that alpha adrenergic blockers are not necessary for safe surgery. Half of 60 patients at one institution underwent excision without preoperative alpha blockade. There were no strokes or myocardial infarctions, and there was only one postoperative death, which was caused by a pre-existing cerebral tumor [52]. As calcium ion transport is essential for release of catecholamines from chromaffin cells, calcium channel blockers are used for control of blood pressure and preoperative preparation at some centers. There are several case reports and a French study of pheochromocytoma patients treated with calcium channel blockers alone [48,53] prior to surgery. In another study of 113 patients, those who received preoperative alpha blockade had more perioperative cardiovascular complications and required more perioperative fluid than those receiving calcium channel blockers [54].

Studies have shown no difference in intraoperative hemodynamics and blood loss between open versus laparoscopic approaches, and patients leave the hospital sooner with laparoscopic surgery [55]. Splenic injury and splenectomy can be a complication in an open anterior abdominal approach [45].

The postoperative patient may remain hypertensive up to 2 weeks after excision. If hypertension persists, urinary catecholamines should be checked to ensure no additional tumor remains. If catecholamines are normal, the patient may be one of about 25% of pheochromocytoma patients whose

hypertension persists after surgical excision caused by other concomitant disease, such as essential or renal hypertension [56]. Because norepinephrine and epinephrine contribute to insulin resistance, hypoglycemia may develop and persist into the postoperative period once the tumor is removed [57]. Glucose should be included in perioperative fluids, and blood sugars should be monitored frequently intraoperatively and postoperatively. Of course, those patients who undergo bilateral adrenalectomy for bilateral disease will need steroid replacement. Partial bilateral adrenalectomies are being done more frequently in patients with bilateral disease to prevent the need for life-long replacement, but these patients need to be monitored closely for recurrent disease [58].

### **The patient on chronic glucocorticoids**

Surgery is a physiologic stress that activates the hypothalamic-pituitary-adrenal (HPA) axis and results in increased corticotropin (ACTH) and cortisol secretion. Exogenous glucocorticoids can suppress the HPA axis, and the patient on chronic glucocorticoids may not produce sufficient levels of ACTH and cortisol during and after surgery to meet physiologic needs. Adrenal insufficiency with hypotension and shock may occur. The evidence that this does in fact occur is mainly anecdotal. There are a few case studies, however, that show confirmed clinical and biochemical evidence of intraoperative adrenal insufficiency in patients who did not receive perioperative glucocorticoids after stopping them shortly before surgery [59]. To prevent this life-threatening complication, supplemental glucocorticoids (“stress dose” steroids) are given perioperatively to those patients with documented or presumed HPA axis suppression. Two questions need to be answered by the provider caring for the patient on chronic glucocorticoids who is going to surgery: Is it likely that the patient’s dose and duration of glucocorticoid therapy has caused HPA suppression? If the patient is suppressed, what dose of supplemental glucocorticoids should be given?

#### *Suppression of the HPA axis*

There is wide variability in HPA suppression in patients on exogenous glucocorticoids that in general does not correlate well with age, sex, duration, or amount of dose. Nevertheless, it seems fairly clear from studies that oral glucocorticoids equivalent to less than 5 mg of prednisone in a single morning dose for any duration of time, alternate day short-acting glucocorticoids (cortisone, hydrocortisone, prednisone, prednisolone, or methylprednisolone) given in a morning dose, and any dose of glucocorticoids given for less than 3 weeks do not cause clinically significant suppression of the HPA axis [60–62]. By contrast, any patient who has taken more than 20 mg of prednisone or its equivalent per day for more than 3 weeks or who is clinically cushingoid

has probable suppression of the HPA axis [63]. HPA suppression in patients on intermediate regimens is much more variable and may depend on individual rates of drug metabolism and clearance [62,64]. Superpotent topical steroids at doses of 2 g per day have caused HPA axis suppression in patients [65,66]. HPA suppression can occur in patients treated with inhaled corticosteroids at doses of 0.8 mg/day or more of fluticasone propionate, though clinically significant adrenal insufficiency is rare [67,68].

The duration of functional HPA axis suppression after glucocorticoids have been stopped is debatable. Older studies showed delayed biochemical recovery on tests of pituitary and adrenal function up to 1 year after cessation of glucocorticoids [69,70], but the clinical importance of these test results is unclear. Because of these studies, however, most anesthesia and endocrine texts recommend perioperative supplemental glucocorticoids in patients who have had HPA axis suppressive doses of glucocorticoids within 1 year of surgery.

### *Testing the HPA axis*

Patients who are on intermediate doses of glucocorticoids or who cannot give a good history of dose, duration, or tapering of therapy can undergo testing of the HPA axis if there is sufficient time to do so before surgery. Because the high dose (250 µg) ACTH stimulation test is supraphysiologic, response to it may mask a partially suppressed adrenal gland, and many now recommend the low dose (1 µm) ACTH stimulation test for assessment of the HPA axis [71].

Patients may have a normal response to surgical stress despite laboratory evidence of HPA suppression. In two studies, patients on chronic steroids were given their usual daily glucocorticoid dose but no glucocorticoid supplementation while hospitalized for surgery or medical illness. HPA suppression was evaluated with an ACTH stimulation test. No patient with an abnormal ACTH test developed clinical adrenal insufficiency [72,73]. The studies raise interesting questions, and some have used them to argue that supplemental glucocorticoids are unnecessary. The number of patients studied was small, however, and for now, the data are insufficient to discount the ACTH test or its results in surgical patients.

### *Supplemental glucocorticoid regimens*

Because the status of the patient's HPA axis is often uncertain, the decision to give perioperative supplemental glucocorticoids must weigh the risk of additional glucocorticoids in the perioperative period against the likelihood of adrenal insufficiency developing without them. Glucocorticoids have many side effects that can affect surgical outcome, including hypertension, fluid retention, psychiatric disturbance, increased risk of infection, gastrointestinal bleeding, impaired wound healing, and hyperglycemia. One

way to mitigate the risks of additional glucocorticoids is to give the lowest protective dose for the shortest period of time necessary. Older regimens for glucocorticoid replacement included high doses of up to 300 mg of hydrocortisone per day for several days. A consensus paper [59] recommended that clinicians replace glucocorticoids only in amounts equivalent to the normal physiologic response to surgical stress, which in turn depends on the type and duration of surgery. ACTH and cortisol rise during induction of anesthesia, surgery, extubation, and recovery from anesthesia [74]. Up to 200–500 mg of cortisol can be secreted per day during severe stress but rates of more than 200 mg per day in the 24 hours after surgery are rare [59]. Cortisol levels may average 50–75 mg per day for 1–2 days in a moderate stress surgery and 100–150 mg per day for 2–3 days for major stress surgery [75].

Table 3 makes specific recommendations on supplemental glucocorticoids based on likely HPA axis suppression and the anticipated stress of surgery. As the physiologic stress of local anesthesia or minor surgery is low,

Table 3  
Perioperative supplemental glucocorticoid regimens

- 
- No HPA axis suppression:
    1. Less than 5 mg of prednisone or equivalent per day for any duration
    2. Alternate-day single morning dose of short-acting glucocorticoid of any dose or duration
    3. Any dose of glucocorticoid for less than 3 weeks  
Rx: Give usual daily glucocorticoid dose during perioperative period
  - HPA axis suppression documented or presumed:
    1. More than 20 mg of prednisone or equivalent per day for 3 weeks or more
    2. Cushingoid appearance
    3. Biochemical adrenal insufficiency on low-dose ACTH stimulation test
      1. Minor procedures or local anesthesia  
Rx: Give usual glucocorticoid dose before surgery  
No supplementation
      2. Moderate surgical stress  
Rx: 50 mg IV hydrocortisone prior to induction of anesthesia, 25 mg hydrocortisone every 8 hours thereafter for 24–48 hours, then resume usual dose
      3. Major surgical stress  
Rx: 100 mg IV hydrocortisone prior to induction of anesthesia, 50 mg hydrocortisone every 8 hours for 48–72 hours, then resume usual dose
  - HPA axis suppression uncertain:
    1. 5–20 mg of prednisone or its equivalent for 3 weeks or more
    2. 5 mg of greater of prednisone or its equivalent for 3 weeks or more in the year prior to surgery
      1. Minor procedures or local anesthesia  
Rx: Give usual glucocorticoid dose before surgery  
No supplementation
      2. Moderate or major surgical stress  
Check low-dose ACTH stimulation test to determine HPA axis suppression or  
Give supplemental glucocorticoids as if suppressed.
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*Abbreviations:* ACTH, adrenocorticotropic hormone; HPA, hypothalamic–pituitary–adrenal axis.

patients need take only their usual daily glucocorticoid dose prior to these procedures. If a patient's daily glucocorticoid dose is equivalent to the target cortisol levels of the surgery, no supplemental glucocorticoids are necessary. Though it is common to do so, it is not necessary to taper supplemental glucocorticoids over the duration of time they are given [59].

Topical and inhaled corticosteroids can suppress the HPA axis but rarely cause clinical adrenal insufficiency. These patients do not need supplemental glucocorticoids prior to surgery. Finally, it is important to remember that supplemental glucocorticoids may need to be resumed or continued at higher doses or for longer periods of time if the patient develops a significant postoperative complication such as infection or infarction.

## **Summary**

Whenever possible, endocrine disorders should be identified and evaluated prior to surgery. A plan for perioperative management of diabetes should be based on the type of diabetes, what diabetes medications are taken, the status of diabetes control, and what type of surgery is planned. Perioperative management of diabetes must include bedside glucose monitoring.

Patients with mild hypothyroidism can safely proceed with elective surgery. Elective surgery should be postponed for patients with moderate or severe hypothyroidism. Patients who have mild hyperthyroidism can undergo elective surgery with preoperative beta blockade. Elective surgery should not be done on patients with moderate or severe hyperthyroidism until they are euthyroid.

Patients with pheochromocytoma need to be identified and properly treated before surgery to prevent perioperative cardiovascular complications. Patients who take endogenous steroids should have the status of their HPA axis determined prior to surgery. If the patient is undergoing moderate or major surgical stress and has documented or presumed HPA suppression, then stress doses of steroids should be give perioperatively.

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