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Perioperative Evaluation and Management of Endocrine Disorders

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Abstract

Evaluation of endocrine issues is a sometimes overlooked yet important component of the preoperative medical evaluation. Patients with diabetes, thyroid disease, and hypothalamic-pituitary-adrenal axis suppression are commonly encountered in the surgical setting and require unique consideration to optimize perioperative risk. For patients with diabetes, perioperative glycemic control has the strongest association with postsurgical outcomes. The preoperative evaluation should include recommendations for adjustment of insulin and noninsulin diabetic medications before surgery. Recommendations differ based on the type of diabetes, the type of insulin, and the patient's predisposition to hyperglycemia or hypoglycemia. Generally, patients with thyroid dysfunction can safely undergo operations unless they have untreated hyperthyroidism or severe hypothyroidism. Patients with known primary or secondary adrenal insufficiency require supplemental glucocorticoids to prevent adrenal crisis in the perioperative setting. Evidence supporting the use of high-dose supplemental corticosteroids for patients undergoing long-term glucocorticoid therapy is sparse. We discuss an approach to these patients based on the dose and duration of ongoing or recent corticosteroid therapy. As with other components of the preoperative medical evaluation, the primary objective is identification and assessment of the severity of endocrine issues before surgery so that the surgeons, anesthesiologists, and internal medicine professionals can optimize management accordingly.

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In this part of the series on preoperative evaluation and perioperative care, we focus on the most common endocrine issues affecting surgical patients: diabetes, thyroid disease, and the role of stress-dose corticosteroids for patients with actual or potential hypothalamic-pituitary-adrenal (HPA) axis suppression. These topics were chosen because they are likely to be the most frequently encountered endocrine issues addressed by internal medicine physicians in the perioperative setting.

PERIOPERATIVE MANAGEMENT OF PATIENTS WITH DIABETES

Diabetes and Perioperative Risk

The physiologic changes associated with surgical procedures include up-regulation of catecholamines, cortisol, and inflammatory cytokines, which subsequently decrease insulin sensitivity and increase secretion of glucagon and growth hormone.[1] In patients with insulin resistance, these hormonal changes are enhanced. This process leads to a catabolic state with up-regulation of gluconeogenesis, glycogenolysis, lipolysis, proteolysis, and ketogenesis, resulting in hyperglycemia and potentially ketoacidosis in severely insulin-deficient patients.[1] These physiologic changes contribute to the increased perioperative morbidity and mortality rates observed among patients with diabetes.[2] Diabetic patients are also more likely to have associated conditions that affect the risk of perioperative complications, including cardiovascular disease, hypertension, renal disease, cerebrovascular disease, autonomic neuropathy, and obesity.

Patients with diabetes have an elevated postoperative mortality rate both short-term (first 21 days) and long-term (7 years)

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after noncardiac surgery compared with operation-matched nondiabetic patients, 3.5% vs 0% and 37.2% vs 15%, respectively.[3] Most deaths were attributed to cardiovascular disease. A recent retrospective study of over 10.5 million patients undergoing major noncardiac operations reported an increased risk of major adverse cardiovascular or cerebrovascular events in patients with uncontrolled diabetes, as defined by billing code, with a relative risk of 1.41 (95% CI, 1.38-1.43) when compared with patients without diabetes.[4] Interestingly, in this large study population, patients with well-controlled diabetes were not at increased risk of major adverse cardiovascular or cerebrovascular events.[4] Other studies have found that diabetic patients are more likely to have postoperative respiratory infections, surgical site infections, urinary tract infections, acute kidney injury, intensive care unit admission, and increased hospital length of stay than patients without a diagnosis of diabetes.[5-7]

Preoperative Screening for Diabetes

The United States Preventive Services Task Force recommends screening for diabetes in adults aged 40 to 70 years who are overweight or obese and repeating screening every 3 years if values are normal.[8] Similarly, the American Diabetes Association (ADA) recommends screening in overweight adults who have an additional risk factor including a history of cardiovascular disease, hypertension, hyperlipidemia, polycystic ovarian syndrome, or gestational diabetes, a first-degree relative with diabetes, or a higher-risk race or ethnicity, eg, African American, Latino, Native American, or Asian.[9] Although these recommendations are not specific to patients undergoing surgery, it is reasonable to screen these patients preoperatively if they have not been screened in the past 3 years. Patients with prediabetes should be screened annually.[9] A recent systematic review concluded that there is not sufficient evidence to support routine preoperative testing of blood glucose or hemoglobin A_{1c} (HbA_{1c}) in otherwise healthy patients undergoing elective noncardiac surgical procedures because testing did not reduce postoperative mortality or morbidity in the perioperative period.[10] However, the authors noted that it is reasonable to screen patients undergoing joint replacement or vascular surgery because in these specific groups, there was an association between elevated preoperative HbA_{1c} values and the incidence of cardiac and infectious complications.[10-13] Because of the high volume of undiagnosed diabetes in surgical patients, it is reasonable to recommend testing either fasting blood sugar or HbA_{1c} in all patients who would qualify for screening under the United States Preventive Services Task Force or ADA guidelines and all patients scheduled to undergo major orthopedic joint replacement or vascular operations.

Preoperative Testing in Patients with Diabetes

In patients with diabetes, it is reasonable to obtain an HbA_{1c} level to assess glycemic control if no level has been obtained in the past 3 months. However, whether there is an association between preoperative HbA_{1c} level and perioperative risk is still unclear. Perioperative glucose levels (the day of surgery through postoperative day 3) more strongly correlate with surgical complication rates than preoperative HbA_{1c}.[14] Glycemic targets in the perioperative period are discussed in more detail subsequently.

ARTICLE HIGHLIGHTS

- Perioperative glucose levels more strongly correlate with surgical complication rates than preoperative HbA1c.
- Recommendations for preoperative insulin dosing differ based on the type of diabetes, the type of insulin, and the patient's predisposition to hyperglycemia or hypoglycemia.
- For thyroid disease, surgical plans only need to be adjusted for patients with untreated hyperthyroidism or severe hypothyroidism.
- The need for stress-dose corticosteroids is determined by the invasiveness of the operation, the dose and duration of corticosteroid exposure, and further testing of the HPA axis as needed.

TABLE 1. Perioperative Management of Noninsulin Diabetic Medications

Medication (example)	Day of surgery	Notes
α-Glucosidase inhibitors (acarbose, miglitol)	Withhold	• Mechanism of action is to decrease intestinal glucose absorption; no effect in fasting state • Resume when usual diet resumed
Dipeptidyl peptidase-4 inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin)	Take	• Low risk of hypoglycemia due to glucose-dependent mechanism
Glucagon-like peptide-1 agonists (exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, semaglutide)	Withhold	• Slow gastric motility, which may delay restoration of gastrointestinal function postoperatively • Risk of hypoglycemia • Resume when usual diet resumed
Meglitinide (repaglinide, nateglinide)	Withhold	• Risk of hypoglycemia • Resume when usual diet resumed
Metformin	Withhold/Take	• May take if no concern for renal insufficiency or nephrotoxic exposure, eg, intravenous contrast media • Resume when usual diet resumed • Do not resume if patient is hemodynamically unstable or dehydrated or in setting of renal insufficiency given increased risk of lactic acidosis
Sodium-glucose cotransporter-2 inhibitors (canagliflozin, empagliflozin, dapagliflozin, ertugliflozin)	Withhold	• Withhold 3 d prior to surgery (4 d for ertugliflozin) to avoid risk of diabetic ketoacidosis • Resume when usual diet resumed • If patient took sodium-glucose cotransporter-2 inhibitor the morning of major surgery, monitor for ketosis, consider perioperative insulin and glucose therapy
Sulfonylureas (chlorpropamide, gliclazide, glimepiride, glipizide, glyburide, tolazamide)	Withhold	• Hypoglycemic effect can be prolonged • Resume when usual diet resumed
Thiazolidinediones (pioglitazone, rosiglitazone)	Withhold	• Resume when usual diet resumed • Withhold if patient has hemodynamic instability, heart failure, or hepatic dysfunction postprocedure • Associated with increased intravascular volume

Fructosamine has been reported to correlate more closely with perioperative risk than HbA_{1c}.[15] A measure of glycated protein, fructosamine reflects serum glucose levels over the preceding 2 to 3 weeks, as opposed to 2 to 3 months. In patients with diabetes undergoing total joint arthroplasty, elevated fructosamine levels (>292 μmol/L [to convert value to mmol/L, multiply by 0.001]), but not elevated HbA_{1c} levels, were associated with a significantly higher risk of postoperative deep infection,

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readmission, and operative reintervention.[15] Fructosamine testing is not widely used in practice currently but may be considered, particularly in patients in whom HbA_{1c} levels may not be accurate (eg, those with anemia, sickle cell disease or trait, asplenia, or splenomegaly) or if a patient has recently made changes to their diabetic medication regimen over the past several weeks. The cost of serum fructosamine testing is typically lower than the cost for HbA_{1c}.

There is no clear evidence for an HbA_{1c} level cutoff for surgery. A retrospective study of veterans undergoing joint replacement found that postponing surgery because of an HbA_{1c} level higher than 8% resulted in reduced complication rates compared with those seen in the nondiabetic population.[16] Considering the available evidence, we believe it is reasonable to postpone elective surgery in patients with an HbA_{1c} level higher than 8.0% if doing so allows for intensification of the diabetic regimen and improvement of perioperative glycemic control.[17] We also recommend postponing elective surgery for diabetic ketoacidosis, hyperosmolar hyperglycemic state, or glucose level above 300 mg/dL.

Renal function assessed with serum creatinine concentration should be performed in patients with diabetes undergoing elevated-risk operations. A thorough assessment of cardiovascular risk following the American College of Cardiology/American Heart Association guidelines, as reviewed in previous articles in this series, is also important in this population.[18]

Preoperative Carbohydrate Loading

Preoperative carbohydrate drinks are increasingly being included in Enhanced Recovery After Surgery (ERAS) protocols because they have been shown to prevent dehydration and improve postoperative well-being and insulin resistance.[19] However, the vast majority of studies regarding preoperative carbohydrate loading have excluded patients with diabetes.[20] Carbohydrate loading may be harmful for diabetic patients if it causes preoperative hyperglycemia. Furthermore, it is unlikely to be beneficial for any patients with type 1 diabetes because they are insulin deficient rather than insulin resistant.[19] Given the lack of evidence, carbohydrate loading is not currently recommended for patients with diabetes.

Preoperative Management of Noninsulin Diabetic Medications

Noninsulin antidiabetic medication regimens need to be adjusted in the perioperative period to minimize the risk of hypoglycemia while the patient is fasting. In general, these medications should be withheld starting the morning of the procedure and may be restarted on discharge or when the patient has resumed a normal diet (Table 1).[1] This recommendation applies to metformin, glucagon-like peptide-1 agonists, sulfonylureas, and thiazolidinediones. We typically control glucose with insulin in the perioperative period until patients have resumed their normal eating patterns.

It was once recommended that metformin be withheld the day before surgery. However, more recent guidelines recommend stopping metformin once fasting begins and restarting once the patient is eating and drinking normally.[21,22] A meta-analysis did not identify any cases of lactic acidosis in over 70,000 patient-years of metformin use.[23] Therefore, in patients without renal dysfunction or anticipated exposure to nephrotoxic agents, such as intravenous (IV) contrast media, it may not be necessary to withhold metformin even the morning of surgery, especially if there is poor baseline glycemic control.[24]

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors should be held for 3 days before surgery to avoid the risk of diabetic ketoacidosis.[25] Diabetic ketoacidosis is a rare adverse effect of SGLT-2 inhibitors, which may be precipitated by surgery. The diabetic ketoacidosis associated with SGLT-2 inhibitors is frequently seen in the setting of euglycemia, so the diagnosis may be delayed or missed. Because the average half-life for SGLT-2 inhibitors is about 12.5 hours, it is reasonable to withhold these medications for 3 days before major surgery to ensure that the drug is no longer having a metabolic

TABLE 2. Preoperative Insulin Management for Patients With Type 1 Diabetes[a]

Insulin type	Evening before surgery	Morning of surgery
Long-acting insulin (glargine, detemir, degludec)	Normal dose (consider 50% dose if patients is prone to hypoglycemia[b])	Normal dose (consider 50% dose if patient is prone to hypoglycemia[a,b])
Intermediate-acting insulin (NPH)	Normal dose (consider 70%-80% dose if patient is prone to hypoglycemia[b])	50% Dose
Regular human insulin, rapid-acting insulin analogues (aspart, lispro, glulisine)	Normal dose	Withhold
Insulin pump	Normal dose	Normal basal rate, withhold short-acting

[a]NPH = neutral protamine Hagedorn.

[b]Patients who experience hypoglycemia when fasting, have a glucose decrease of more than 40 mg/dL (to convert value to mmol/L, multiply by 0.0555) overnight, whose basal insulin makes up over 60% total daily insulin dose, are malnourished, or have renal or hepatic disease.

effect.[25-27] The US Food and Drug Administration updated the SGLT-2 inhibitor prescribing information in March 2020 to recommend stopping canagliflozin, dapagliflozin, and empagliflozin at least 3 days before surgery and ertugliflozin at least 4 days before surgery.[28] Sodium-glucose cotransporter 2 inhibitors can be restarted once normal oral intake is resumed and the acute-phase response of surgery has resolved.[26] These medications serve to reduce long-term diabetes and cardiovascular complications, and so they do not need to be resumed immediately, especially after major surgery.

Dipeptidyl peptidase-4 inhibitors can be safely continued throughout the perioperative period.[1] Studies of medical and surgical patients who were taking home oral diabetes medications or low-dose insulin regimens found that hospitalized patients treated with sitagliptin had glycemic control similar to that of patients treated with a basal bolus insulin regimen, without increased hypoglycemic events.[29,30]

If a patient accidentally takes an oral antidiabetic agent the morning of elective surgery, the operation does not need to be postponed. The two exceptions for which postponement of surgery may be considered would be for an SGLT-2 inhibitor before a major operation or a sulfonylurea. If an SGLT-2 inhibitor is taken before major surgery, the patient should be monitored for ketosis until the physiologic stress of surgery has resolved or for about 72 hours after the last dose.[26] If a sulfonylurea is taken before surgery, the patient should be closely monitored for hypoglycemia.

Preoperative Insulin Management

During the initial preoperative assessment, it is important to review the patient's home insulin regimen and recent fasting glucose measurements in order to provide instructions on exactly what insulin doses should be taken the day before and the morning of surgery. Recommendations differ based on the type of diabetes, the insulin regimen, and the patient's predisposition to hypoglycemia.

Insulin Management for Patients With Type 1 Diabetes

For patients with type 1 diabetes (Table 2), it is important that long-acting basal insulin not be withheld in order to prevent the development of ketoacidosis. The normal basal insulin dose should be given the day before and the day of surgery. The only exception to giving the full dose of basal insulin is if the basal insulin dose is thought to be inappropriately high.[17] This scenario would include patients who

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TABLE 3. Preoperative Insulin Management for Patients With Type 2 Diabetes[a,b]

Insulin type	Evening before surgery	Morning of surgery
Long-acting insulin (glargine, detemir, egludec)	75%-80% Dose (consider full normal dose if patient has history of fasting hyperglycemia, consider 50% dose if patient is prone to hypoglycemia)	50% Dose
Intermediate-acting insulin (NPH)	75%-80% Dose	50% Dose (consider withholding if fasting morning glucose level is <120 mg/dL)
Regular human insulin, rapid-acting insulin analogues (aspart, lispro, glulisine)	Normal dose	Withhold
Insulin pump	Normal dose	60%-80% Normal basal rate, withhold short-acting

[a]NPH = neutral protamine Hagedorn.
[b]SI conversion factor: To convert glucose value to mmol/L, multiply by 0.0555.

experience frequent episodes of hypoglycemia, especially nocturnal or early morning hypoglycemia, have a sharp decrease in glucose of more than 40 mg/dL (to convert value to mmol/L, multiply by 0.0555) overnight, or whose basal insulin makes up over 60% of their total daily insulin dose. Patients who are malnourished or have renal or hepatic insufficiency are also at increased risk for hypoglycemia with fasting. In these cases, a 50% reduction in long-acting insulin would be recommended whenever the patient usually takes basal insulin, either the evening before or the morning of surgery. The target preoperative glucose level is 100 to 180 mg/dL.

Intermediate-acting insulin (eg, neutral protamine Hagedorn [NPH]) should be reduced by 50% the morning of surgery because it provides mealtime coverage for the midday meal, which usually will be skipped the day of surgery. The full evening dose of NPH should be given the day before surgery.[22,31] In patients prone to hypoglycemia, 70% to 80% of the evening NPH dose can be given.

Short-acting insulin (regular human insulin) and rapid-acting insulin analogues (insulin aspart, lispro, and glulisine) should be withheld the day of surgery while the patient is fasting. No adjustment is needed the day before surgery if the patient is eating normally. Patients with clinical features similar to those of patients with type 1 diabetes should be treated as such. This includes patients with histories of severe hyperglycemia or ketoacidosis, recurrent hypoglycemic episodes, or postpancreatectomy diabetes.

Similarly, patients with cystic fibrosis–related diabetes who have fasting hyperglycemia and are receiving a basal-bolus insulin regimen should receive their usual basal dose in the perioperative period with prompt resumption of prandial coverage when oral feedings are started in order to avoid the detrimental effects of postprandial hyperglycemia, to which they are prone.

Insulin Management for Patients With Type 2 Diabetes

The degree to which long-acting basal insulin doses should be reduced is less clear-cut for patients with type 2 diabetes. These patients have residual insulin production and thus are not predisposed to ketoacidosis. Therefore, it may be reasonable to reduce the basal insulin dose while the patient is fasting. Dosing recommendations differ based on whether the patient takes long-acting insulin in the evening or in the morning.

A study of patients with type 2 diabetes undergoing ambulatory surgery who took their basal insulin once daily in the evening found that those who took 75% of their usual dose were most likely to achieve the target

blood glucose level on the day of surgery.[32] Another study supported taking 80% of the evening dose with the exception of patients whose typical fasting blood glucose level was 150 mg/dL or greater because those patients had less preoperative hyperglycemia if they took their full evening dose.[33] The Society for Ambulatory Anesthesia recommends that patients take their usual long-acting insulin dose the evening before surgery, unless there is a history of nocturnal or morning hypoglycemia, and 75% to 100% of the long-acting insulin dose the morning of surgery.[22] The ADA recommends taking the full evening long-acting insulin dose and 60% to 80% of long-acting insulin the morning of surgery.[34]

At our institution, we recommend reducing the evening long-acting basal insulin dose by 50% if there is concern for nocturnal or morning hypoglycemia, especially if the basal insulin is more than 60% of the total daily insulin dose. We recommend reducing any long-acting morning basal insulin dose by 50% for most patients (Table 3).

For intermediate-acting insulin (NPH), patients with type 2 diabetes should take 75% to 80% of the evening dose and 50% of the morning dose. If the morning fasting blood glucose level is less than 120 mg/dL, the morning dose of NPH should be withheld.[17,22,31,34]

If the patient is taking a fixed combination of intermediate-acting and short-acting insulin (eg, NPH/regular), 50% of the premixed insulin can be taken the morning of surgery provided the fasting glucose level is over 150 mg/dL. Otherwise, the morning dose should be withheld.

Insulin Pumps

There is very limited evidence regarding the use of insulin pumps in the perioperative period. For patients with type 1 diabetes, the basal rate should not be adjusted. For patients with type 2 diabetes, the basal rate can be decreased to 60% to 80% of the normal dose starting the morning of surgery. Unless the planned procedure is less than 2 hours with an anticipated quick recovery, we recommend discontinuing the insulin pump and starting an IV insulin infusion intraoperatively. The pump will need to be placed in a position outside the surgical field, and the anesthesiologist must have access to the insulin pump during surgery.

Postoperatively, we either involve our inpatient diabetes team to assist with pump management or switch to a subcutaneous multidose injection regimen while the patient is in the hospital. Patient self-management of insulin pumps is permitted postoperatively if their mental status is satisfactory and they have a good understanding of pump use. In that case, we would provide patients with capillary blood glucose data and the carbohydrate content of their meals, which will be used for bolus calculations. Data entry into their pumps and bolus delivery should be supervised by nursing staff, and pump settings should be reviewed daily by the consulting diabetes team.

More studies are needed to confirm the reliability of both continuous glucose monitors and closed-loop algorithms in the perioperative setting. Therefore, for patients using sensor-augmented insulin pumps or closed-loop insulin delivery systems, we recommend using the pump in manual mode and entering capillary blood glucose data instead of relying on the sensor.

Perioperative Glycemic Targets

Perioperative hyperglycemia is associated with increased length of stay in the hospital and intensive care unit, wound infections, and myocardial infarctions.[6,31,34-36] Cardiac surgery patients with intraoperative hyperglycemia have increased risk of postoperative death and pulmonary and renal complications.[37,38] For each 20-mg/dL increase in the mean glucose level, there is a 30% increased risk of adverse events.[37]

A retrospective cohort study of over 11,000 patients undergoing elective colon, rectal, and bariatric operations focused on blood glucose levels on the day of surgery and postoperative days 1 and 2. Patients with glucose levels greater than 180 mg/dL had an increased risk of infection, death, reoperative interventions, and anastomotic failures.[39] There were decreasing rates of adverse events with better levels of glucose control, the lowest rates with

glucose levels less than 130 mg/dL. Those with hyperglycemia on postoperative days 1 and 2 had higher rates of infection than those with intraoperative hyperglycemia, illustrating the importance of glycemic control in the early postoperative period.[39]

Interestingly, perioperative hyperglycemia in nondiabetic patients has repeatedly been found to have worse outcomes than hyperglycemia in patients with diabetes.[40,41] This result may be a reflection of the greater surgical stress or illness severity leading to hyperglycemia in nondiabetic patients. Patients with diabetes were more likely to receive insulin than patients without diabetes at each blood glucose level, which may contribute to improved outcomes as well.[41]

The ADA recommends a target glucose range of 80 to 180 mg/dL in the perioperative period.[34] Tighter glycemic control has not been found to improve outcomes and has been associated with increased hypoglycemia.[42-44] The ADA recommends monitoring blood glucose levels at least every 4 to 6 hours while a patient is fasting and before meals for a patient who is eating. If a patient is receiving IV insulin, more frequent monitoring from every 30 minutes to every 2 hours is required.[34]

Basal Bolus Insulin Dosing vs Sliding Scale

For patients who are fasting, basal insulin plus a supplemental correction scale is preferred over sliding-scale insulin alone. For patients who are eating, basal insulin plus short-acting insulin with meals and a correction insulin regimen is recommended. Basal bolus regimens have been associated with improved glycemic control and lower rates of perioperative complications compared with sliding-scale regimens alone.[45,46] Point-of-care glucose levels should be checked immediately before meals. If oral intake is poor or uncertain, it may be safer to administer mealtime insulin after eating in order to cover the amount of ingested carbohydrates.

A recent study of hospitalized patients compared 70/30 premixed NPH/regular combination insulin to a basal-bolus regimen. There was comparable glycemic control between the 2 groups but increased hypoglycemia in the premixed insulin group. Therefore, premixed insulin is not recommended for inpatient use.[47]

Patients who are receiving continuous enteral or parenteral nutrition should have short-acting insulin every 4 to 6 hours to correct hyperglycemia. In critical care patients, IV insulin infusions are the preferred modality, as they have been found to best achieve glycemic targets. Insulin infusion dose adjustments should be based on a validated written or computerized protocol.[34]

Hypoglycemia

Ideally, diabetic patients undergoing elective surgery should be scheduled earlier in the day if possible to decrease the risk of hypoglycemia and other adverse metabolic effects of prolonged fasting. If patients do become hypoglycemic in the preoperative fasting period, glucose tablets or glucose gel should be used. Clear liquids including juice without pulp can be administered until 2 hours before surgery.

Postsurgical patients with diabetes are at increased risk for hypoglycemia for multiple reasons. They are fasting the day of surgery and may have no or decreased oral intake for several days thereafter, perhaps exacerbated by postoperative nausea, vomiting, and constipation. Once transient hyperglycemia (related to the stress of surgery, stress-dose corticosteroids, or dexamethasone used preoperatively to prevent nausea and vomiting) resolves, the basal insulin dose may need to be reduced. Symptoms of hypoglycemia may be masked by sedation from anesthetic and analgesic medications. According to the guidelines for inpatient diabetic management, when a glucose value of 70 mg/dL or less is noted, the patient's current insulin regimen should be reassessed.[34] Most severe hypoglycemic episodes (glucose level <40 mg/dL) in the hospital are preceded by a prior episode of hypoglycemia (glucose level <70 mg/dL).[48] We recommend an even more aggressive approach to reduce the risk of hypoglycemia and generally adjust the insulin regimen to target

blood glucose levels in the 100- to 180-mg/dL range.

PERIOPERATIVE MANAGEMENT OF PATIENTS WITH THYROID DISEASE

Screening for Thyroid Disease

Asymptomatic patients without a history of thyroid disease do not require routine preoperative screening for thyroid dysfunction. However, a thyrotropin level should be obtained in patients who present with symptoms or physical examination findings suggestive of thyroid dysfunction as part of the preoperative evaluation.[49]

Evaluation of Patients With Known Thyroid Disease

In patients with known thyroid disease who are receiving treatment, thyroid function should be assessed preoperatively unless euthyroidism has been documented within the past 3 to 6 months.[49] In patients with a large goiter, a careful evaluation of the airway, including imaging if needed, is important to assess for risk of airway compromise. In these situations, communication with the perioperative care team is recommended in order to design an appropriate plan for safely securing the airway.[50]

Perioperative Complications of Hypothyroidism

The perioperative risks in patients with untreated hypothyroidism vary by degree of thyroid dysfunction and are most often seen in patients with severe hypothyroidism.[51] Potential perioperative complications in hypothyroid patients involve nearly every organ system, including precipitating myxedema coma and cardiac or respiratory compromise. Patients with severe hypothyroidism are at increased risk of multiple cardiovascular complications including reduced cardiac output (by as much as 30%-50%), intraoperative hypotension, coronary events, bradycardia, arrhythmias, and prolonged QT interval resulting in ventricular tachycardia and torsades de pointes. Respiratory complications include impaired hypoxic and hypercapnic respiratory drive, respiratory muscle weakness, and increased prevalence of obstructive sleep apnea.[49] Additional concerns include difficult airway due to laryngeal myxedema, macroglossia, and sensitivity to anesthetic agents.[50-52] Postoperatively, hypothyroidism predisposes the patient to ileus, neuropsychiatric complications, coagulopathies, and impaired wound healing.[49,51-53] Myxedema coma, characterized by altered mental status, hypotension, bradycardia, hypothermia, and metabolic derangements, is a rare and feared complication of severe hypothyroidism that can be precipitated by surgery, with a mortality rate up to 80%.[49]

When Should Surgery Be Postponed for Hypothyroidism?

For this review, we classify hypothyroidism as mild (subclinical hypothyroidism), moderate (elevated thyrotropin level and mildly reduced total thyroxine level [$\geq$0.5 μg/dL; to convert to nmol/L, multiply by 12.871), or severe (myxedema coma, severe symptoms, or free thyroxine level <0.5 ng/dL) to determine perioperative care. Patients with untreated or inadequately treated mild/subclinical hypothyroidism can safely undergo surgery without delay. There is no consensus for timing of elective surgery in patients with moderate hypothyroidism. In a retrospective cohort study of patients undergoing noncardiac operations, no difference in mortality, wound, or cardiovascular outcomes was observed among patients with moderate untreated hypothyroidism, treated hypothyroidism, or euthyroid patients.[53] Thus, in mild to moderate hypothyroidism, adverse outcomes are unlikely, and postponing elective surgery is likely unnecessary.[53]

Patients with severe hypothyroidism, however, are at greatly increased perioperative risk, and elective surgery should be delayed until effectively treated. If urgent or emergent surgery is required, hormone replacement therapy should be initiated immediately with IV levothyroxine, using a loading dose of 200 to 500 μg followed by 50 to 100 μg daily.[49] If there is concern

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regarding the presence or precipitation of myxedema coma, IV liothyronine should be given simultaneously, and testing for adrenal insufficiency should be strongly considered. The only exception to the preoperative initiation of thyroid hormone replacement may be patients requiring urgent cardiac revascularization, in which thyroid hormone replacement may worsen cardiac ischemia.[49,54]

Perioperative Thyroid Hormone Management

In patients with treated hypothyroidism who are clinically euthyroid, thyroid hormone supplements can be safely withheld postoperatively for a few doses until the patient is able to take medication by mouth. Levothyroxine has a half-life of 7 days. Thus, it is only after 5 to 7 missed oral doses that parenteral supplementation with IV levothyroxine should be initiated. The IV dose should be 60% to 80% of the daily oral dose.[49,51,52,54]

Perioperative Complications of Hyperthyroidism

The perioperative risks of hyperthyroidism also involve multiple organ systems due to thyroid hormone's wide-ranging effects. Of particular concern are cardiovascular complications secondary to a hyperdynamic circulatory state. Vasodilation, decreased systemic vascular resistance, and alterations in the renin-angiotensin-aldosterone system resulting in sodium and water retention lead to increased cardiac output by 50% to 300% and predispose the patient to high-output heart failure.[49] Symptoms of myocardial ischemia may be precipitated or worsened. An increased incidence of atrial fibrillation is seen in up to 10% to 20% of patients with overt hyperthyroidism and subclinical hyperthyroidism.[49-51]

Additional complications are related to the catabolic state associated with severe hyperthyroidism.[50] Anorexia with malnutrition and hypoalbuminemia, hyperthermia, hyponatremia, hypercalcemia, and myopathy with generalized and respiratory muscle weakness are among the systemic effects increasing surgical risk.[50,51]

The greatest perioperative risk to the patient with thyrotoxicosis is thyroid storm, a rare but life-threatening manifestation of hyperthyroidism characterized by hyperthermia, tachycardia, and altered mentation, which may culminate in cardiovascular collapse and death. Thyroid storm usually occurs during, or in the hours after, the operation. Presenting symptoms may be difficult to distinguish from malignant hyperthermia, serotonin syndrome, neuroleptic malignant syndrome, or pheochromocytoma crisis.[49,50,54]

When Should Surgery Be Postponed for Hyperthyroidism?

Patients with subclinical hyperthyroidism (asymptomatic and normal free thyroxine) may proceed to surgery.[49,54] In light of the significant perioperative risks, elective surgery should be delayed in those with overt hyperthyroidism until the patient is euthyroid, which can be achieved in a few weeks with appropriate treatment. Medical therapy for treated hyperthyroidism should be continued perioperatively. Perioperative β-blockade may be considered in hyperthyroid patients when time allows for safe preoperative titration of the dose, ideally with initiation at least 7 days before noncardiac surgery. Alternatively, anesthesiologists can use short-acting β-blockers intraoperatively as needed.

Management of Hyperthyroidism in Urgent or Emergent Surgery

Patients with severe hyperthyroidism requiring urgent or emergent surgery require close perioperative monitoring with use of invasive cardiovascular monitoring devices. Premedication with β-blockade, antithyroid agents, and possibly corticosteroids should be administered. Preferred β-blockers include propranolol, which may be used intravenously during surgery and has the additional benefit of inhibiting conversion to active thyroid hormone, or an esmolol drip, which allows for rapid titration because it is short-acting.[49,54] Antithyroid drugs, specifically thionamides (methimazole and propylthiouracil), decrease thyroid hormone synthesis and should be given orally or rectally. When there is an urgent need to

TABLE 4. Interpretation of Morning Cortisol and Corticotropin Stimulation Tests[a]

Test	Recommendation
Morning corticotropin test	
Cortisol (8 AM, at least 24 h after last corticosteroid)	
<5 μg/dL	Give supplemental corticosteroids[b]
5-10 μg/dL	Consider corticotropin stimulation test vs empiric supplemental corticosteroids
>10 μg/dL	No supplemental corticosteroids needed
Corticotropin stimulation test	
Cortisol (30-60 min after giving 250 μg corticotropin)	
<18 μg/dL	Give supplemental corticosteroids
≥18 μg/dL	No supplemental corticosteroids needed

[a]SI conversion factor: To convert corticol values to nmol/L, multiply by 27.588.
[b]See Table 5 for dosing.

rapidly stabilize thyrotoxicosis, iodine should be given 1 hour after thionamide administration to block the organification of iodide and decrease thyroid hormone synthesis. In addition, stress-dose glucocorticoids should be given to address low adrenal reserve and prevent conversion from thyroxine to triiodothyronine. A standard regimen is hydrocortisone at 100 mg IV every 8 hours the day of surgery, tapered over 3 days.[49,54]

PERIOPERATIVE MANAGEMENT OF PATIENTS WITH ADRENAL INSUFFICIENCY: STRESS-DOSE CORTICOSTEROIDS

In patients undergoing long-term treatment with corticosteroids, secondary adrenal insufficiency can develop due to inhibition of the hypothalamic-pituitary-adrenal (HPA) axis. Not long after the first publication in 1949 reporting that corticosteroids were helpful in treating rheumatoid arthritis,[55] two case reports were published describing patients who died after surgery shortly after corticosteroids had been stopped.[56,57] Perioperative stress-dose corticosteroids have been the standard of practice ever since, although the evidence supporting this practice is still sparse.

Early recommendations were based on incorrect assessments of how much cortisol is secreted under physiologic stress and how long those increases last.[57] We now know that cortisol secretion rarely exceeds 200 mg/d following surgery and is often a third or a fourth of that with less invasive surgeries.[58,59]

There are still many unanswered questions about who needs supplemental stress-dose corticosteroid therapy perioperatively. One is how quickly patients regain adequate HPA function after stopping corticosteroids. A meta-analysis assessing rates of adrenal insufficiency after use of corticosteroids found that a substantial number of patients remained adrenally insufficient 6 months after stopping corticosteroids.[60] It is not clear what doses of topical, inhaled, or injected corticosteroid result in HPA suppression, although higher doses and longer durations increase the risk.[60,61] We also are not sure if an abnormal result on a corticotropin stimulation test makes the use of supplemental corticosteroids necessary.[62] Finally, because of the frequent use of preoperative dexamethasone for nausea and vomiting prophylaxis, the need for additional corticosteroid dosing is less clear.

There are no good data regarding the development of perioperative hypotension and the need for rescue corticosteroids and fluids among those patients not treated with stress-dose corticosteroids. There has not been an organized effort to collect these data, perhaps because the use of perioperative supplementation is so well established and/or

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TABLE 5. Perioperative Supplemental Corticosteroid Dosing[a]

Surgery type	Example	Suggested corticosteroid dose[b]
Superficial	Dental surgery Biopsy	No supplemental corticosteroids
Minor	Inguinal hernia repair Hand surgery	25 mg IV hydrocortisone before incision
Moderate	Hysterectomy Total joint replacement	50 mg IV hydrocortisone before incision, then 25 mg every 8 h for 1-2 d
Major	Cardiopulmonary bypass Trauma Prolonged surgery Surgery that involves delayed oral intake	100 mg IV hydrocortisone before incision, then 50 mg every 8 h for 2-3 d

[a]IV = intravenous.
[b]In addition to patient's usual daily dose.

because of the frequent use of dexamethasone prophylaxis for nausea and vomiting. Conversely, there is also no evidence that perioperative supplementation using current dosing recommendations leads to impaired wound healing, increased risk of infection, clinically significant hyperglycemia, or other complications, although they are all biologically plausible. Supplementation is common because we fear the consequences of postoperative adrenal insufficiency, even if it is rare, more than the risks of short-term corticosteroids.[61]

Our general approach to perioperative corticosteroids, similar to other previously published approaches,[59,63] is as follows.

Who Does Not Need Supplemental Corticosteroids?

The following groups do not require any additional perioperative corticosteroids because suppression of the HPA axis is unlikely:

- Patients who have been taking corticosteroids less than 3 weeks
- Patients who are taking less than the equivalent of 5 mg of prednisone daily (assuming they had not been taking higher doses previously)
- Patients undergoing superficial procedures (eg, cataract extraction, biopsy, dental surgery)

When Are Supplemental Corticosteroids Recommended Without Additional Testing?

Perioperative supplemental corticosteroids are recommended for the following subset of patients:

- Patients with primary adrenal insufficiency or secondary adrenal insufficiency due to hypopituitarism
- Patients with clinical Cushing syndrome secondary to corticosteroid exposure
- Patients taking oral corticosteroid doses greater than or equal to 5 mg prednisone daily (or equivalent) for more than 3 weeks during the past 3 months
- Patients receiving high-dose inhalation glucocorticoid therapy (eg, beclomethasone, 1.5 mg/day; fluticasone, >8 μg/kg daily)

Who Should Have Additional Testing?

A patient having elective surgery who does not fit within one of the aforementioned categories may benefit from additional testing to assess for HPA axis suppression. This guideline includes patients not currently taking corticosteroids but who

have been exposed to corticosteroids (≥5 mg prednisone for at least 3 weeks) over the past year. We would also recommend further testing for anyone who has been exposed to high-dose topical glucocorticoid therapy (eg, clobetasol propionate, betamethasone) or multiple corticosteroid injections. We recommend first checking a morning cortisol level at 8 AM, at least 24 hours after the last dose of glucocorticoids. Based on the morning cortisol result, a corticotropin stimulation test may be warranted (Table 4).

Urgent or emergent surgery should not be delayed for testing, and in this case, we recommend deferring to clinical judgment based on the dose and duration of corticosteroid exposure and the suspected likelihood of HPA axis suppression.

Stress-Dose Corticosteroid Dosing

Different surgeries lead to different increases in cortisol production, so the amount of corticosteroid supplementation needed depends on the type of surgery.[64,65] Recommendations on the amount of supplementary corticosteroids are not based on randomized controlled trial data but rather expert opinion based on physiologic data. At our institution, we typically dose supplemental corticosteroids as outlined in Table 5.

Patients with secondary adrenal insufficiency should have normal mineralocorticoid function, so fludrocortisone is not needed perioperatively. Even in patients with primary adrenal insufficiency who cannot take anything by mouth, adequate hydrocortisone doses and intravenous fluids make fludrocortisone unnecessary in the short term.

Most recommendations suggest having patients take their usual daily corticosteroid dose and then receive the first dose of supplemental hydrocortisone before the operation starts. Although patients taking more than 50 mg of prednisone or its equivalent daily are already getting more corticosteroid exogenously than they would ever make endogenously, recommendations do not change for these patients.

Patients who do not receive corticosteroid supplementation and later develop hypotension that is not responsive to usual intraoperative or perioperative management should receive 100 mg of IV hydrocortisone, followed by 50 mg every 6 hours for at least 24 hours.[59,61]

CONCLUSION

Surgical patients with endocrine issues require special consideration during preoperative evaluation and postoperative management. Initial assessment should focus on establishing the patient's current status, ie, the degree of glycemic control for patients with diabetes, thyroid function for patients with thyroid disease, and risk of HPA axis suppression for patients receiving long-term corticosteroid therapy. This assessment will guide subsequent intraoperative and postoperative recommendations. For patients with diabetes, intraoperative and postoperative glycemic control is the most important determinant of surgical outcomes. For thyroid disease, surgical plans only need to be adjusted for patients with untreated hyperthyroidism or severe hypothyroidism. For patients receiving long-term corticosteroid therapy, the need for stress-dose corticosteroids is determined by the invasiveness of the operation, the dose and duration of corticosteroid exposure, and further testing of the HPA axis as needed. As with other components of the preoperative medical evaluation, the primary objective is identification of these issues before surgery so that the surgeons, anesthesiologists, and internal medicine providers professionals can optimize management accordingly.

Abbreviations and Acronyms: **ADA** = American Diabetes Association; **HbA1$_c$** = hemoglobin A1$_c$; **HPA** = hypothalamic-pituitary-adrenal; **IV** = intravenous; **NPH** = neutral protamine Hagedorn; **SGLT-2** = sodium-glucose cotransporter 2

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The Thematic Review Series on Perioperative Medicine will continue in an upcoming issue.

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