Patients with endocrinopathies frequently present to the operating room. Although many of these disorders are managed on a chronic basis, patients may have acute changes in the perioperative period that, if left unrecognized, can have a negative effect on perioperative morbidity and mortality. It is imperative that anesthesiologists understand the implications of the surgical stress response on hormonal flux. This article focuses on the 4 most commonly encountered endocrinopathies: diabetes mellitus (DM), hyperthyroidism, hypothyroidism, and adrenal insufficiency. Specific challenges pertaining to patients with pheochromocytoma are also discussed.

DM
Diabetes is the most common endocrinopathy in the United States. Familiarity with its pathogenesis and management is therefore critical for perioperative clinicians. Approximately 90% of patients with DM are classified as type 2 and the remainder are type 1. It is estimated that more than 50% of this entire population will require surgery at some point during their lifetime. From a resource utilization standpoint, the average patient with DM spends up to 50% more time in the hospital postoperatively than a patient without DM undergoing the same procedure. Complications that are a direct result of this disease (neuropathy, retinopathy, nephropathy, and vasculopathy) often culminate in the need for surgery.

KEYWORDS
- Endocrine
- Perioperative
- Diabetes
- Hyperthyroidism
- Hypothyroidism
- Adrenal insufficiency
- Pheochromocytoma
Type 1 DM (T1DM) is a consequence of the destruction and loss of pancreatic β cells (insulin producing). On the contrary, type 2 DM (T2DM) is a disease characterized by the interaction of genetic and environmental factors (stress, diet, and amount of exercise), culminating in insulin resistance, abnormal β-cell function and, ultimately, the development of overt T2DM. T2DM results when compensatory increases in insulin secretion can no longer keep plasma glucose levels within normal limits because of abnormal β-cell mass and function and inappropriate release of glucagon by pancreatic α cells.

Although these 2 classes effectively discriminate most patients with diabetes, it is important for the perioperative clinician to understand that other conditions may result in a similar phenotype, such as pancreatitis and pancreatic cancer. Patients destined to develop T2DM will have a prediabetic state of impaired glucose tolerance (IGT) diagnosed by a fasting blood glucose level greater than 100 mg/dL or 2-hour postprandial glucose level of 140 mg/dL or greater after a standard glucose challenge. This finding is critical as it has been shown that patients coming into hospital with previously unrecognized abnormal glucose tolerance, or overt DM, have worse outcomes and a greater number of complications during the hospitalization, often in association with surgical procedures. Major efforts should be instituted to identify these patients before or on admission and criteria for those at special risk have recently been delineated.

The ability of perioperative clinicians to risk stratify these patients appropriately and develop an interventional strategy depends on the individual patient, and the associated pathologic condition. Although anesthesiologists are rarely involved in the long-term care of these patients, the consequences of uncontrolled diabetes (ie, electrolyte imbalances, dehydration, wound infection) in the perioperative period can be life threatening. Therefore, appropriate risk stratification and an optimal interventional strategy are necessary.

It is imperative to do a careful preoperative assessment for all patients as the patient with DM requires a systematic approach because the disease affects numerous organ systems (Table 1). Furthermore, although the surgical stress response is similar for a given procedure, patients with DM (particularly those with T1DM) are less able to counteract the effects of the gluconeogenic and glycolytic hormones (ie, cortisol, epinephrine, glucagon, growth hormone) that are released, all of which counteract the effect of insulin and may contribute to hyperglycemia.

Before examining the patient, there are several laboratory values that can help discern the severity of disease. Glycosylated hemoglobin (HbA1C) values can reflect the degree of hyperglycemia to which red blood cells (RBC) have been exposed. Because the average lifespan of an RBC is 120 days, the HbA1C is an indicator of glycemic levels over that period of time (although it is more strongly related to the prior 8–12 weeks). A normal value is up to 6%, but some patients with values greater than 5.5% may have IGT. The American Diabetes Association goal for DM control is less than 7%. Values more than 8% correspond to average blood glucose level of more than 180 mg/dL and indicate poor glycemic control.

Because diabetes is a leading cause of renal failure, measurement of renal function can give insight into the severity of disease. Furthermore, of particular concern to the perioperative clinician, patients with DM with renal insufficiency are at greater risk for hypoglycemia given the prolonged half-life of insulin and sulfonylureas. By identifying these patients preoperatively, more frequent (every 30–60 minutes) monitoring of blood glucose may be anticipated. Although a serum creatinine value itself does not
diagnose renal impairment, in the steady state it gives a good estimate of glomerular filtration rate (GFR) via the Cockcroft-Gault equation:\(^{10}\):

\[
\text{GFR} = \frac{140 - \text{age}}{\frac{72 \times \text{serum creatinine}}{\text{weight} \times (0.85 \text{ if female})}}
\]

Preoperative evaluation of patients with DM should focus on some of the more common association and sequelae of the disease process (Table 1). These patients are at increased risk for cerebrovascular accidents, myocardial infarctions, acute renal failure, and postoperative wound complications. This risk may be mitigated with control of perioperative hyperglycemia. Musculoskeletal manifestations are common and may predict difficulties with laryngoscopy and endotracheal intubation.\(^{11}\) A positive prayer sign (inability to approximate fingers and palms with fingers extended) may be an indicator of joint rigidity.\(^{12}\) Such complications are important to note in the perioperative period and provisions should be taken to minimize further exacerbation.

The major goals for these patients pertinent to their endocrinopathy should be minimizing hyperglycemia and avoiding hypoglycemia, hypovolemia, and hypo- or hyperkalemia. In addition, minimizing the length of time these patients remain nil by
mouth is important. Surgery and anesthesia invoke a stress response in patients that is characterized by hypersecretion of counterregulatory hormones (eg, glucagon, norepinephrine, cortisol, and growth hormone). This response culminates in increased gluconeogenesis, glycogenolysis, and peripheral insulin resistance. Endogenous insulin levels are dramatically increased in the face of injury despite often profound hyperglycemia (ie, relative insulin deficiency). The effect of this altered hormonal milieu may culminate in diabetic ketoacidosis (DKA) in patients with T1DM and hyperosmolar hyperglycemic nonketosis in patients with T2DM. Understanding this hormonal imbalance is fundamental to appreciating the fine endocrine balance these patients withstand in the perioperative period (Fig. 1). On the one hand, the surgical stress response initiates counterregulatory hormone secretion and relative insulin deficiency, culminating in hyperglycemia. On the other, perioperative fasting with increased endogenous and exogenous insulin can easily cause profound hypoglycemia. Thus, a perioperative strategy that anticipates this condition and aims to restore normoglycemia should be undertaken.

Although the approach to outpatient diabetic management is to aim for the lowest sugar possible without undue hypoglycemia, a similar perioperative goal is less realistic and potentially dangerous. Although there are no current guidelines on perioperative glycemic control, the American College of Endocrinology has released a position statement on inpatient glycemic control. Understanding that the perioperative period is unique, a reasonable approach would be to maintain blood glucose levels less than 200 mg/dL intraoperatively and less than 150 mg/dL postoperatively, but to avoid levels less than 80 mg/dL. This strategy would avoid severe hyperglycemia and minimize hypoglycemia. Patients who are insulin dependent often require a change in their scheduled dosing dependent on how long they are nil by mouth before surgery, the frequency of their insulin administration, and when the case is scheduled (Box 1). Thiazolidinediones (TZD) can be held on the morning of surgery, and secretagogues must be held preoperatively. However, the biguanide metformin, which has been associated with the development of lactic acidosis, should be withheld 24 hours preoperatively and restarted 48 to 72 hours postoperatively once normal renal function has been restored.

Fig. 1. The glycemic balance in the perioperative period. (Adapted from Kohl BA, Schwartz S. Surgery in the patient with endocrine dysfunction. Anesthesiol Clin 2009;27(4):687–703; with permission.)
Long-acting sulfonylureas (ie, chlorpropramide), although rarely used, are best withheld 48 to 72 hours preoperatively to avoid potential hypoglycemia. Incretins may be given (incretin mimetics subcutaneously and dipeptidyl peptidase 4 inhibitors by mouth with a sip of water on the morning of surgery) because, in the absence of insulin or secretagogues, they do not cause hypoglycemia and seem particularly effective in reducing perioperative hyperglycemia as they counteract the effect of steroids on decreasing β-cell function, best demonstrated in a murine model. Antihyperglycemic agents (TZDs and incretins) and secretagogues may be restarted once enteral intake is permitted, although metformin is commonly avoided postoperatively in the hospital in case intercurrent events ensue that might change renal function acutely (eg, hypotension, iodine dye–induced renal dysfunction, sepsis) and risk lactic acidosis. Box 1 summarizes perioperative insulin therapy recommendations in those patients (T1DM and T2DM) who routinely require insulin. In general, all of these patients should be scheduled as first case of the day to minimize a significant endocrine imbalance.

**Box 1**

**Perioperative management of insulin-dependent diabetes**

- **Night before procedure**
  - Continue usual dose of PM glargine/NPH or mixture (can recommend two-thirds usual dose if tightly controlled) the night before surgery (as long as taking usual by mouth intake the night before the operation)
  - For insulin pump users: continue usual overnight basal rate

- **Morning of procedure**
  - No boluses of short-acting hypoglycemics unless blood sugar level is greater than 200 mg/dL and greater than 3 hours preoperative
  - May place on insulin drip or give usual dose of glargine if routinely taken in morning
  - For insulin pump users: continue usual basal rate and infuse D5 throughout operation
  - If on NPH or other insulin mixture:
    - No short-acting insulin within 3 to 4 hours of procedure (ie, no mixture preoperatively)
    - Give half usual intermediate-acting insulin, with D5, at controlled rate throughout procedure
    - If performing operation without continuous D5, give no insulin preoperatively

- **Special situations**
  - **Emergency surgery**
    - No bolus of short-acting hypoglycemics preoperatively. Frequent (every 30–60 minutes) monitoring of blood sugar level throughout operation. Start insulin infusion if blood sugar level is greater than 200 mg/dL
  - **Cardiac surgery**
    - Continue insulin infusion as needed to maintain blood glucose level at 100 to 150 mg/dL in first 3 postoperative days.

**Abbreviations**: D5, 5% dextrose containing solution; NPH, neutral protamine Hagedorn.

(Adapted from Kohl BA, Schwartz S. Surgery in the patient with endocrine dysfunction. Anesthesiol Clin 2009;27(4):687–703; with permission.)
There remains a paucity of data to guide the clinician on intraoperative glycemic control. The population that has been most heavily scrutinized has been cardiac surgery. There remains significant clinical equipoise regarding the potential benefit of tight intraoperative glycemic control even in this subset of patients.\textsuperscript{25–30} However, although no formal recommendations have been made, most clinicians would agree that maintaining plasma glucose level less than 200 mg/dL intraoperatively is reasonable. Similar consensus exists for the noncardiac surgical population.\textsuperscript{31}

Postoperatively, attempts should be made to initiate enteral intake as soon as possible. This process should be undertaken carefully, and in consultation with a nutritionist familiar with the needs of patients with diabetes.\textsuperscript{32} Postoperative glycemic control has been (and continues to be) investigated thoroughly. Although there seems to be benefit with glycemic control in relation to postoperative surgical site infection,\textsuperscript{5,33,34} there continues to be significant equipoise as this treatment modality relates to other morbidities and mortality.\textsuperscript{35,36}

HYPERTHYROIDISM

The causes of hyperthyroidism are myriad. However, by far, the most common cause in the United States is Graves disease. This is an autoimmune disorder caused by antibody generation directed at thyroid-stimulating hormone (TSH) receptors, causing an increase in thyroid hormone production. Clinical signs and symptoms of hyperthyroidism include tachycardia, atrial fibrillation, fever, tremor, goiter, and ophthalmopathy. Other manifestations include gastrointestinal symptoms such as diarrhea, nausea, and emesis. Not all patients present with the classic symptomatology or laboratory findings. Patients with subclinical (masked) hyperthyroidism often are asymptomatic and frequently have normal free thyroid hormone levels with suppressed TSH. This entity is more common in the geriatric population. In clinically overt hyperthyroidism free thyroid hormone (T\textsubscript{4} and T\textsubscript{3}) levels are frequently mildly increased; however, TSH is usually suppressed. In states of thyrotoxicosis, free T\textsubscript{4} levels can be dramatically increased. T\textsubscript{3} and T\textsubscript{4} have direct inotropic and chronotropic effects on the heart. In addition, thyroid hormones have a direct effect on vascular smooth muscle, causing a decrement in systemic vascular resistance and mean arterial blood pressure. As a result, the renin-angiotensin-aldosterone system is activated, enhancing sodium reabsorption and increasing circulating blood volume, increasing cardiac output by 50\% to 300\% (Fig. 2).\textsuperscript{37,38} Chronically increased levels of these hormones may limit the ability of patients to respond to the stress of surgery and can culminate in cardiovascular collapse.\textsuperscript{39–41} The perioperative clinician must be familiar with the diagnosis and treatment of hyperthyroidism as failure to identify and treat appropriately can drastically increase mortality.

Patients with hyperthyroidism should take their antithyroid medications on the morning of surgery.\textsuperscript{42} For those patients with uncontrolled hyperthyroidism who are presenting for elective surgery, their surgical procedure should be postponed until they are on a stable medical regimen to reduce their risk of thyroid storm.\textsuperscript{43} For those patients presenting for urgent or emergent surgery, it is incumbent on the anesthesiologist to have ready access to drugs that block the systemic effects of excess thyroid hormone. Such drugs include \(\beta\)-blockers, antithyroid medications (including propylthiouracil [PTU] and methimazole), and iodine. \(\beta\)-Blockers not only directly inhibit sympathetic activation but also inhibit the peripheral conversion of T\textsubscript{4} to T\textsubscript{3} (the most active thyroid hormone). Thionamides, such as PTU and methimazole, are actively transported into the thyroid gland and inhibit further production of hormone. Furthermore, PTU inhibits peripheral conversion of T\textsubscript{4} to T\textsubscript{3}.\textsuperscript{44} Inorganic iodide,
although necessary for normal thyroid function, in excess manifests an antithyroid action known as the Wolff-Chaikoff effect.\textsuperscript{45} Potassium iodide is given enterally as either Lugol solution (8 mg iodide per drop) or saturated solution of potassium iodide (SSKI) and is usually administered preoperatively for thyroid surgery as it decreases the vascularity of the gland.\textsuperscript{46} Inorganic iodide should not be administered before thionamide treatment as it may initially increase the amount of thyroid hormone released and precipitate thyroid storm (Jod-Basedow effect). Anesthetic agents that are vagolytic or sympathomimetic (eg, pancuronium, ephedrine, epinephrine, norepinephrine, atropine) are best avoided in patients with thyrotoxicosis.\textsuperscript{19}

The most feared perioperative complication that usually arises from either undiagnosed or undertreated hyperthyroidism is thyroid storm. Thyroid storm can occur any time in the perioperative period, although it usually occurs either intraoperatively or in the first 48 hours postoperatively. The mortality of thyroid storm is 10\% to 75\% and it requires monitoring in a critical-care environment.\textsuperscript{47} Symptoms are nonspecific and include hyperpyrexia up to 41.1°C (106°F), tachycardia, and delirium.\textsuperscript{48} Other conditions that should be considered on the differential diagnosis include malignant hyperthermia, neuroleptic malignant syndrome, and pheochromocytoma. As the mortality of this entity is high if left untreated and the diagnosis is purely clinical (supported by laboratory data), it is often necessary to treat empirically before confirmation.\textsuperscript{49} Treatment of thyroid storm includes thionamides, β-blockers (goal heart rate <90 beats per minute), and antipyretics (or external cooling measures).\textsuperscript{19} Acetaminophen is preferred to salicylates as the latter may exacerbate thyrotoxicosis by decreasing thyroid protein binding and increasing free $T_3$ and $T_4$.\textsuperscript{49} A search for the precipitating cause of thyroid storm should be undertaken immediately. The most common cause in the perioperative period is infection (sepsis). Blood, urine, and sputum cultures should be obtained; however, empiric antibiotics are not recommended.\textsuperscript{50} For those patients who are volume depleted, particularly if chronic

![Cardiovascular effects of thyroid hormone. (From Klein I, Danzi S. Thyroid disease and the heart. Circulation 2007;116:1725; with permission.)](image-url)
Hyperthyroidism exists, volume resuscitation with the addition of dextrose should be administered to replace depleted glycogen stores.  

**HYPOTHYROIDISM**

Hypothyroidism is a common endocrinopathy in the United States that affects about 1% of all patients and is more prevalent in females. Primary hypothyroidism accounts for 95% of all cases and is characterized by low thyroid hormone levels (free $T_4$ <5 pmol/L) in the face of normal or increased TSH (often $>10$ mU/L). Common signs and symptoms of hypothyroidism include lethargy, fatigue, anorexia, headaches, hoarse voice, depression, and cold intolerance. The most common noniatrogenic cause is chronic autoimmune thyroiditis (Hashimoto thyroiditis). There are myriad iatrogenic causes with which the perioperative clinician needs to be familiar. Surgical thyroid resection or radioactive ablations are common causes that can frequently be anticipated. Less obvious, however, are treatment of hyperthyroidism or other pituitary and hypothalamic disorders (Sheehan syndrome, pituitary dysfunction after head trauma). Various drugs can induce hypothyroidism, including lithium, amiodarone, iron, and cholestyramine. The surgical stress response in addition to general anesthesia may also incite hypothyroidism or, more commonly, the classic euthyroid sick syndrome. After induction of general anesthesia, total $T_3$ levels decrease and remain low for at least 24 hours. Understanding the implications of hypothyroidism on the morbidity and mortality of surgical patients may allow the perioperative clinician to anticipate complications and preemptively manage them.

Similar to hyperthyroidism, hypothyroidism affects multiple organ systems and encompasses a wide clinical spectrum. The most clinically important of these is the cardiovascular system. Although plasma catecholamine levels are generally within normal limits, $\beta$-adrenergic receptor function is depressed and results in an imbalance of $\alpha$- and $\beta$-adrenergic activity, with $\alpha$ predominating. In general, a deficiency in thyroid activity culminates in depressed cardiac function (inotropy and chronotropy), and increased systemic vascular resistance. The pulmonary system is affected as there may be depressed responses to hypercarbia and hypoxemia and, in more severe cases, decreased lung diffusion capacity. The renin-angiotensin-aldosterone complex responds to this situation by excreting sodium (> free water) culminating in hyponatremia and intravascular volume depletion.

The preferred treatment of hypothyroidism is tetraiodothyronine ($T_4$, levothyroxine) replacement and patients should preferably be rendered euthyroid before surgery. The more active hormone ($T_3$) is less stable but is converted in vivo intracellularly. The half-life of levothyroxine is approximately 1 week and therefore it is not imperative that patients take their dose the morning of surgery. If intravenous dosing is necessary, half the enteral dose is equivalent. There is controversy in hypothyroid patients with known ischemic heart disease or presenting for coronary revascularization. Rapid replenishment of thyroid function risks increasing myocardial oxygen demand, causing ischemia. However, delay in therapy may place the patient at risk of developing myxedema coma. Currently, the consensus is that if a patient needs urgent cardiac revascularization, they should undergo the procedure before replacement therapy; however, many endocrinologists recommend starting at least low dose $T_4$ in consultation with the cardiologist.

Patients presenting for surgery with hypothyroidism can be grouped into 3 categories: (1) hypothyroid patients well controlled on thyroid medications, (2) mild to moderately hypothyroid patients, and (3) patients presenting with or developing severe hypothyroidism (myxedema coma) perioperatively. There is little to do with
the first group other than be aware of their thyroid replacement dosing and be hyper-
acute to signs and symptoms of worsening hypothyroidism postoperatively, including
delirium, prolonged ileus, infection without fever, and myxedema coma. Preoperative
sedation in this group should be minimized as these patients can be exquisitely sensi-
tive to narcotics and benzodiazepines. Most patients with mild to moderate hypothy-
roidism can undergo surgery without a disproportionate increase in perioperative
risk.55,60,61 Close attention to airway patency in the postoperative period is necessary
as there have been reports of airway obstruction in hypothyroid patients.62 Intraoper-
ative fluid replacement should be with dextrose containing normal saline. Controlled
ventilation is recommended as these patients are at risk for hypoventilation. In those
patients who present for surgery with severe hypothyroidism (depressed mental
status, pericardial effusion, and heart failure) or in whom treatment is deemed neces-
sary before urgent/emergent surgery (severely depressed T4 and T3), intravenous lev-
othyroxine (200–500 \( \mu g \) given during 30 minutes) should be administered, followed by
a daily dose of 50 to 100 \( \mu g \) intravenously.63 As many patients with hypothyroidism
also have adrenal insufficiency (and because thyroid replacement may precipitate
adrenal crisis), glucocorticoids should be administered concurrently.19

Myxedema coma is rare and usually presents postoperatively. It is commonly
precipitated by additional insults such as infection, cold exposure, sedatives, analge-
sics, and various other medications. Although the mortality of this entity has been
reported to be as high as 80%, it seems to be decreasing in recent years likely
because of increased awareness and improved diagnostic testing.59,64,65 Myxedema
coma is characterized by severely depressed mental status (sometimes coma or
seizure), hypothermia, bradycardia, hyponatremia, heart failure, and hypopnea.
Although maintenance of normothermia is tempting, the resulting vasodilatation
may cause cardiovascular collapse in someone with intravascular volume depletion,
cardiac insufficiency, and pericardial effusion/tamponade and should be performed
extremely carefully, if at all.59 Myxedema coma is a medical emergency and necessi-
tates urgent administration of levthyroxine. An initial intravenous bolus of 200 to 500
\( \mu g \) should be given followed by 50 to 100 \( \mu g/d \). Dehydration is frequently present and
aggressive volume resuscitation with dextrose and normal saline should be instituted.
Again, intravenous glucocorticoids should be administered (eg, 50 mg hydrocortisone
4 times a day) because of frequent concomitant adrenal insufficiency. Resolution of
symptoms, if properly treated, should be seen within 24 hours.

ADRENAL INSUFFICIENCY

The hypothalamic-pituitary-adrenal (HPA) axis is central to a patient’s ability to
generate a surgical stress response. A defect anywhere in this cycle has dramatic
consequences in the perioperative period. Whereas tuberculosis used to be the
main cause of primary adrenal insufficiency (AI), autoimmune adrenalitis is now the
most common cause. Other causes of primary AI include infections, adrenalectomy,
and sepsis.66,67 However, of greater importance to perioperative clinicians is
secondary AI. Secondary AI is characterized by atrophy of the adrenal cortex and
occurs when insufficient adrenocorticotropic hormone (ACTH) is released to stimu-
late the adrenal cortex. It is most commonly caused by exogenous glucocorticoid
administration, which suppresses hypothalamic corticotrophin-releasing hormone
and pituitary ACTH. Although there is remarkable variability in individual response
to a particular dose and length of treatment with steroids, in general any patient
who has received the equivalent of 20 mg per day of prednisone for greater than 5
days is at risk for suppression of the HPA axis and if they have been on therapy for
approximately 1 month they may have HPA suppression for up to 6 to 12 months after stopping therapy. Additionally, an equivalent dose of prednisone 5 mg (or less) for any period of time will not usually suppress the HPA axis significantly. Other modes of steroid administration should be noted preoperatively as topical, inhaled, and regional administration of glucocorticoids may all cause adrenal suppression. In addition, these generalizations pertain to the patient taking steroids in the morning. A lower dose of steroids in the evening may inhibit the normal diurnal ACTH release and affect the way that patient is able to respond to a surgical stress.

Although glucocorticoids alone are not vasoactive, they mediate vascular tone by increasing responsiveness to catecholamines. This effect occurs at a local tissue level (ie, not centrally mediated) and likely is mediated by inhibition of prostacyclin production. Mineralocorticoid deficiency does not have the same effect. Mineralocorticoid (ie. aldosterone) secretion is primarily regulated by the renin-angiotensin system. A deficiency in ACTH (by glucocorticoid administration) will not result in aldosterone deficiency.

Tests to detect perioperative adrenal suppression or identify patients who will respond to supplemental glucocorticoids have been neither sensitive nor specific. However, the short ACTH stimulation test is able to assess adrenocortical function reliably. If this test is abnormal preoperatively, supplemental perioperative glucocorticoid administration is justified. If the risk for perioperative adrenal suppression is significant a systematic approach should be taken to determine if steroid supplementation is necessary. The decision should be based on suspicion (from history and physical examination), acuity of the operation, and anticipated severity of the procedure. If there is a high suspicion for the presence or development of AI and the procedure is emergent, steroids should be administered. If there is less urgency and time allows, an ACTH stimulation test should be performed to see if the adrenal gland appropriately responds to supraphysiologic doses of ACTH. Even if a preoperative ACTH stimulation test is normal and the patient is at high risk for perioperative AI, if unexplained hypotension persists despite volume repletion, steroids should be administered in a dose consistent with the level of injury. Postoperatively, steroids should be continued until the stress response diminishes (usually 48 hours).

The presence of unexplained nausea, vomiting, hypotension, orthostasis, change in mental status, hyponatremia, or hyperkalemia should warrant checking T4, TSH, and random plasma cortisol and, depending on the urgency of the situation, may require empiric therapy with stress-dose steroids and possibly T4. In addition, recrudescence of a stressor (eg, postoperative infection) may warrant reinstitution of supplemental glucocorticoids.

One drug that warrants mention in patients suspected of or at high risk of AI is etomidate. Etomidate is a frequently used anesthetic induction agent. Although it is a particularly attractive option for patients who are hemodynamically unstable, its effect of inhibiting steroid synthesis may precipitate acute AI and is best avoided in this population.

**PHEOCHROMOCYTOMA**

Pheochromocytomas are rare neuroendocrine tumors, usually located in the adrenal medulla (although they may be found in extra-adrenal tissues) originating in catecholamine-producing chromaffin cells. The 10-10-10 rule is a reminder that 10% of these tumors are bilateral, 10% are extra-adrenal, and less than 10% are malignant. Most pheochromocytomas synthesize and secrete norepinephrine, although hypersecretion of epinephrine can also be seen. Signs and symptoms include periodic flushing, palpitations, sweating, headaches, and hypertension. Patients usually present
perioperatively for (not despite) their pheochromocytoma. However, some patients may present with their first catecholamine crisis during routine surgery and thus familiarity with this syndrome is critical.

If a diagnosis of pheochromocytoma is suspected, the initial recommended test is measurement of plasma-free metanephrines, as the sensitivity is reportedly 99%. Thus, a negative test essentially excludes this diagnosis. Urinary vanillylmandelic acid levels have much higher specificity (95%). Once there is biochemical evidence of a catecholamine-secreting tumor, radiographic imaging studies are performed to localize the tumor (usually magnetic resonance imaging or nuclear imaging).

The end-organ that is most negatively affected in this syndrome is the cardiovascular system. Chronic, often severe, hypertension can frequently be corroborated with abnormal electrocardiography (ECG) findings (repolarization abnormalities, ventricular hypertrophy, nonspecific ST-T wave changes, and QTc interval prolongation). Some of these abnormalities will resolve after removal of the tumor. The most common condition seen in these patients is a hypertrophic cardiomyopathy secondary to norepinephrine-induced hypertension. As most of these tumors are nonmalignant, surgery may be curative in more than 90% of cases.

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Fig. 3. Algorithm for perioperative steroid administration. Minor procedures include those performed under local anesthesia or those less than 1 hour in duration; moderate procedures include most vascular surgeries or orthopedic procedures; major procedures include larger prolonged operations such as esophagectomy or those using cardiopulmonary bypass. The short ACTH stimulation involves administration of 250 μg i.v. synthetic ACTH (Cortrosyn, cosyntropin) followed by a plasma cortisol collection in 30 minutes. A plasma cortisol concentration greater than 18 to 20 μg/dL is consistent with normal adrenal function. i.v., intravenous; stim, stimulation. (Adapted from Kohl BA, Schwartz S. Surgery in the patient with endocrine dysfunction. Anesthesiol Clin 2009;27(4):687–703; with permission.)

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Careful preoperative preparation for the patient with pheochromocytoma is necessary. Failure to premedicate properly can increase perioperative mortality dramatically. The goal entails adequate α- and β-adrenergic blockade. Current recommendations are that phenoxybenzamine (a long-acting noncompetitive α-adrenergic antagonist) be initiated approximately 1 to 2 weeks preoperatively. Because the half-life of this drug is 24 to 36 hours, patients often require large amounts of intravenous fluid postoperatively and may be somnolent during this time because of central α2-adrenoceptor blockade. Roizen and colleagues recommended the following criteria for establishing adequate preoperative α-adrenergic blockade: (1) blood pressure should be no higher than 160/90 mmHg in the 24 hours preoperatively, (2) orthostatic hypotension should be present, (3) there should be no ST-T wave changes on ECG for 1 week preoperatively, and (4) there should be no more than 1 premature ventricular contraction every 5 minutes. For those patients with persistent tachycardia or hypertension, a β-blocker can be initiated 3 to 5 days before surgery. There is a theoretic risk of inciting unopposed α-agonism if β-antagonists are started first, culminating in severely increased vascular resistance. Metyrosine (a competitive inhibitor of tyrosine hydroxylase) has also been used successfully preoperatively. Tyrosine hydroxylase facilitates conversion of tyrosine to Dopa, and is the rate-limiting step in catecholamine synthesis. Metyrosine depletes tumor stores of catecholamines. Institution of early α-antagonism in addition to realization that these patients are frequently severely hypovolemic has dramatically decreased the perioperative mortality in these patients.

Echocardiography can be valuable in detecting overall systolic and diastolic function. Left ventricular hypertrophy is present in most of these patients; however, ventricular dilatation is a more ominous sign. For this reason, some have suggested obtaining a preoperative echocardiogram regardless of blood pressure.

Attempts to minimize hemodynamic fluctuations pre- and intraoperatively are advisable. Sufficient preoperative anxiolysis is warranted. In addition to standard monitors, careful hemodynamic monitoring is necessary and an intra-arterial catheter should be placed before anesthetic induction. Furthermore, several large-bore intravenous catheters should be placed (rapid volume administration is often necessary) and serious consideration should be given to central intravenous access for administration of vasoactive medications. Placement of a pulmonary artery catheter is not necessary, although may be helpful in the presence of significant cardiac disease. Agents that either directly or indirectly increase catecholamine levels, such as ketamine and ephedrine, should be avoided. In addition, morphine (which causes histamine release) has been associated with and felt to be a trigger of pheochromocytoma crisis. Meperidine and droperidol have also been associated with severe hypertension and are best avoided. Intraoperative hypertensive crises are best treated with rapid-acting direct vasodilators (eg, nitroprusside, nitroglycerine, nicardipine).

Postoperatively these patients may continue to be hypertensive for up to 1 week because of increased catecholamine levels in adrenergic nerve endings. Alternatively, aggressive preoperative adrenergic blockade may render the patient hypotensive postoperatively, usually for 24 to 48 hours, at which point most of the phenoxybenzamine has been eliminated. An improved understanding of the pathophysiology of this disease in addition to numerous investigations studying various techniques has dramatically improved perioperative outcome.

**SUMMARY**

Patients with endocrine dysfunction present unique challenges to perioperative clinicians. DM is the most common endocrinopathy in patients presenting for surgery.
Numerous investigations have shown that the increased mortality formerly seen in these patients can be dramatically minimized (compared with their counterparts without DM) with careful glycemic management. It is always advisable to normalize, as best as possible, the endocrinopathy or hemodynamic consequences before surgery (particularly in hypo- and hyperthyroidism, and pheochromocytoma). AI often presents intra- or postoperatively and thus being familiar with the signs and symptoms allows the perioperative clinician to be acutely aware and institute immediate therapy if necessary.

REFERENCES


