Surgery on the Patient with Endocrine Dysfunction

Benjamin A. Kohl, MD, a,*, Stanley Schwartz, MD b, c

Patients with preoperative endocrinopathies represent a particular challenge not only to anesthesiologists but also to surgeons and perioperative clinicians. The "endocrine axis" is complex and has multiple feedback loops, some of which are endocrine and paracrine related, and others that are strongly influenced by the surgical stress response. Familiarity with several of the common endocrinopathies facilitates management in the perioperative period. This review focuses on 4 of the most common endocrinopathies: diabetes mellitus, hyperthyroidism, hypothyroidism, and adrenal insufficiency. Perioperative challenges in patients presenting with pheochromocytoma are also discussed.

DIABETES MELLITUS

Diabetes, by far the most common endocrinopathy, affects almost 20 million Americans. Roughly 90% of these patients are classified as type 2, and the remainder are type 1. It is estimated that upwards of 50% of this entire population will require surgery at some point during their lifetime.1 Likewise, from a resource use standpoint, the average patient with diabetes spends up to 50% more time in the hospital postoperatively than a patient without diabetes undergoing the same procedure.2 It is often the complications that are a direct result of this disease (neuropathy, retinopathy, nephropathy, and vasculopathy) that culminate in the need for surgery. Type 1 diabetes mellitus (T1DM) is a consequence of the destruction and loss of pancreatic β-cells (insulin producing). This destruction is believed to be mediated by autoimmune
processes and is likely T cell mediated. Patients with T1DM will often have other autoimmune processes, most commonly thyroid disease. On the contrary, type 2 diabetes mellitus (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.

These 2 classes effectively discriminate most patients with diabetes, but it is important for the perioperative clinician to understand that other pathologies may result in a similar phenotype, such as pancreatitis and pancreatic cancer. It should also be recognized that patients destined to develop T2DM will have a prediabetic state of impaired glucose tolerance diagnosed by a fasting blood glucose greater than 100 mg/dL or 2-hour postprandial glucose greater than or equal to 140 mg/dL after a standard glucose challenge. This situation is critical as it has been shown that patients coming into the hospital with previously unrecognized abnormal glucose tolerance, or overt diabetes, 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 appropriately risk stratify these patients and develop an interventional strategy is dependent on the individual patient and the associated pathology. 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. The patient with diabetes requires a systematic approach as the disease affects numerous organ systems (Table 1). Furthermore, although the surgical stress response is similar for a given procedure, patients with diabetes (particularly 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 have been exposed. Because the average lifespan of an red blood cell is 120 days, the HbA1C level 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 impaired glucose tolerance. The goal of the American Diabetes Association (ADA) for control of diabetes is an HbA1C level less than 7%; this can be considered as adequate control. Values more than 8% correspond to average blood glucose levels greater 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, diabetic patients 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 can be anticipated. Although a serum creatinine value does not
diagnose renal impairment, in the steady state it gives a good estimate of the glomerular filtration rate (GFR) using the Cockcroft-Gault equation:\(^1\)

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

Finally, preoperative evaluation of patients with diabetes mellitus should focus on some of the more common associations 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.\(^12\) A positive “prayer sign” (inability to approximate fingers and palms with fingers extended) may be an indicator of joint rigidity.\(^13\) Such complications are important to note in the perioperative period and provisions should be made to minimize further exacerbation.

<table>
<thead>
<tr>
<th>Complications</th>
<th>Perioperative Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathies</td>
<td>Heel pads, avoid heating pads</td>
</tr>
<tr>
<td>Peripheral sensory</td>
<td></td>
</tr>
<tr>
<td>Cystopathy</td>
<td>Inability to urinate, overflow incontinence, UTIs, consider straight catheterization</td>
</tr>
<tr>
<td>Gastroparesis</td>
<td>Watch for medications that slow gastric motility, reflux esophagitis/gastritis</td>
</tr>
<tr>
<td>GFR</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemic unawareness</td>
<td>Frequent monitoring</td>
</tr>
<tr>
<td>CV autonomic neuropathy</td>
<td>Arrhythmias, telemetry</td>
</tr>
<tr>
<td>Silent ischemia, angina without chest</td>
<td>Watch for unexplained dyspnea, hypotension, arrhythmias</td>
</tr>
<tr>
<td>pain</td>
<td></td>
</tr>
<tr>
<td>Retinopathy</td>
<td>Blurred vision with either worse control or with sudden improvement in chronic DMOOC</td>
</tr>
<tr>
<td>Lens</td>
<td></td>
</tr>
<tr>
<td>Proliferative retinopathy</td>
<td>Rule out preoperatively if no routine eye examination in past year</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>Careful decision on the use of intravenous iodinated contrast</td>
</tr>
<tr>
<td>Hyporenin, hypoaldosterone state</td>
<td>Watch for hyperkalemia</td>
</tr>
<tr>
<td>Macrophage dysfunction with blood</td>
<td>Increased risk of infections; increased risk of fungal disease with parenteral nutrition</td>
</tr>
<tr>
<td>sugar &gt;150</td>
<td>Avoid hypotension</td>
</tr>
<tr>
<td>Increased risk of infections</td>
<td>Delays wound healing</td>
</tr>
<tr>
<td>Other conditions</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Statins valuable in hospital</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Treat, watch potassium level, edema, pulse rate</td>
</tr>
</tbody>
</table>

**Abbreviations:** CV, cardiovascular; DMOOC, diabetes mellitus out of control; UTI, urinary tract infection.
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” (NPO) 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. Indeed, 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 (HHNK) 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 hand, perioperative fasting with increased endogenous and exogenous insulin can easily cause profound hypoglycemia. Thus, a perioperative strategy that anticipates such pathology 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. There are no current guidelines on perioperative glycemic control, but 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 at less than 200 mg/dL intraoperatively and less than 150 mg/dL postoperatively, but avoid levels greater 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 NPO 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

**Fig. 1.** The glycemic balance in the perioperative period.
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 documented.\textsuperscript{20,21} Long-acting sulfonylureas (ie, chlorpropamide), although rarely used, are best withheld 48 to 72 hours preoperatively to avoid potential hypoglycemia.\textsuperscript{22} Incretins may be given (incretin mimetics subcutaneously and dipeptidyl peptidase (DPP)-IV inhibitors by mouth with a sip of water on the morning of surgery); 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 \(\beta\) cell function, best demonstrated in a murine model.\textsuperscript{23–25} 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 (hypotension, iodine dye induced renal dysfunction, sepsis, and so forth) and lead to the risk of lactic acidosis. \textbf{Box 1}

\begin{table}[h]
\centering
\begin{tabular}{|l|}
\hline
\textbf{Perioperative management of patients with insulin-dependent diabetes} \\
\hline
\textbf{Night before procedure} \\
\quad - Need basal insulin at all times to avoid diabetic ketoacidosis \\
\textbf{Morning of procedure} \\
\quad - No boluses of short-acting hypoglycemics unless blood sugar is greater than 200 mg/dL and greater than 3 hours preoperatively \\
\quad - May place on insulin drip OR give usual dose of glargine if routinely taken in morning \\
\quad - For insulin pump users, continue usual basal rate and infuse D5 throughout operation \\
\quad - If on NPH or other insulin mixture: \\
\quad \quad - No short-acting insulin within 3 to 4 hours of procedure (ie, no mixture preoperatively) \\
\quad \quad - Give half the usual intermediate-acting insulin, with D5, at controlled rate throughout procedure \\
\quad \quad - If doing operation without continuous D5, give no insulin preoperatively \\
\textbf{Special situations} \\
\quad - Emergency surgery \\
\quad \quad - No bolus of short-acting hypoglycemics preoperatively. Frequent (every 30–60 minutes) monitoring of blood sugar throughout operation. Start insulin infusion if blood sugar is greater than 200 mg/dL \\
\quad - Cardiac surgery \\
\quad \quad - Continue insulin infusion as needed to maintain blood glucose at 100 to 150 mg/dL in first 3 postoperative days \\
\hline
\end{tabular}
\caption{Perioperative management of patients with insulin-dependent diabetes}
\end{table}
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.

There are a paucity of data to guide the clinician on intraoperative glycemic control. Those undergoing cardiac surgery have been most heavily scrutinized. Unfortunately, there remains significant clinical uncertainty regarding the potential benefit of tight intraoperative glycemic control even in this subset of patients. However, although no formal recommendations have been made, most clinicians would agree that maintaining plasma glucose below 200 mg/dL intraoperatively is reasonable. Similar consensus exists for the noncardiac surgical population.

Postoperatively, attempts should be made to initiate enteral intake as soon as possible. Enteral intake should be started carefully and in consultation with a nutritionist familiar with the needs of diabetic patients. 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, there continues to be significant discussion on how this treatment modality relates to other morbidities and mortality.

**HYPERTHYROIDISM**

The causes of hyperthyroidism are myriad. However, by far the most common cause is Graves disease. Graves disease 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. It is important to recognize that not all patients present with the classic symptomatology or laboratory findings. Patients with subclinical ("masked") hyperthyroidism are often 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 (T4 and T3) levels are frequently mildly elevated, however TSH is usually suppressed. In states of thyrotoxicosis, free T4 levels can be dramatically increased. T3 and T4 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 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). Chronically elevated levels of these hormones may limit the ability of patients to respond to the stress of surgery and can culminate in cardiovascular collapse. 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. 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. 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 β-blockers, antithyroid medications (including propylthiouracil and methimazole), and iodine. β-Blockers not only directly inhibit sympathetic...
activation but also inhibit the peripheral conversion of T₄ to T₃ (the most active thyroid hormone). Thionamides, such as propylthiouracil (PTU) and methimazole, are actively transported into the thyroid gland and inhibit further production of hormone. Furthermore, PTU inhibits peripheral conversion of T₄ to T₃.\textsuperscript{45} Finally, although necessary for normal thyroid function, inorganic iodide in excess will manifest an antithyroid action known as the Wolff-Chaikoff effect.\textsuperscript{46} 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{47} 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{20}

The most feared perioperative complication that usually arises from undiagnosed or undertreated hyperthyroidism is thyroid storm. Thyroid storm can occur anytime 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 the patient must be monitored in a critical care environment.\textsuperscript{48} Symptoms are nonspecific and include hyperpyrexia (up to 41.1°C [106°F]), tachycardia, and delirium.\textsuperscript{49} Other conditions that should be considered in 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{50} Treatment of thyroid storm includes thionamides, β-blockers (goal heart rate <90 bpm), and antipyretics (or external cooling measures).\textsuperscript{20} Acetaminophen is preferred over salicylates as the latter may exacerbate thyrotoxicosis by decreasing thyroid protein binding and increasing free T₃ and T₄.\textsuperscript{50} 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{51} Finally, for those patients who are volume depleted, particularly if chronic hyperthyroidism exists, volume
resuscitation with the addition of dextrose should be administered to replace depleted glycogen stores.52

HYPOTHYROIDISM

Hypothyroidism is a common endocrinopathy in the United States affecting about 1% of all patients and is more prevalent in women.48 Primary hypothyroidism accounts for 95% of all cases and is characterized by low thyroid hormone levels (free T4 <5 pmol/L) in the face of normal or elevated 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 many iatrogenic causes that the perioperative clinician needs to be familiar with. Surgical thyroid resection or radioactive ablations are common causes that can frequently be anticipated. Less obvious, however, include treatment of hyperthyroidism or other pituitary and hypothalamic disorders (Sheehan syndrome, pituitary dysfunction after head trauma).53 A variety of 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.54 After induction of general anesthesia, total T3 levels decrease and remain low for at least 24 hours.55 Understanding the implications of hypothyroidism on the morbidity and mortality of surgical patients may allow the perioperative clinician to anticipate complications and manage preemptively.56

Similar to hyperthyroidism, hypothyroidism affects multiple organ systems and encompasses a wide clinical spectrum. The most clinically important of these is the cardiovascular system. Whereas plasma catecholamine levels are generally within normal limits, β-adrenergic receptor function is depressed and results in an imbalance of α and β adrenergic activity, with α 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 hypoxemia57 and, in more severe cases, decreased lung diffusion capacity.58 The renin-angiotensin-aldosterone complex responds to this by excreting sodium (greater than free water) culminating in hyponatremia and intravascular volume depletion.

The preferred treatment of hypothyroidism is tetraiodothyronine (T4, levothyroxine) replacement and patients should preferably be rendered euthyroid before surgery. The more active hormone (T3) 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.43 If intravenous dosing is necessary, one half the enteral dose is equivalent. There is controversy about 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.59 Currently, the consensus is that if a patient needs urgent cardiac revascularization, they should undergo the procedure before replacement therapy,60,61 however many endocrinologists will recommend starting at least low dose T4 in consultation with the cardiologist.

Patients presenting for surgery with hypothyroidism can be grouped into 3 broad categories: (1) hypothyroid patients well controlled on thyroid medications; (2) mild to moderately hypothyroid patients; (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 hyperacute 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 sensitive to
narcotics and benzodiazepines. Most patients with mild to moderate hypothyroidism
can undergo surgery without a disproportionate increase in perioperative risk.\textsuperscript{56,61,62}

Close attention to airway patency in the postoperative period is necessary as there
are reports of airway obstruction in hypothyroid patients.\textsuperscript{63} Intraoperative 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 necessary before urgent/
emergent surgery (severely depressed T\textsubscript{4} and T\textsubscript{3}), intravenous levothyroxine (200–500
mg given over 30 minutes) should be administered, followed by a daily dose of 50–100
mg intravenously.\textsuperscript{64} As many patients with hypothyroidism also have adrenal insuffi-
ciency (and thyroid replacement may precipitate adrenal crisis), glucocorticoids
should be administered concurrently.\textsuperscript{20}

Myxedema coma is rare and usually presents postoperatively. It is commonly
precipitated by additional insults such as infection, cold exposure, sedatives and anal-
gesics, and a variety of 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
due to an increased awareness and improved diagnostic testing.\textsuperscript{60,65,66} 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; normothermia should be
performed extremely carefully, if at all.\textsuperscript{60} Myxedema coma is a medical emergency
and necessitates urgent administration of levothyroxine. An initial intravenous bolus
of 200 to 500 mg should be given followed by 50 to 100 mg/d. Dehydration is
frequently present and aggressive volume resuscitation with dextrose and normal
saline should be instituted. Intravenous glucocorticoids should be administered (eg,
hydrocortisone 50 mg four times a day) because concomitant adrenal insufficiency
is not uncommon. Resolution of symptoms, if properly treated, should be seen within
24 hours.

\textbf{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. Tuberculosis used to be the main cause
of primary adrenal insufficiency (AI), but autoimmune adrenalitis is now the most
common cause. Other causes of primary AI include infections, adrenalectomy, and
sepsis.\textsuperscript{67,68} 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 stimulate the adrenal
cortex. It is most commonly caused by exogenous glucocorticoid administration,
which suppresses hypothalamic corticotropin releasing hormone (CRH) 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/d 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.69–71 Similarly, an equivalent dose of prednisone 5 mg (or less) for any period
of time will usually not significantly suppress the HPA axis.72 Other modes of steroid
administration should be noted preoperatively as topical, inhaled, and regional admin-
istration of glucocorticoids may cause adrenal suppression.73 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.73

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 produc-
tion.74,75 It is important to understand that 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.73

Tests to detect perioperative adrenal suppression or, perhaps more importantly,
identify patients who will respond to supplemental glucocorticoids have been neither
sensitive nor specific.73,76–78 However, the short ACTH stimulation test is able to reli-
ably assess adrenocortical function.76,79 If this test is abnormal preoperatively, supplemen-
tal 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 (Fig. 3). The decision
should be based on suspicion (from history and physical examination), acuity of the
operation and anticipated severity of the procedure. It is our opinion that 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 responds appropri-
ately to supraphysiologic doses of ACTH. Finally, even if a preoperative ACTH stimu-
lation 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).80 The presence of
unexplained nausea, vomiting, hypotension, orthostasis, change in mental status,
hyponatremia, or hyperkalemia, should warrant checking T₄, TSH, 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 for patients suspected of or at high risk of AI is eto-
midate. 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.81,82

PHEOCHROMOCYTOMA

Pheochromocytomas are rare neuroendocrine tumors, usually located in the adrenal
medulla (although they may occur in extraadrenal tissues) originating in catechol-
amine-producing chromaffin cells. The “10-10-10” rule is a reminder that 10% of
these tumors are bilateral, 10% are extraadrenal 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 (VMA) 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 MRI or nuclear imaging).

Not surprisingly, the end organ that is most negatively impacted in this syndrome is the cardiovascular system. Chronic, often severe, hypertension can frequently be corroborated with abnormal 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.\textsuperscript{85} The most common pathology 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.\textsuperscript{86}

Careful preoperative preparation of the patient with pheochromocytoma is necessary. Failure to properly premedicate can increase perioperative mortality dramatically.\textsuperscript{86} The goal entails adequate $\alpha$- and $\beta$-adrenergic blockade. Current recommendations are that phenoxybenzamine (a long-acting noncompetitive $\alpha$-adrenergic antagonist) be initiated roughly 1 to 2 weeks preoperatively.\textsuperscript{87,88}

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 due to central $\alpha_2$-adrenoceptor blockade. Roizen and colleagues\textsuperscript{89} recommended the following criteria for establishing adequate preoperative $\alpha$-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) no ST-T wave changes on ECG for 1 week preoperatively; and (4) no more than 1 premature ventricular contraction every 5 minutes. For those patients with persistent tachycardia or hypertension, a $\beta$-blocker can be initiated 3 to 5 days before surgery.\textsuperscript{60}

There is a theoretical risk of inciting unopposed $\alpha$-agonism if $\beta$-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 dihydroxyphenylalanine (DOPA), and is the rate-limiting step in catecholamine synthesis. Metyrosine depletes tumor stores of catecholamines. Institution of early $\alpha$ antagonism in addition to realization that these patients are frequently severely hypovolemic has dramatically decreased perioperative mortality in these patients.\textsuperscript{90} Echocardiography can be extremely 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.\textsuperscript{91}

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 intraarterial 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.\textsuperscript{92} Placement of a pulmonary artery catheter is not necessary, although may be helpful in the presence of significant cardiac disease.\textsuperscript{93,94} Agents that 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.\textsuperscript{95} Meperidine and droperidol have also been associated with severe hypertension and are best avoided.\textsuperscript{96} 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 due to elevated catecholamine levels in adrenergic nerve endings. Alternatively, aggressive preoperative adrenergic blockade may render the patient hypertensive postoperatively, usually for 24 to 48 hours at which point most of the phenoxybenzamine has been eliminated. With improved understanding of the pathophysiology of this disease in addition to numerous investigations studying various techniques, perioperative outcome has improved dramatically.\textsuperscript{87}
SUMMARY

Patients with endocrine dysfunction present unique challenges to perioperative clinicians. Diabetes mellitus 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 (to the level of their nondiabetic counterparts) with careful glycemic management. It is always advisable to normalize, as best as possible, the endocrinopathy or hemodynamic consequences before surgery, particularly in cases of hypo- and hyperthyroidism and pheochromocytoma. Adrenal insufficiency 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


