Endocrine Disorders that Cause Diabetes

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Keypoints
- Endocrine causes of diabetes are mainly a result of an excess of hormones that are counter-regulatory to insulin, and act by inhibiting insulin secretion and/or action.
- Acromegaly is almost always secondary to growth hormone-secreting adenomas of the anterior pituitary somatotrophs and disturbs glucose homeostasis in up to approximately 50% of patients.
- Cushing syndrome is caused by excessive levels of glucocorticoids and disturbs glucose homeostasis to some degree in over 50% of cases.
- Pheochromocytoma is a tumor of the chromaffin cells, which in 90% of cases is located in the adrenal medulla and causes hyperglycemia in approximately 50% of cases.
- Glucagonoma and somatostatinoma are rare islet cell tumors that produce hormones that inhibit the secretion and action of insulin.
- Thyrotoxicosis commonly causes mild glucose intolerance, but overt diabetes only occurs in a tiny minority.
- Other endocrinopathies such as primary aldosteronism and primary hyperparathyroidism can disturb glucose homeostasis.
- Polycystic ovarian syndrome occurs in 5–10% of women of reproductive age and associates with some degree of glucose intolerance or diabetes resulting from insulin resistance in approximately 50% of cases.

Introduction
The primary focus of this chapter is on those endocrine disorders that cause hyperglycemia and where effective treatment of the endocrinopathy can be expected to normalize the blood glucose concentration. These conditions mostly reflect excessive secretion of "counter-regulatory" hormones, the metabolic actions of which oppose those of insulin by inhibiting its secretion, action, or both.

Acromegaly

Etiology, incidence and clinical features of acromegaly
Acromegaly comprises a constellation of symptoms and signs caused by excessive growth hormone (GH) secretion that leads to bony and soft tissue overgrowth accompanied by cardiovascular and metabolic pathology (Figure 17.1a; Table 17.1) [1]. It affects approximately 60 people per million [2] and, in 99% of cases, is caused by a pituitary adenoma, most commonly larger than 1 cm in diameter (a “macroadenoma”; Figure 17.1b). A tiny minority of cases are caused by excessive secretion of GH-releasing hormone (GHRH) from a hypothalamic gangliocytoma or a carcinoid tumor of the lung or pancreas [1]. A small percentage of acromegaly occurs within the wider endocrine syndrome of multiple endocrine neoplasia type 1 (MEN1) caused by mutations in the tumor suppressor gene, MENIN [3]. MEN1 can also include glucagonomas and somatostatinomas, both of which are separately capable of causing secondary diabetes. Commonly, acromegaly has been present for a decade prior to diagnosis [4]. This long-standing hypersecretion of GH provides the time necessary for the characteristic external features of the disorder to develop (Figure 17.1a; Table 17.1).

Features of disturbance to glucose tolerance in acromegaly
Glucose intolerance or overt diabetes is common in acromegaly because of the direct hyperglycemic effects of GH excess (Figure 17.2). Overt diabetes has been reported in a range of 19–56% of patients with acromegaly, while impaired glucose intolerance (IGT) affects 16–46% [5–8]. Diabetes is most frequent in patients with higher GH levels [9,10]. There is also a correlation between serum insulin-like growth factor 1 (IGF-I), and both fasting and post-prandial glucose. In fact, placing age-adjusted IGF-I values into rising quartiles correlated very accurately to decreasing insulin sensitivity such that serum IGF-I levels could predict insulin sensitivity more accurately than either random GH levels or the nadir value following glucose tolerance testing [11].

Clinically, diabetes in acromegaly usually resembles the type 2 form (T2DM), with most patients not needing insulin therapy but being maintained with oral hypoglycemic agents or diet alone...
GH can induce insulin resistance when infused into normal subjects [12,13], and insulin resistance is a consistent feature of people with acromegaly [14,15]. Insulin action is impaired in both the liver and extrahepatic tissues, with decreases in both the suppression of hepatic glucose production and in insulin-dependent glucose disposal [13,15]. For instance, impairment of insulin-mediated activation of glycogen synthase has been demonstrated in skeletal muscle [16–18]. Insulin resistance may also be exacerbated by the lipolytic action of GH, generating non-esterified fatty acids (NEFAs) which act on the liver to increase glucose production and in muscle to inhibit glucose utilization (via the “glucose–fatty acid” cycle) (Figure 17.2). Where pancreatic compensation is adequate, an exaggerated insulin secretory response creating hyperinsulinemia can counterbalance the insulin resistance and maintain euglycemia. Similar to the natural history of deteriorating blood glucose control in T2DM, eventually β-cell compensation fails, the insulin response is impaired and hyperglycemia ensues [14]. This has been termed the Starling curve of the pancreas (see Figure 11.1).

**Diagnosis and treatment of acromegaly**
GH release is normally pulsatile with intervening periods of low level or undetectable hormone, whereas secretion from pituitary adenomas is autonomous. Therefore, the diagnosis can be deduced from a series of random serum measurements where GH is consistently detected. An alternative, better diagnostic test takes advantage of the negative feedback on GH secretion by glucose. A failure of serum GH to suppress to below 2 mU/L (approximately 1 μg/L) within 3 hours of 75 g oral glucose is diagnostic of acromegaly. A further option, particularly suited as the initial screening test of outpatients, is measurement of serum IGF-I, which if raised above sex- and age-matched controls is diagnostic of acromegaly, unless there is a possibility of GH abuse [1]. It is noteworthy that the diagnosis of acromegaly can be difficult in patients with type 1 diabetes mellitus (T1DM) where GH hypersecretion is observed. Whereas this might compromise the use of serum GH as a diagnostic biomarker of a somatotroph adenoma, IGF-I values tend to be low in poorly controlled T1DM indicative of the state of GH resistance. Thus, raised serum IGF-I values...
remain a confident predictor for a diagnosis of acromegaly in people with T1DM. Having diagnosed acromegaly, magnetic resonance imaging (MRI) of the anterior pituitary defines the extent of the adenoma (Figure 17.1b).

Based on this investigation, symptoms, patient wishes and co-morbidity, and GH levels, treatment can be either surgical, medical or radiotherapy (Table 17.2) [1,19]. When the tumor is a macroadenoma, especially if it extends beyond the pituitary fossa, curative surgery becomes unlikely or impossible; however, surgery can be useful for “debulking” and rapid lowering of serum GH levels in patients who are highly symptomatic, or where the tumor has encroached upon the optic chiasm and affected visual fields. The standard approach is trans-sphenoidal, either via the nostril or from behind the upper lip. Once the sphenoid sinus has been traversed and midline access to the sella turcica gained, tumor is removed from the anteroinferior aspect causing the residual tissue to drop back down into or towards the pituitary fossa. Tumor beyond the fossa, in locations such as the cavernous sinus, cannot be approached directly, hence the reason why surgery for large tumors is not anticipated to be curative [19]. Conversely, cure can be commonly achieved for over 50% of microadenomas (<1 cm diameter). The reported ranges vary widely according to expertise.

Medical therapy, most commonly using somatostatin analogs, is effective at both lowering GH levels and shrinking the tumor volume [1,20,21]. Approximately 60% of patients respond to somatostatin analogs because of the presence of predominantly

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**Table 17.1 Clinical features of acromegaly.**

<table>
<thead>
<tr>
<th>Musculoskeletal</th>
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<tbody>
<tr>
<td>Protruding mandible (prognathia) with lower teeth separation</td>
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<tr>
<td>Big tongue (macroglossia)</td>
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<tr>
<td>Enlarged forehead (frontal bossing)</td>
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<tr>
<td>Large hands and feet (carpal tunnel syndrome, tight rings, increasing shoe size)</td>
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<tr>
<td>Osteoarthritis from abnormal joint loading</td>
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<tr>
<td>Increased stature (gigantism; if GH excess occurs prior to epiphyseal closure)</td>
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<tr>
<th>Skin</th>
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<tr>
<td>Irritating, thickened, greasy (increased sebum production)</td>
<td></td>
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<tr>
<td>Excessive sweating</td>
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<tr>
<th>Cardiovascular</th>
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<tr>
<td>Dilated cardiomyopathy causing cardiomegaly and cardiac failure</td>
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<tr>
<td>Hypertension</td>
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<table>
<thead>
<tr>
<th>Metabolic</th>
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<tbody>
<tr>
<td>Impaired glucose tolerance or potentially diabetes</td>
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<table>
<thead>
<tr>
<th>General</th>
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<tbody>
<tr>
<td>Headaches</td>
<td></td>
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<tr>
<td>Tiredness, often very disabling and lowers quality of life/ability to work</td>
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<tr>
<th>Local tumor effects</th>
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<tr>
<td>Compression of the optic chiasm (superior tumor growth) or cranial nerves III, IV and/ or VI (lateral tumor growth into cavernous sinus)</td>
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</table>

GH, growth hormone.

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**Table 17.2 Treatment of acromegaly (Adapted from Holt and Hanley [130] .)**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td><strong>Trans-sphenoidal surgery</strong></td>
<td>Invasive and requires general anesthetic</td>
</tr>
<tr>
<td>Rapid effect</td>
<td>Non-curative for large extrasellar tumors</td>
</tr>
<tr>
<td>Can restore vision in optic nerve compression</td>
<td></td>
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<tr>
<td>Might be curative if complete resection</td>
<td></td>
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<tr>
<td><strong>Somatostatin analog drugs</strong></td>
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</tr>
<tr>
<td>Non-invasive</td>
<td>Monthly intramuscular injection</td>
</tr>
<tr>
<td>May shrink tumor</td>
<td>Expensive</td>
</tr>
<tr>
<td>Decreases GH in ∼60% of patients</td>
<td>Gastrointestinal side effects (commonly diarrhea)</td>
</tr>
<tr>
<td></td>
<td>Unlikely to be curative (i.e. continuous therapy needed)</td>
</tr>
<tr>
<td><strong>Pegvisomant</strong></td>
<td></td>
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<tr>
<td>Non-invasive</td>
<td>Expensive</td>
</tr>
<tr>
<td>Blocks GH action</td>
<td>GH concentrations remain elevated</td>
</tr>
<tr>
<td><strong>Radiotherapy</strong></td>
<td></td>
</tr>
<tr>
<td>Non-invasive</td>
<td>Slow to act — may take up to 10 years</td>
</tr>
<tr>
<td>Likely to shrink tumor</td>
<td>Standard external three-beam radiotherapy likely to cause</td>
</tr>
<tr>
<td>Likely to reduce GH levels</td>
<td>hypopituitarism by destroying other pituitary cell types</td>
</tr>
<tr>
<td>Might be curative</td>
<td></td>
</tr>
</tbody>
</table>

GH, growth hormone.

Figure 17.2 Mechanisms of hyperglycemia and diabetes in acromegaly. Diabetes develops if β-cells fail to compensate for the increased demand for insulin. IGT, impaired glucose tolerance; NEFA, non-esterified fatty acid.
Part 4 Other Types of Diabetes

type 2 and type 5 somatostatin receptors on the tumor cell surface [1,21]. The analogs can be administered subcutaneously; however, once it is clear that they are tolerated, the most common formulation is month-long intramuscular depot preparations. They can be used either prior to surgery, with the goal of operating on a shrunken tumor, on a long-term basis in place of surgery or post-surgery where GH levels have not been normalized.

Some GH-secreting adenomas co-express dopamine receptors more characteristic of prolactinomas [21]. Indeed, 25% of cases of acromegaly show raised levels of both prolactin and GH possibly indicating a tumor cell phenotype more consistent with the somatotrophinoma from which it is thought that somatotrophs (GH secretion) and lactotrophs (prolactin secretion) terminally differentiate. In these instances, dopamine agonists, as used in hyperprolactinemia, can be useful, especially as they can be administered orally, and allow reduction in dosage of the more expensive intramuscular depot somatostatin analogs. This opportunity to use lower doses of somatostatin analogs may also lessen their side-effects, such as gastrointestinal disturbance (most commonly diarrhea) and gallstones. It has recently been questioned, however, whether commonly used ergot alkaloid derived dopamine agonists, such as cabergoline, cause fibrotic side-effects, especially involving heart valves [22,23]. Despite concerns from regulatory agencies, the prevailing view from endocrinologists is that the doses of these agents used to treat endocrine disorders (compared with the therapeutic regimens in Parkinson disease) are not problematic. In any case, alternative non-ergot derived agents, such as quinagolide, are available. Bromocriptine is less commonly used because of the almost inevitable side-effects of nausea. Responsiveness to both dopamine and somatostatin analog therapy can be easily assessed at the start of treatment by hourly measurement of serum GH over 8 hours following the administration of a test dose of each agent given sequentially on two consecutive days.

The last decade has seen the appearance of a new clinical agent that blocks GH action. GH induces signal transduction via binding to its receptor as a dimer. Pegvisomant has been developed as a GH antagonist by preventing this dimerization and thus inhibiting GH action. This leaves elevated GH levels from the somatotroph adenoma but, nevertheless, pegvisomant is effective at reversing the clinical features of acromegaly [1,24]. The major problem with its use in many countries has been its prohibitive cost. Concern over tumor growth because of loss of negative feedback (a scenario akin to Nelson syndrome following bilateral adrenalectomy in Cushing disease) seems unfounded [1,24].

Radiation therapy is most commonly administered as conventional three-field external beam radiotherapy [1]. It is effective at lowering GH and IGF-I levels [25]. This approach delivers approximately 4500 Gy to the pituitary region with the total dose calculated such that the optic chiasm receives less than 8 Gy. An alternative is stereotactic radiotherapy (also known as γ-knife therapy or radiosurgery), which by using more sources can focus a higher concentration of radiation to a defined area of tumor. Whereas the latter modality allows greater preservation of adjacent normal pituitary tissue, the former approach is a more all-encompassing strategy to ensure tumor destruction, albeit with a higher post-therapy incidence of hypopituitarism. The choice is important as there is evidence that pituitary radiotherapy is associated with increased morbidity and mortality from subsequent cerebrovascular disease meaning that repeat therapy is not undertaken lightly [26].

**Outcome of acromegaly and disturbance to glucose tolerance**

Unless there are cogent reasons against, attempts should be made to normalize GH excess in acromegaly to decrease the morbidity and mortality associated with the disorder [1,26]. Curative treatment is best defined by a nadir serum GH of less than 2 mU/L upon 75 g oral glucose challenge. Hyperglycemia may worsen in a few patients, presumably those with a stronger underlying tendency to T2DM, when treated with somatostatin analogs because these drugs also suppress insulin secretion [29,30]. In the longer term, somatostatin analogs tend to improve glucose tolerance [31,32]. Insulin sensitivity is also improved with pegvisomant therapy in patients with both glucose intolerance and diabetes [33–36]. If hyperglycemia persists after serum GH levels have been normalized then the patient should be considered as having T2DM. One caveat to this is the possibility of GH deficiency as part of hypopituitarism post-surgery or radiotherapy [14]. GH deficiency causes centripetal fat deposition, which would itself cause or accentuate insulin resistance and potential loss of euglycemia.

Generally, diabetic complications are considered rare in acromegaly. Nevertheless, it is worth considering GH action in the context of both macrovascular and microvascular diabetic complications. Untreated GH excess increases cardiovascular morbidity and mortality and, potentially, abnormalities of glucose metabolism occurring in acromegaly could contribute to hypertension which affects over 50% of patients with acromegaly [5]. GH has been linked to proliferative diabetic retinopathy ever since resolution of diabetic retinopathy was noted in a woman who developed rapid-onset pan-hypopituitarism [37,38], so much so that hypophysectomy was used as treatment prior to the advent of laser photocoagulation [38]. This view is supported by the observations that patients with diabetes who are GH-deficient rarely develop retinopathy [39], and an experimental study in mice demonstrated that inhibition of GH secretion ameliorated diabetic retinopathy [40]. Patients with diabetes who are acromegalic, however, do not show an increased incidence of diabetic retinopathy [41,42]. Data on the progression of diabetic retinopathy treated with either pegvisomant or somatostatin analog are contradictory, and the outcome of larger trials are awaited [38].

**Effects of diabetes on GH–IGF-I axis**

Dysregulation of the GH–IGF-I axis has been well documented in T1DM. The main disturbances include increased GH secretion (Figure 17.3), paradoxically associated with decreased serum
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Inhibited by insulin but independently of GH, and IGFBP-3 (molecular weight 44 kDa), which is GH-dependent [47], IGFBP-1 levels are increased in T1DM as a result of portal and hepatic insulin deficiency (Figure 17.4) [43], and increase with worsening insulin deficiency and rising HbA1c concentrations (Figure 17.5). Increased IGFBP-1 levels have been shown to inhibit IGF-I bioactivity. Portal insulin deficiency in T1DM can thus account for
vascular pathology (Figure 17.7; Table 17.3) [50–52]. It occurs most commonly as a side effect of synthetic glucocorticoids administered exogenously for conditions such as rheumatoid arthritis or reversible airways disease. Endogenous Cushing syndrome arises in approximately two-thirds of cases from adrenocorticotropic hormone (ACTH) secreting corticotroph adenomas of the anterior pituitary which affect 5–10 individuals per million. In one-fifth of cases, the cause is a glucocorticoid-secreting tumor of the adrenal cortex and in one-tenth of cases is secondary to syndromes of ectopic ACTH secretion, most commonly from small cell carcinoma of the lung or, more rarely, carcinoid tumors [50–52]. Cushing syndrome is more common in women than men.
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Predisposed to diabetes (e.g., those with a family history of the disorder) [7,50,53]. It resembles T2DM because glucocorticoid excess causes hyperglycemia primarily by inducing insulin resistance, reflected by hyperinsulinemia [53]. Insulin-stimulated glucose uptake and utilization by peripheral tissues are both reduced, while hepatic glucose production is greatly increased through stimulation of gluconeogenesis [50,54]. This results from the direct activation of hepatic gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase (PEPCK), and an increasing supply of glucogenic substrates (amino acids and glycerol) generated by muscle proteolysis and peripheral adipose tissue lipolysis (Figure 17.8) [55]. Glucocorticoids also have permissive effects on the gluconeogenesis induced by epinephrine (adrena-

Figure 17.7 Cushing syndrome in a 53-year-old hypertensive man presenting with diabetes that required insulin to control hyperglycemia. Features included back pain from osteoporotic vertebral collapse, proximal myopathy that prevented him from climbing stairs, characteristic rounded facies (a) and truncal obesity with violaceous striae (c). After removal of the 10-mm corticotroph pituitary adenoma, his facial appearance returned to normal (b), as did blood pressure and blood glucose.

Men, with a greater predilection for corticotroph adenomas as the underlying pathology. Prolonged excessive levels of cortisol, the major glucocorticoid in humans, either directly from an adrenocortical tumor or from excessive ACTH causing bilateral hyperfunctional adrenal cortices, causes the characteristic external features of the disorder to develop and results in excess cardiovascular morbidity and mortality (Fig. 17.7a; Table 17.3) [50–52].

Features of disturbance to glucose tolerance in Cushing syndrome

Impairment of glucose tolerance is observed in 30–60% of cases [7,50,53]. Overt diabetes occurs in 20–50%, arguably in patients predisposed to diabetes (e.g., those with a family history of the disorder) [7,50,53]. It resembles T2DM because glucocorticoid excess causes hyperglycemia primarily by inducing insulin resistance, reflected by hyperinsulinemia [53]. Insulin-stimulated glucose uptake and utilization by peripheral tissues are both reduced, while hepatic glucose production is greatly increased through stimulation of gluconeogenesis [50,54]. This results from the direct activation of hepatic gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase (PEPCK), and an increasing supply of glucogenic substrates (amino acids and glycerol) generated by muscle proteolysis and peripheral adipose tissue lipolysis (Figure 17.8) [55]. Glucocorticoids also have permissive effects on the gluconeogenesis induced by epinephrine (adrena-
tests with high sensitivity have been designed (Table 17.4). Circulating cortisol is relatively high during the day and low at bedtime. Maintained daytime levels at night indicate excess. This can be tested by measuring midnight serum cortisol, although this requires prior acclimatization of inpatients for at least 24 hours and quiet surroundings as cortisol levels rise with minimal stress. Where assays have been validated, bedtime salivary cortisol measurement can be very useful as patients can post samples to the laboratory from home. Levels are approximately 10% of those in serum so care must be taken to avoid contamination with blood (e.g. from brushing teeth).

The “low dose” dexamethasone suppression tests interrogate the potential loss of physiologic negative feedback at the cortico-troph leading to autonomous ACTH secretion. The formal 48-hour test is marginally more specific [51]; however, it is also more inconvenient to perform in the outpatient setting compared with the overnight 1 mg suppression test. Caution needs to be exercised in patients where dexamethasone metabolism is enhanced (e.g. by antiepileptic medication) as this can lead to false-positive results. An alternative screening test examines total excretion of cortisol in a 24-hour urine collection, commonly on several occasions, as an integrated assessment of one day’s adrenocortical function. It is usual for endocrinologists to apply more than one of these various screening tests, which, if failed, provides proof of excess glucocorticoids and a diagnosis of Cushing syndrome.

Several endocrine tests have been developed to differentiate the various etiologies of endogenous Cushing syndrome (Table 17.4) [50–52]. Undetectable serum ACTH indicates an adrenocortical

[Figure 17.8] Mechanisms of hyperglycemia and diabetes in Cushing syndrome. NEFA, non-esterified fatty acids; PEPCK, phosphoenolpyruvate carboxykinase.
especially intrasellar ones, usually retain a partial capacity for ACTH causing Cushing syndrome. Corticotroph adenomas, to distinguish between anterior pituitary and ectopic sources of production by the anterior pituitary. It can be particularly challenging source of excessive cortisol causing suppression of ACTH secre-

Table 17.4 Diagnosis of Cushing syndrome from endogenous causes.

<table>
<thead>
<tr>
<th>Test</th>
<th>Interpretation</th>
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<tr>
<td><strong>Screening tests to diagnose Cushing syndrome</strong></td>
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<tr>
<td>Midnight serum cortisol measurement or bedtime salivary cortisol assay</td>
<td>Maintained daytime levels at night-time indicates autonomous cortisol production of Cushing syndrome</td>
</tr>
<tr>
<td>Serum cortisol &gt;50 nmol/L at following 9 AM consistent with Cushing syndrome</td>
<td></td>
</tr>
<tr>
<td>Serum cortisol &gt;50 nmol/L at following 9 AM consistent with Cushing syndrome</td>
<td></td>
</tr>
<tr>
<td>Formal low-dose DST (0.5 mg × 8 doses 6-hourly ending at 3 AM)</td>
<td>Elevated values support diagnosis of Cushing syndrome</td>
</tr>
<tr>
<td>24-hour urinary free cortisol measurement</td>
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</table>

| **Tests to localize cause of cortisol excess** |                                                          |
| Serum ACTH measurement | If suppressed, indicates autonomous adrenocortical overproduction of cortisol (e.g. an adrenocortical adenoma) |
| If serum ACTH detectable: |                                                          |
| High dose dexamethasone suppression test (2 mg × 8 doses 6-hourly ending at 3 AM) | >50% suppression of 9 AM serum cortisol from pre- to post-test indicates anterior pituitary source; <50% suppression indicates extrapituitary “ectopic” source of ACTH |
| Bilateral IPS sampling | Gradient from IPS to periphery of >2:1 supports anterior pituitary source (test can also incorporate CRH administration; see text) |
| MRI (can include gadolinium enhancement) | Should only be considered once biochemical evidence of pituitary source obtained. Helpful for surgeon in planning trans-sphenoidal surgery |

ACTH, adrenocorticotropic hormone; CRH, corticotropin releasing hormone; DST, dexamethasone suppression test; IPS, inferior petrosal sinus; MRI, magnetic resonance imaging.

source of excessive cortisol causing suppression of ACTH secretion by the anterior pituitary. It can be particularly challenging to distinguish between anterior pituitary and ectopic sources of ACTH causing Cushing syndrome. Corticotroph adenomas, especially intrasellar ones, usually retain a partial capacity for negative feedback; the “high dose” dexamethasone suppression test, administered as eight 2-mg doses every 6 hours, can be expected to reduce cortisol levels by at least 50%. As this cause underlies the original description of the disorder by Harvey Cushing in 1912, pituitary-driven glucocorticoid excess is called Cushing disease. Extrapituitary tumors secreting ectopic ACTH less commonly display this degree of negative feedback such that ACTH levels and consequently cortisol levels are likely to be higher. Although these tumors may be relatively indolent carcinoids, more commonly they are aggressive carcinomas of the bronchus characterized by a rapid onset of symptoms within a few months, marked hypokalemia and weight loss. The high level of POMC gene expression and dysregulated post-translational processing also leads to significant melanocyte stimulating hormone (MSH) secretion resulting in skin pigmentation. Venous sampling of the bilateral inferior petrosal sinuses can distinguish between ectopic or anterior pituitary sources of excessive ACTH. For pituitary sources, a gradient in ACTH levels of at least 2:1 (or 3:1 after the injection of 100 μg corticotropin releasing hormone [CRH] intravenously) should be found between central and peripheral samples. Although it can be very useful, bilateral inferior petrosal sinus sampling (BIPSS) also carries the risk of thrombosis in approximately 1% of cases, meaning that its use by endocrinologists is not always considered warranted. This is especially true where preceding biochemical tests have been conclusive and MRI shows clear radiologic evidence for a tumor. Where biochemistry is supportive of a pituitary source of ACTH excess, but the MRI is equivocal, even after gadolinium enhancement, BIPSS can help to lateralize a corticotroph adenoma by detecting a clear gradient between the right and left sinuses or vice versa. Sources of ectopic ACTH, most commonly in the chest, can be imaged with fine cut computerized tomography (CT), MRI or by using isotope-labeled scintigraphy to detect somatostatin receptors present on approximately two-thirds of ectopic ACTH-secreting carcinoid tumors. Autonomous cortisol-secreting tumors of the adrenal cortex can be imaged satisfactorily by CT or MRI when it can be possible to make assessment of functionality according to lipid content; features of high lipid content implying a tumor with active steroidogenesis.

Wherever possible, curative approaches are undertaken to normalize cortisol secretion as Cushing syndrome carries a high morbidity and markedly increases mortality from cardiovascular causes [50–52,58]. For adrenocortical sources, unilateral adrenalectomy is performed. For ectopic ACTH-secreting tumors, excision of carcinoids is potentially curative, whereas the natural history of carcinoma of the bronchus with ectopic hormone secretion usually makes palliative care more appropriate. Medical therapy to treat corticotroph adenomas remains disappointing. Some excitement was gained for high dose peroxisome proliferator-activated receptor γ (PPAR-γ) agonists but larger trials have been disappointing. Pituitary tumors are treated by either trans-sphenoidal surgery or radiotherapy when the indications and complications are largely the same as for those described in the section on acromegaly. The fact that ACTH-secreting adenomas are commonly microadenomas can increase the chances of curative surgery, although this remains heavily operator-dependent. If surgery is delayed, suppressants of adrenocortical steroidogenesis such as ketoconazole or metyrapone can be used temporarily where patients are highly symptomatic [50–52]. In extremis, bilateral adrenalectomy provides a rapid resolution of excessive cortisol secretion, although the total loss of negative feedback to a corticotroph adenoma can result in dangerous pituitary tumor growth that becomes refractory to further treatment, a scenario called Nelson syndrome. In patients where ACTH levels continue...
to rise, concomitant radiotherapy to the anterior pituitary can help reduce the risk of this problem arising.

**Outcome of Cushing syndrome and disturbance to glucose tolerance**

After successful surgery, the patient is reliant on external glucocorticoid administered as oral hydrocortisone, but a return of cortisol secretion from the adrenal gland(s) can be anticipated over ensuing weeks. Commonly, a physiologic return of diurnal rhythm is never achieved postoperatively [59]. For some, the extensiveness of anterior pituitary surgery, or the long-term suppression either of normal corticotrophs (pituitary or ectopic ACTH secreting tumors) or normal adrenocortical cells (cortisol-secreting tumors) causes a permanent state of hypocortisolism because of underactivity of remaining tissue. This can require continued hydrocortisone administration as for patients with Addison disease, except that mineralocorticoid replacement should not be required.

With successful treatment of Cushing syndrome (Figure 17.7), glucose intolerance may resolve. In such instances, when the patient might be entirely dependent on replacement doses of hydrocortisone, care needs to be taken not to cause hypoglycemia by continued antidiabetes medication. By contrast, persisting abnormalities are relatively common, most likely associated with persistent visceral obesity and metabolic syndrome [59]. On close analysis in one case series, there was a marked persistence of visceral obesity and glucose intolerance in approximately 60% of patients who fulfilled criteria for remission of Cushing syndrome [60].

**Effects of diabetes on hypothalamic–anterior pituitary–adrenal cortex axis**

Evidence of overactivity of the hypothalamic–pituitary–adrenal (HPA) axis has been reported in children, adolescents and adults with diabetes, including moderate increases in urinary free cortisol excretion, plasma cortisol and ACTH concentrations [61–64]. These abnormalities have been related to the duration of diabetes [62,63] and to the presence of diabetic neuropathy [64]. Serum cortisol levels fall as metabolic control improves [65].

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**Pheochromocytoma**

**Etiology, incidence and clinical features of pheochromocytoma**

Pheochromocytomas are catecholamine-secreting tumors arising from the chromaffin cells of the adrenal medulla (Figure 17.9) [66,67]. Approximately 10% lie in extra-adrenal sites (paragangliomas) along the sympathetic chain in para-aortic or chest regions and approximately 10% are bilateral. Although most pheochromocytomas are sporadic, advances in molecular genetics have demonstrated that a hereditary basis underlies approximately one-fifth to one-quarter of diagnoses, not just in well-known syndromes, such as MEN2, von Recklinghausen neurofibromatosis and von Hippel–Lindau disease [66]. Such advances have also associated particular genetic defects to tumor type. For instance, succinate dehydrogenase subunit B (SDHB) and succinate dehydrogenase subunit D (SDHD) mutations are more frequent in extra-adrenal tumors [66]. Mutations in SDHB are more commonly associated with a malignant phenotype [68]. The risk of malignancy also increases with tumor size [68].

The clinical manifestations of pheochromocytoma are largely caused by hypersecretion of catecholamines, classically as a triad of symptoms: headaches, sweating and tachycardia [69]. Hypertension is the most common clinical finding and occurs in 80–90% of cases. It can be paroxysmal or sustained, the latter occurring especially in children and in noradrenaline-secreting tumors [66]. Other symptoms may be secondary to the co-secretion of various other peptide hormones such as vasoactive intestinal peptide (VIP), substance P, atrial natriuretic factor, endothelin-1, CRH and GHRH [70]. The normal adrenal medulla predominantly secretes epinephrine, converted from norepinephrine by methylation. This reaction is governed by the enzyme phenylethanolamine-N-methyltransferase (PNMT), the expression of which is dependent on high concentrations of cortisol draining centripetally from the outer adrenal cortex towards the adrenal vein [69]. For this reason, larger tumors with more marked disturbance of the normal anatomy or extra-adrenal pheochromocytomas are notable for predominantly secreting norepinephrine as conversion to epinephrine is compromised.

**Features of disturbance to glucose tolerance in pheochromocytoma**

Hyperglycemia occurs in up to approximately 50% of patients with pheochromocytoma. The prevalence of diabetes is approximately 35% [71]. Its presence in a young hypertensive person of normal body weight should raise suspicion of pheochromocytoma. The predominant mechanism is catecholamine-mediated reduction in insulin sensitivity and insulin secretion, predominantly caused by epinephrine rather than norepinephrine (Figure 17.10) [72,73]. Epinephrine inhibits β-cell insulin secretion via stimulation of α2-adrenergic receptors [74]. In the liver, epinephrine activates β2-adrenoceptors to enhance glycogenolysis transiently and gluconeogenesis in a more sustained fashion [75–77]. This hepatic gluconeogenesis is fueled by the precursors, lactate, alanine and glycerol, generated by β3-adrenergic stimulation of muscle glycolysis and adipose tissue lipolysis. Lipolysis in adipose tissue is also stimulated via the β3- and β2-adrenoceptors. In addition, epinephrine can impair glucose utilization in muscle through direct β2-adrenergic effects. The predominance of these β2-adrenergic effects probably explains why epinephrine, with its higher affinity for β2-receptors, is more potent than norepinephrine in producing hyperglycemia [75,77]. All these effects are potent mechanisms that raise blood glucose, explaining why epinephrine release is an important component in correcting hypoglycemia after inhibition of insulin and increased glucagon secretion in the hierarchy of counter-regulatory responses (see Chapter 33).
be meticulous to prevent both a hypertensive crisis during manipulation of the tumor and cardiovascular collapse after its removal. This is achieved by initial \( \alpha \)-receptor blockade followed by beta-blocker. The order of implementation is important to prevent a hypertensive crisis from unopposed \( \alpha \)-adrenoceptor stimulation. The preoperative \( \alpha \)-adrenergic blockade often controls hypertension, but has less effect on glucose intolerance [75,78]. In malignant pheochromocytoma where surgery is not possible, adrenolytic drugs, such as mitotane, can be used palliatively.

**Outcome of pheochromocytoma and disturbance to glucose tolerance**

Removal of the tumor corrects the metabolic abnormalities. If presentation, diagnosis and treatment have occurred without undue delay, it also resolves the hypertension [56,75,78,79].

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**Figure 17.9** Pheochromocytoma in a 75-year-old man with recent-onset type 2 diabetes treated with a sulfonylurea, who was admitted on an emergency basis with severe chest pain and hypertension (blood pressure 240/130 mmHg). Blood glucose on admission was 27 mmol/L. Urinary catecholamine excretion was greatly increased, and a pheochromocytoma of the right adrenal was demon-
Glucagonoma is a rare tumor of the α-cell of the pancreatic islet. Although practice varies, greater understanding of the molecular genetics of pheochromocytoma makes clinical genetics input advisable; some laboratories now undertake germline mutation analyses in seemingly isolated tumors [66]. It is also straightforward to exclude hyperparathyroidism by measuring serum calcium as this simple test, if normal, goes a long way to excluding MEN1. Some clinics offer annual follow-up screening for pheochromocytoma by 24-hour urine collection. Patients with pheochromocytomas caused by identified genetic disorders should be followed up at least annually in dedicated clinical genetics endocrinology clinics.

**Effects of diabetes on adrenal medulla function**

Function of the adrenal medulla may be selectively impaired in patients with long-standing diabetes and hypoglycemia unawareness; attenuation of the epinephrine response to hypoglycemia can delay the restoration of normal serum glucose levels. Epinephrine responses can remain normal to other stimuli, indicating failure of sympathetic activation at a specific, possibly hypothalamic, level (see Chapter 33).

**Other endocrine conditions causing disturbance of glucose tolerance**

**Glucagonoma**

Glucagonoma is a rare tumor of the α-cell of the pancreatic islet. The first clear-cut case was reported in 1942, but the “glucagonoma syndrome” (in a series of nine patients with similar symptoms) was not described until 1974 [80,81]. It may form part of MEN1 caused by mutations in the tumor suppressor gene, MENIN [82]. In a series of 21 patients [83], the syndrome’s most striking clinical features were weight loss (71%), necrolytic migratory erythema (67%) (Figure 17.11a), diabetes (38%), cheilosis or stomatitis (29%) and diarrhea (29%). In this report, patients with the combination of necrolytic migratory erythema and diabetes mellitus were diagnosed more rapidly (after a mean of 7 months), but some cases remain undetected for years. Glucagonoma should always be considered in patients with diabetes and unexplained weight loss or a chronic skin rash.
Other causes of hyperglucagonemia (e.g. severe stress, hepatic and renal failure, poorly controlled diabetes, small-bowel malabsorption and synthetic androgenic drugs) [80, 81]. Surgical removal of the tumor is the treatment of choice, but 50% of tumors have metastasized to the liver by the time of diagnosis (Figure 17.11b) [83]. Treatment can then be completed by hepatic artery embolization and/or chemotherapy; somatostatin analogs can also suppress glucagon secretion. The rash may respond to normalization of glucagon levels following removal of the tumor or the use of somatostatin analogs; the administration of zinc, a high-protein diet and control of the diabetes with insulin may also help [80, 81, 83].

**Somatostatinoma**

Somatostatinomas are extremely rare tumors arising in 1 in 40 million individuals from δ-cells of the pancreatic islet or enteroendocrine cells of the duodenum and ampulla of Vater [84]. They may be sporadic or as part of genetic syndromes, such as MEN1 [84]. The first two somatostatinomas were found incidentally during cholecystectomy [85, 86], but a subsequent case was
The first VIP-secreting tumor was recognized by Verner and Morrison in 1958 [88]. Classic features are caused by elevated circulating VIP levels and include watery diarrhea (pancreatic cholera), hypokalemia and achlorhydria [89]. Hypercalcemia and glucose intolerance occur in half of the patients, but overt diabetes is unusual; hyperglycemia is probably secondary to the glycogenolytic effect of VIP and/or to hypokalemia, which can impair both insulin secretion and insulin sensitivity. Diagnosis is aided by serum assay for fasting VIP levels. The tumors are usually large and have metastasized from the pancreatic tail by the time of diagnosis. Debulking surgery forms the mainstay of treatment and 10-year survival is approximately 40% [89].

VIPoma

Hyperthyroidism

Hyperthyroidism is defined by overproduction of thyroid hormones. Hyperthyroidism leads to thyrotoxicosis; the manifestations of increased circulating thyroid hormones (Table 17.5) [90]. Ignoring the association of autoimmune hyperthyroidism (Graves disease) with T1DM, thyrotoxicosis per se can disturb glucose tolerance in approximately one-third of individuals, with diabetes occurring in a further 8% of patients [91]. There is evidence for insulin resistance as the primary defect [90,91], especially in those who are overweight [92], although insulin secretion may also be impaired [91,93]. Glucose production and expression of the hepatocyte glucose transporter 2 (GLUT-2) protein are also impaired [91,93]. Glucose intolerance has been implicated with delayed or reduced insulin release has been implicated with delayed or reduced insulin responses following oral glucose challenge. Removal of the aldosterone may exert other diabetogenic effects on glucose metabolism, although this remains unclear [98]. Glucose intolerance has been reported in approximately 50% of patients [99]. This is generally mild and overt diabetes is unusual. Defective insulin release has been implicated with delayed or reduced insulin responses following oral glucose challenge. Removal of the aldosterone may correct these defects [99].

Primary hyperaldosteronism

Primary hyperaldosteronism was originally described by Conn in 1955 in a patient with hypertension, hypokalemia and neuromuscular symptoms associated with an adrenocortical adenoma secreting aldosterone [69]. A benign adenoma is the most common primary cause (65%) with bilateral hyperplasia accounting for 30% of cases. A handful of cases are brought about by a genetic recombination event between the genes encoding two closely related steroidogenic enzymes. This causes aldosterone secretion under the regulation of ACTH, which is suppressible by glucocorticoids [69]. Although debate is active over whether more subtle normokalemic aldosterone excess is a wider cause of hypertension, the relevance of primary hyperaldosteronism to glucose tolerance relies largely on the hypokalemia, which is part of the classic Conn syndrome as low serum potassium impairs insulin secretion [56,69]. Others have questioned whether aldosterone might exert other diabetogenic effects on glucose metabolism, although this remains unclear [98]. Glucose intolerance has been reported in approximately 50% of patients [99]. This is generally mild and overt diabetes is unusual. Defective insulin release has been implicated with delayed or reduced insulin responses following oral glucose challenge. Removal of the aldosterone may correct these defects [99].

Primary hyperparathyroidism

Primary hyperparathyroidism is secondary to hypersecretion of parathyroid hormone (PTH), usually by a parathyroid adenoma and less commonly by parathyroid hyperplasia [100]. The prevalence of diabetes in primary hyperparathyroidism is approximately threefold higher than in the general population [101–103], with some cases requiring insulin therapy. Insulin resistance with
hyperinsulinemia is generally held responsible, with raised intra-
cellular calcium limiting cellular glucose uptake [103]. It has been
debated whether parathyroidectomy for primary hyperparathy-
roidism improves glucose homeostasis: some reports argue that
it is beneficial for both diabetes and impaired glucose tolerance
[104,105] while others find less effect [106,107]. Possibly this
relates to duration and severity of the calcium disturbance. With
the widespread availability of serum biochemistry, hyperparathy-
roidism is shifting from a symptomatic disorder to an asympto-
matic one where serum calcium tends to be only marginally
elevated. In the latter scenario, glucose tolerance appears less
affected [108].

**Hypopituitarism with growth hormone deficiency**

In children, lack of GH increases insulin sensitivity such that
young GH-deficient children tend to develop fasting and readily
provoked hypoglycemia [109,110]. Using insulin tolerance tests,
GH-deficient children were more insulin-sensitive than short
children with normal GH secretion [109]. This exaggerated
insulin sensitivity attenuates with age and puberty, possibly fol-
lowing increased gonadal steroid production [109] such that
adults with GH deficiency demonstrate insulin resistance [12].
Given that GH excess is diabetogenic and acute GH administra-
tion raises fasting glucose and fasting insulin levels, and reduces
insulin sensitivity [14,17], the value of GH replacement to
improve glucose tolerance is likely to be related to whether it can
be administered physiologically.

Given this challenge, it is not surprising that the long-term
results of GH replacement are somewhat conflicting [12]: a 30-
month study showed a deterioration in glucose tolerance and
insulin sensitivity despite an increase in lean body tissue and a
reduction of fat mass [111]; another study of 6 months’ duration
found rises in fasting glucose and HbA1c, without effects on
peripheral or hepatic sensitivity [112]; however, a 5-year trial
concluded that GH replacement decreased HbA1c levels [113].
Another study, evaluating the impact of GH therapy in GH-
deficient patients during transition from childhood to adulthood,
showed that the beneficial effects of chronic treatment on body
composition did not overcome the direct antagonistic effects on
insulin action [114]. Insulin secretion may also deteriorate during
GH administration [111]. Thus, the replacement of GH in hypo-
pituitary patients with diabetes is contentious: long-term treat-
ment with GH may improve insulin sensitivity via improvements
in body composition; however, such patients need to be moni-
tored regularly and overtreatment that might lead to the deve-
lopment of diabetes should be avoided [12,115].

**Endocrine disorders that associate with diabetes**

Several endocrine disorders that are associated with T1DM
because of a common etiology and similar pathology (e.g. autoim-
mune adrenalitis [Addison disease] or autoimmune thyroid
disease). Attention in these disorders is warranted for the onset of
new autoimmune pathologies. In patients with T1DM, screening
can be justified to exclude hyperthyroidism or hypothy-
roidism by measuring serum thyroid stimulating hormone (TSH)
annually. The development of Addison disease in patients with
T1DM markedly increases sensitivity to insulin such that unan-
ticipated hypoglycemic reactions occur as dose requirements
fall. Even in the absence of diabetes and insulin therapy,
Addison disease can cause hypoglycemia, especially in children.
Rare conditions resembling T1DM with associated endocrinopa-
thies, such as the autoimmune polyglandular syndromes or
POEMS syndrome may occur. Monogenic causes of diabetes that
affect other endocrine organs are covered in Chapter 15. Examples
(and their respective endocrine disorder) include the various
types of hemochromatosis (primary hypogonadism), Wolfram
syndrome (diabetes insipidus) and Kearns–Sayre syndrome
(hypoparathyroidism, hypogonadism and hypopituitarism).
Here, polycystic ovarian syndrome (PCOS) is addressed as a
complex endocrine disorder that includes insulin resistance. The
hormonal alterations in PCOS share relevance with some of the
mechanisms underlying glucose homeostasis in pregnancy and
obesity, covered in Chapters 53 and 14, respectively.

**Polycystic ovarian syndrome**

PCOS is defined as clinical or biochemical hyperandrogenism
with oligo- or anovulation where other definable causes have
been excluded [116–120]. Some definitions incorporate the
detection of multiple ovarian cysts into the diagnosis [119,120],
although these occur in approximately half of patients with
Cushing syndrome and are non-discriminatory (Figure 17.12).
PCOS occurs in 5–10% of women of reproductive age
and is characterized primarily by insulin resistance although there
is also evidence of β-cell dysfunction [123,124]. Impaired glucose
tolerance and T2DM are present in nearly 40% and 7.5–10%,
respectively, of women with PCOS, with the former having a
tendency to progress to T2DM and being associated with an
approximate threefold higher risk of gestational diabetes
[123,124]. These data are confounded to some degree by the
effect of obesity, but the incidence of PCOS remains increased
across ethnicities whereas obesity rates vary [124]. Indeed,
it can be argued that PCOS in women with normal BMI repre-
sents the most severe form of the disorder where genetic screen-
ing programs are most likely to identify PCOS susceptibility
genes.

The source of the androgens is both the adrenal cortex and
the ovary [124]. The raised insulin levels can stimulate
androgen production by the ovary and interfere with other
aspects of ovarian function. Within the adrenal cortex, where
insulin receptors are expressed in the zona fasciculata of the
adrenal cortex [125], there is some evidence that insulin can
influence glucocorticoid versus sex steroid precursor production
[124].

The diagnosis of PCOS is one of exclusion, meaning that clinical
and biochemical findings are only supportive of the condition
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Serum estradiol is detectable and usually >200 pmol/L. Endocrine abnormalities include increases in serum luteinizing hormone (LH) leading to a raised LH:FSH (follicle stimulating hormone) ratio, androstenedione and testosterone concentrations. Serum sex hormone-binding globulin (SHBG) levels are commonly low. Ovarian ultrasound is useful to help exclude the presence of a tumor underlying the androgen excess [121].

Further evidence that the condition is caused by insulin resistance comes from its amelioration with exercise and agents that improve insulin sensitivity such as metformin or thiazolidinediones [126]. As well as lowering blood glucose, these agents improve menstrual regularity and increase the chance of ovulatory cycles [126].

References

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