A 35-year-old woman presents to her internist complaining of recent episodes of weakness and tingling in her extremities. She also complains of polyuria, nocturia, and polydipsia. Although her blood pressure has been normal in the past, on the day of this visit it is 160/100 mm Hg. Laboratory studies reveal a serum sodium level of 147 mEq/L, a potassium level of 2.8 mEq/L, and very low serum renin activity.

What is the most likely diagnosis?
Primary hyperaldosteronism, also known as Conn syndrome, is suggested by the patient’s history and her hypertension, hypernatremia, and hypokalemia. Approximately 30%–60% of cases are due to solitary adrenal adenomas in the zona glomerulosa, the aldosterone-secreting layer of the adrenal cortex. Bilateral hyperplasia of the zona glomerulosa can also cause Conn syndrome.

How is aldosterone regulated?
Renin, produced by the juxtaglomerular cells of the kidney, cleaves angiotensinogen (produced by the liver) to form angiotensin I. Angiotensin I, in turn, is cleaved by angiotensin-converting enzyme to form angiotensin II. In response to volume contraction, angiotensin II becomes a potent stimulator of aldosterone synthase, a key enzyme in aldosterone synthesis.

Other key stimuli of aldosterone secretion include decreased plasma sodium and increased plasma potassium.

Another patient presents with similar symptoms, but his laboratory tests show increased serum renin activity. What is his most likely diagnosis?
Hypertension has a variety of causes. Approximately 95% of patients with hypertension have primary or “essential” hypertension, which has no identifiable cause. The remaining patients have secondary hypertension, which is caused by an identifiable underlying etiology such as extra-adrenal hyperstimulation of aldosterone secretion (Table 6-1).

**TABLE 6-1** Distinguishing Features of Primary vs. Secondary Hypertension

<table>
<thead>
<tr>
<th>PRIMARY HYPERTENSION</th>
<th>SECONDARY HYPERTENSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causes</td>
<td>Vascular disease/renal hypoperfusion (renal artery stenosis, decreased effective circulating volume).</td>
</tr>
<tr>
<td>Genetic factors, including conditions such as Barter syndrome and Gitelman syndrome.</td>
<td>Endocrine disorders (renin-secreting tumors, Conn syndrome, Cushing syndrome, pheochromocytoma).</td>
</tr>
<tr>
<td>Labs</td>
<td>Intrinsic renal disease (chronic renal failure, glomerulonephritis).</td>
</tr>
<tr>
<td>Decreased renin levels.</td>
<td>Increased renin levels.</td>
</tr>
</tbody>
</table>

Given the patient’s serum potassium level, what are the most likely findings on electrocardiogram (ECG)?
Typical ECG findings include prominent U waves, flattened T waves, and ST-segment depression (Figure 6-2).


What is the appropriate treatment for this condition, and what are the adverse effects?
If a solitary, aldosterone-secreting adrenal adenoma is found, surgical resection (adrenalectomy) is indicated. Bilateral adrenal hyperplasia is treated medically with an aldosterone antagonist such as spironolactone. Major adverse effects of spironolactone are due to its antiandrogen effects, including gynecomastia, loss of libido, menstrual irregularities, and impotence.
CASE 5

A 36-year-old woman with no significant medical history presents to her primary care physician with a 6-month history of amenorrhea, weight gain, and excessive facial hair growth. She denies any recent diet or medication changes. Her vital signs are notable for a pulse of 80/min and blood pressure of 148/90 mm Hg. Physical examination reveals a well-developed hirsute female with truncal obesity, abdominal striae, and peripheral edema. She has difficulty arising from a chair during her neurological exam. Relevant laboratory findings are as follows:

- Sodium: 140 mEq/L
- Chloride: 92 mEq/L
- Bicarbonate: 25 mEq/L
- Glucose: 225 mg/dL
- Potassium: 3.4 mEq/L

What is the most likely diagnosis?
Cushing syndrome results from excess glucocorticoids, either from increased cortisol production or exogenous glucocorticoid therapy. Common causes include the following:

- Iatrogenic (eg, steroid ingestion, most common).
- Pituitary adenoma (Cushing disease).
- Adrenal tumor/hyperplasia.
- Adrenocorticotropic hormone (ACTH)-producing tumor (most commonly secondary to small cell lung cancer).

What laboratory tests can help confirm the diagnosis?
Screening tools for Cushing syndrome or glucocorticoid excess include the following:

- 24-hour urine free cortisol test. Elevated cortisol level indicates hypercortisolism.
- Dexamethasone suppression test. A normal result is a decrease in cortisol after administration of low-dose dexamethasone. In glucocorticoid excess due to Cushing disease, low-dose dexamethasone will not suppress cortisol levels.

After identifying elevated cortisol levels, what diagnostic tests help define the source of the hormonal abnormality?
Serum ACTH levels:

- High ACTH: Pituitary adenoma or an ectopic ACTH-producing neoplasm.
- Low ACTH: Adrenal tumor/hyperplasia or exogenous glucocorticoid administration.

A high-dose dexamethasone suppression test can differentiate between a pituitary adenoma and an ectopic ACTH-producing tumor. Pituitary adenomas are suppressed by high-dose ACTH, whereas ectopic ACTH-producing tumors usually are not.

What are the appropriate treatments for this condition?
The most appropriate treatment for adrenal tumors is surgery. Treatments for nonresectable tumors or hyperplasia are as follows:

- Ketoconazole: Inhibits glucocorticoid production.
- Metyrapone: Inhibits cortisol formation in adrenal pathway.
- Aminogluthethimide: Inhibits the synthesis of steroids.

What is the regular cycle of cortisol levels in the body?
Cortisol levels peak in the early morning (approximately 8 AM) and reach their lowest levels at midnight. Basal body temperature fluctuates with the cortisol cycle (Figure 6-3).

![Figure 6-3](image_url)
A mother brings her 7-year-old son in to see the pediatrician. She says the boy has been less active and has also begun wetting his bed again, something he had stopped doing 2 years ago. Chart review reveals that within the past year the child’s weight dropped from the 75th percentile to the 50th percentile even though he has been eating and drinking more than usual, the mother reports. Relevant laboratory findings include the following:

| WBC count: 11,400/mm³, normal differential | Creatinine: 1.2 mg/dL |
| Chloride: 100 mEq/L | Potassium: 5.0 mEq/L |
| Blood urea nitrogen: 14 mg/dL | Glucose: 350 mg/dL |
| Sodium: 132 mEq/L |

**What is the most likely diagnosis?**

Autoimmune destruction of pancreatic islet cells results in insulin deficiency (Figure 6-4), leading to type 1 diabetes mellitus (DM). Common presenting symptoms include polydipsia, polyphagia, weight loss, and polyuria (osmotic diuresis secondary to glycosuria).


**What are the two types of this condition?**

Type 1 DM is characterized by absolute insulin deficiency; type 2 DM is characterized by insulin resistance and increased insulin levels. Type 1 DM typically presents in thin individuals younger than 30 years of age. Type 2 DM typically affects obese individuals older than 30 years of age (although it is increasingly seen among younger obese individuals). Both types of diabetes can result in retinopathy, nephropathy, and neuropathy.

**What is diabetic ketoacidosis (DKA)?**

DKA is a life-threatening complication of uncontrolled type 1 DM. In the absence of insulin, increased levels of fatty acids are delivered to the liver, where ketogenesis occurs. This lowers the pH of the blood. Presenting symptoms include Kussmaul hyperpnea (deep respirations), abdominal pain, dehydration, and nausea/vomiting. Patients may have a sweet/fruity/ alcoholic odor to their breath.

**What is the appropriate treatment for DKA?**

Acute DKA requires rapid fluid resuscitation with normal saline, followed by the administration of intravenous insulin and repletion of depleted electrolytes, especially potassium. Administration of bicarbonate to correct the acidic blood pH is usually not recommended unless the acidosis is severe.

Following an episode of DKA, lifelong insulin replacement is required for patients diagnosed with type 1 DM. Oral hypoglycemic agents are effective in type 2 DM but not in type 1.

**What electrolyte abnormalities are frequently associated with DKA?**

DKA is associated with depletion of total body potassium stores through osmotic diuresis. Serum potassium levels may appear normal or elevated even though total body potassium stores are low; this is because intracellular potassium is shifted into the extracellular space in exchange for hydrogen ions to buffer the effects of metabolic acidosis. Treatment of DKA with insulin drives potassium back into cells, and patients undergoing treatment for DKA can thus become profoundly hypokalemic.
A worried mother brings her 12-year-old son to the pediatrician with concerns that he is “too tall.” Both she and the patient's father are relatively short, as are other members of the family. The patient, an avid Little League player, complains only that his baseball cap, mitt, and shoes do not fit any more. On physical examination, the patient is above the growth curve for his age and has large hands and feet, frontal bossing of the cranium, prominent jaw, and coarse facial features with oily skin.

**What is the most likely diagnosis?**

Gigantism, which is caused by excess growth hormone (GH). In patients with fused epiphyses (ie, growth plates), the disease is called acromegaly. In older patients, physical changes may go unnoticed until hats, gloves, and shoes no longer fit.

**What is the pathophysiology of this condition?**

Excess GH can arise from pituitary excess, hypothalamic GH-releasing hormone (GHRH) excess, or an ectopic source. A genetic component of the disease is suggested by the high levels of GH seen in McCune-Albright syndrome and multiple endocrine neoplasia type I.

**How is GH produced?**

GH is produced and stored in the acidophilic cells of the anterior pituitary. Basophilic cells in the anterior pituitary can be recalled with the mnemonic B-FLAT. Basophils: Follicle-stimulating hormone, Luteinizing hormone, Adrenocorticotropic hormone, and Thyroid-stimulating hormone. Acidophils: GH and prolactin.

**How is secretion of GH controlled?**

GH is released in a pulsatile fashion. Secretion is controlled by the hypothalamus (Figure 6-5). GHRH stimulates GH production. Somatostatin interferes with its effect on the pituitary. Insulin-like growth factor-1 (IGF-1) exerts negative feedback to inhibit GH secretion. At puberty, the frequency and amplitude of GH secretory pulses increase because of gonadal hormones. The combination drives the “growth spurt.”

![Feedback control of growth hormone secretion](image)

**How is this condition diagnosed?**

Excess GH production is diagnosed by physiologic testing and brain imaging.

- **Screening:** The best screening test for excess GH secretion is a measurement of serum IGF-1 levels. IGF-1 levels are a more reliable indicator of GH excess than GH levels because IGF-1 remains constant throughout the day whereas GH fluctuates. IGF-1 levels are elevated in acromegaly and gigantism because IGF-1 synthesis is dependent on GH.

- **Confirmatory test:** The diagnosis of GH excess can be confirmed with an oral glucose suppression test. In normal patients, GH levels are suppressed after the administration of a glucose load. In patients with gigantism or acromegaly, GH values may rise, remain unchanged, or suppress only partially.

- **Imaging:** MRI of the pituitary gland may reveal adenoma as the source of excess GH secretion.
**CASE 10**

A 52-year-old woman presents to the clinic with several months’ history of generalized weakness, cold intolerance, and weight gain. Physical examination reveals alopecia, a thick and beefy tongue, myxedema, and delayed deep tendon reflexes. Her heart rate is 55/min and her blood pressure is 100/70 mm Hg. She is not taking any medications. Relevant laboratory findings are as follows:

- Free thyroxine (T₄): 4.5 pmol/L (normal: 10.3–35 pmol/L)
- Thyroid-stimulating hormone (TSH): 31 µU/mL (normal: 0.8–2 µU/mL)
- Cholesterol: 230 mg/dL

What is the most likely diagnosis?
The patient’s cold intolerance, weight gain, myxedema, fatigue, prolonged relaxation phase of deep tendon reflexes, and low free T₄ with high TSH suggest primary hypothyroidism.

What is the most common cause of this condition?
Hashimoto thyroiditis (autoimmune destruction of the thyroid gland). Patients are typically positive for antithyroid peroxidase (antimicrosomal) antibodies. Additional causes of hypothyroidism include Riedel thyroiditis, subacute thyroiditis, and silent thyroiditis. The prevalence of Hashimoto thyroiditis is increased in patients with other autoimmune disease such as vitiligo.

What endocrine disorder is associated with low free T₄ and low serum TSH levels?
Low T₄ levels in the setting of low or normal TSH levels imply secondary hypothyroidism, the most common cause of which is hypopituitarism. Other manifestations of hypopituitarism include sexual dysfunction and diabetes insipidus.

What is the appropriate treatment for this condition?
Levothyroxine (synthetic T₄ hormone). Levels of T₄ typically take 4–6 weeks to reach steady state after initiation of therapy.

How are thyroid hormones produced and metabolized?
Iodine is essential for the production of thyroid hormones in the follicular cells of the thyroid gland. Following T₄ production in the thyroid gland, deiodinases in the peripheral tissues convert T₄ to the active form, T₃.

What are the primary functions of thyroid hormones in the peripheral bloodstream?
T₃ has a role in brain maturation, bone growth, β-adrenergic effects, and increasing the basal metabolic rate.
A 14-year-old Hispanic-American boy with a family history of obesity and hypertension presents to the pediatrician for a mandatory school physical examination. He has no medical complaints. Social history is notable for a sedentary lifestyle. His diet consists of pizza, sandwiches, potato chips, and 2 cups of soda daily. Physical examination reveals a male with an abdominal circumference > 40 inches. His body mass index is 36 kg/m², pulse is 100/min, and blood pressure is 140/95 mm Hg. Skin examination reveals velvety, darkly pigmented patches in the skin folds at the nape of his neck and axilla (Figure 6-6).

**What is the most likely diagnosis?**
Metabolic syndrome, also known as dysmetabolic syndrome, syndrome X, and insulin resistance syndrome.

**What are the diagnostic criteria for this condition?**
The National Cholesterol Education Program Adult Treatment Panel III defines metabolic syndrome as the presence of any three of the following five traits:
- Abdominal obesity (male > 40 inches; female > 35 inches).
- Hypertriglyceridemia (≥ 150 mg/dL).
- Low levels of high-density lipoprotein (HDL) cholesterol (male < 40 mg/dL; female < 50 mg/dL).
- Blood pressure ≥ 130/85 mm Hg.
- Fasting glucose ≥ 110 mg/dL.

**What do the skin findings represent?**
Acanthosis nigricans is a common physical sign of insulin resistance, particularly in Hispanics and African Americans. It may be due to high levels of circulating insulin or insulin-like growth factor receptors in the skin. Other conditions with acanthosis nigricans include polycystic ovarian syndrome and some visceral malignancies.

**What is insulin resistance?**
Insulin resistance (IR) is the state in which endogenous or exogenous insulin produces a less-than-expected biological effect. Patients have elevated blood glucose with normal to elevated insulin levels. Today, IR is nearly universal in obese individuals and is correlated with amount of intra-abdominal fat. Several mechanisms of IR in obesity have been proposed:
- Insulin receptor downregulation.
- Intracellular lipid accumulation.
- Increased free fatty acids that impair insulin action.
- Cytokines and "adipokines," which modify the effect of insulin.

Treatment with metformin can be initiated to increase insulin responsiveness.

**What class of drugs should be avoided in patients with this condition?**
Atypical antipsychotics, such as clozapine, are associated with the metabolic syndrome, particularly weight gain and hypertriglyceridemia. Even for patients without weight gain, the effect on serum triglycerides increases the risk for adverse cardiovascular events.