

HIGH-YIELD SYSTEMS**Endocrine**

“If you skew the endocrine system, you lose the pathways to self.”

—Hilary Mantel

“Sometimes you need a little crisis to get your adrenaline flowing and help you realize your potential.”

—Jeannette Walls, *The Glass Castle*

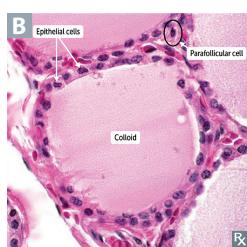
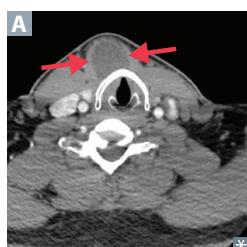
“Chocolate causes certain endocrine glands to secrete hormones that affect your feelings and behavior by making you happy.”

—Elaine Sherman, *Book of Divine Indulgences*

The endocrine system comprises widely distributed organs that work in a highly integrated manner to orchestrate a state of hormonal equilibrium within the body. Generally speaking, endocrine diseases can be classified either as diseases of underproduction or overproduction, or as conditions involving the development of mass lesions—which themselves may be associated with underproduction or overproduction of hormones. Therefore, study the endocrine system first by learning the glands, their hormones, and their regulation, and then by integrating disease manifestations with diagnosis and management. Take time to learn the multisystem connections.

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▶ ENDOCRINE—EMBRYOLOGY

Thyroid development

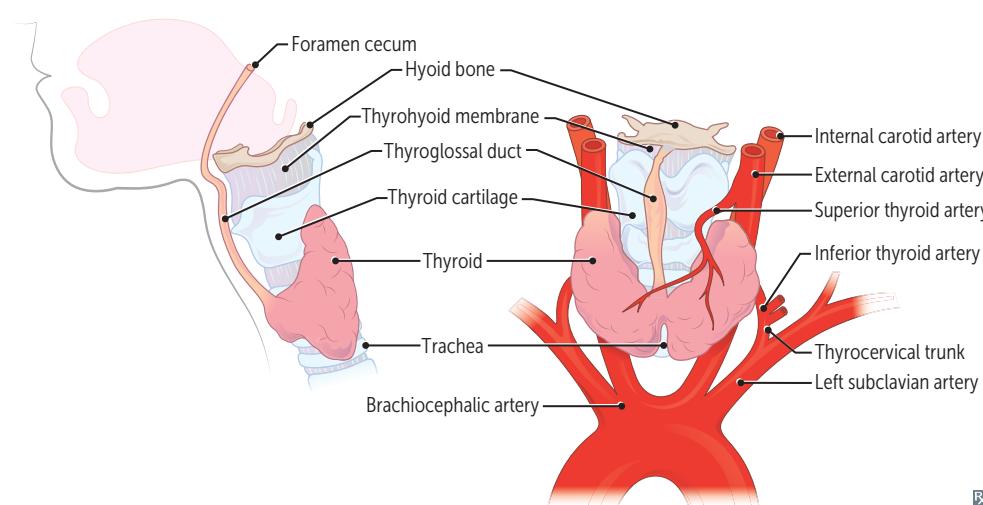
Thyroid diverticulum arises from floor of primitive pharynx and descends into neck. Connected to tongue by thyroglossal duct, which normally disappears but may persist as cysts or the pyramidal lobe of thyroid. Foramen cecum is normal remnant of thyroglossal duct.

Most common ectopic thyroid tissue site is the tongue (lingual thyroid). Removal may result in hypothyroidism if it is the only thyroid tissue present.

Thyroglossal duct cyst **A** presents as an anterior midline neck mass that moves with swallowing or protrusion of the tongue (vs persistent cervical sinus leading to pharyngeal cleft cyst in lateral neck).

Thyroid follicular cells **B** derived from endoderm.

Parafollicular cells arise from 4th pharyngeal pouch.



▶ ENDOCRINE—ANATOMY

Pituitary gland**Anterior pituitary
(adenohypophysis)**

Secretes FSH, LH, ACTH, TSH, prolactin, GH, and β -endorphin. Melanotropin (MSH) secreted from intermediate lobe of pituitary. Derived from oral ectoderm (Rathke pouch).

- α subunit—hormone subunit common to TSH, LH, FSH, and hCG.
- β subunit—determines hormone specificity.

Proopiomelanocortin (POMC) derivatives—
 β -endorphin, ACTH, and MSH. Go **pro** with a **BAM!**

FLAT PeG: FSH, LH, ACTH, TSH, PRL, GH.

B-FLAT: Basophils—FSH, LH, ACTH, TSH.

Acid PiG: Acidophils — PRL, GH.

**Posterior pituitary
(neurohypophysis)**

Stores and releases vasopressin (antidiuretic hormone, or ADH) and oxytocin, both made in the hypothalamus (supraoptic and paraventricular nuclei) and transported to posterior pituitary via neurophysins (carrier proteins). Derived from **neuro**ectoderm.

Adrenal cortex and medulla

Adrenal cortex (derived from mesoderm) and medulla (derived from neural crest).

ANATOMY	HISTOLOGY	1° REGULATION BY	HORMONE CLASS	1° HORMONE PRODUCED
Adrenal gland	Zona Glomerulosa	Angiotensin II	Mineralocorticoids	Aldosterone
Capsule	Zona Fasciculata	ACTH, CRH	Glucocorticoids	Cortisol
Superior surface of kidney	Zona Reticularis	ACTH, CRH	Androgens	DHEA
MEDULLA	Chromaffin cells	Preganglionic sympathetic fibers	Catecholamines	Epi, NE

GFR corresponds with salt (mineralocorticoids), sugar (glucocorticoids), and sex (androgens).

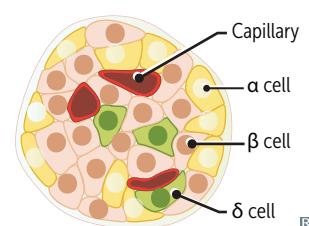
Endocrine pancreas cell types

Islets of Langerhans are collections of α , β , and δ endocrine cells. Islets arise from pancreatic buds.

α = glucagon (peripheral)

β = insulin (central)

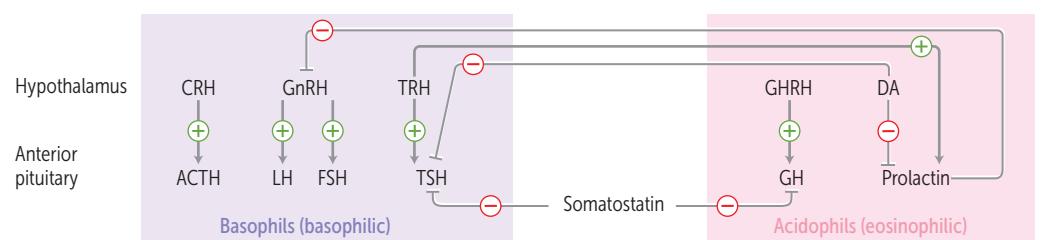
δ = somatostatin (interspersed)

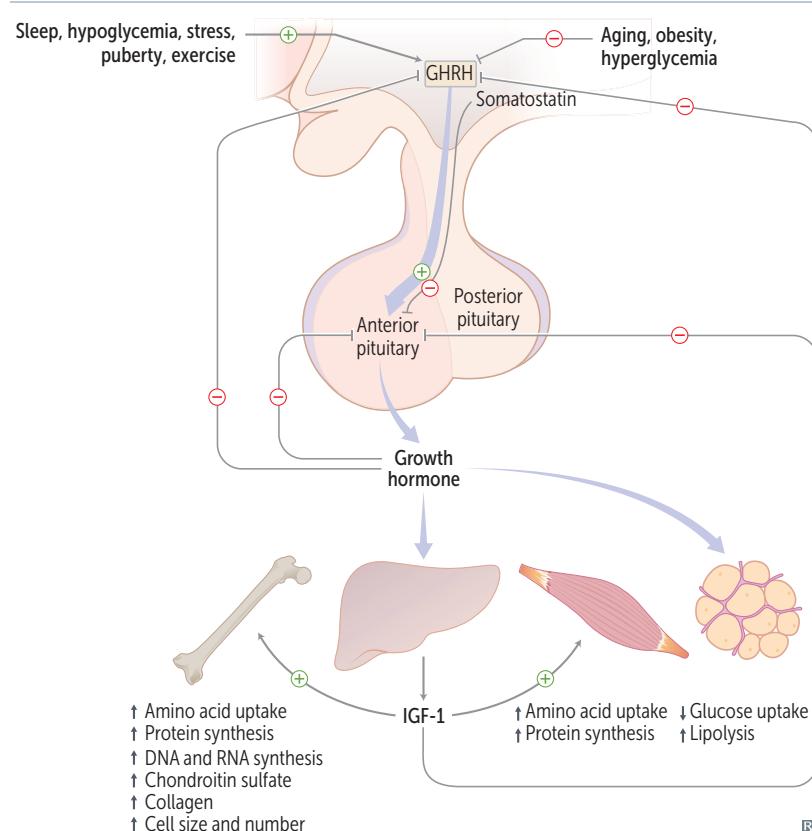


▶ ENDOCRINE—PHYSIOLOGY

Hypothalamic-pituitary hormones

HORMONE	FUNCTION	CLINICAL NOTES
ADH	↑ water permeability of distal convoluted tubule and collecting duct cells in kidney to ↑ water reabsorption	Alcohol consumption → ↓ ADH secretion → polyuria and dehydration
CRH	↑ ACTH, ↑ MSH, ↑ β-endorphin	↓ in chronic glucocorticoid use
Prolactin-inhibiting factor	↓ prolactin, ↓ TSH	Commonly referred to as dopamine Dopamine antagonists (eg, antipsychotics) can cause galactorrhea due to hyperprolactinemia
GHRH	↑ GH	Analog (tesamorelin) used to treat HIV-associated lipodystrophy
GnRH	↑ FSH, ↑ LH	Suppressed by hyperprolactinemia Tonic GnRH analog (eg, leuprolide) suppresses hypothalamic–pituitary–gonadal axis. Pulsatile GnRH leads to puberty, fertility
MSH	↑ melanogenesis by melanocytes	Causes hyperpigmentation in Cushing disease, as MSH and ACTH share the same precursor molecule, POMC
Oxytocin	Causes uterine contractions during labor. Responsible for milk letdown reflex in response to suckling.	Modulates fear, anxiety, social bonding, mood, and depression
Prolactin	↓ GnRH Stimulates lactogenesis.	Pituitary prolactinoma → amenorrhea, osteoporosis, hypogonadism, galactorrhea Breastfeeding → ↑ prolactin → ↓ GnRH → delayed postpartum ovulation (natural contraception)
Somatostatin	↓ GH, ↓ TSH	Also called growth hormone inhibiting hormone (GHIH)
TRH	↑ TSH, ↑ prolactin	↑ TRH (eg, in 1°/2° hypothyroidism) may increase prolactin secretion → galactorrhea



Growth hormone

Also called somatotropin. Secreted by anterior pituitary.

Stimulates linear growth and muscle mass through IGF-1 (somatomedin C) secretion by liver. ↑ insulin resistance (diabetogenic).

Released in pulses in response to growth hormone-releasing hormone (GHRH).

Secretion ↑ during (deep) sleep, hypoglycemia, stress, puberty, exercise.

Secretion ↓ with aging, obesity, hyperglycemia, somatostatin, somatomedin (regulatory molecule secreted by liver in response to GH acting on target tissues).

Excess secretion of GH (eg, pituitary adenoma) may cause acromegaly (adults) or gigantism (children). Treatment: somatostatin analogs (eg, octreotide) or surgery.

Antidiuretic hormone

Also called vasopressin.

SOURCE

Synthesized in hypothalamus (supraoptic and paraventricular nuclei), stored and secreted by posterior pituitary.

FUNCTION

Regulates blood pressure (V_1 -receptors) and serum osmolality (V_2 -receptors). Primary function is serum osmolality regulation (ADH ↓ serum osmolality, ↑ urine osmolality) via regulation of aquaporin channel insertion in principal cells of renal collecting duct.

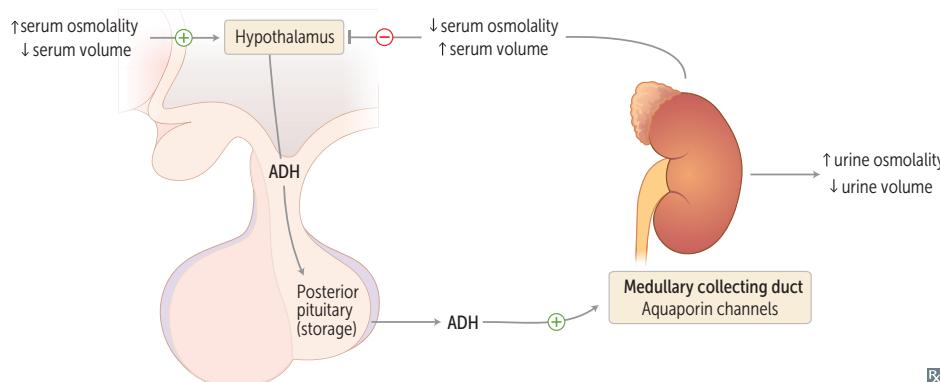
ADH level is ↓ in central diabetes insipidus (DI), normal or ↑ in nephrogenic DI.

Desmopressin (ADH analog) is a treatment for central DI and nocturnal enuresis.

Vasopressin is a potent **vasopressor** that can be used to increase organ perfusion in septic shock.

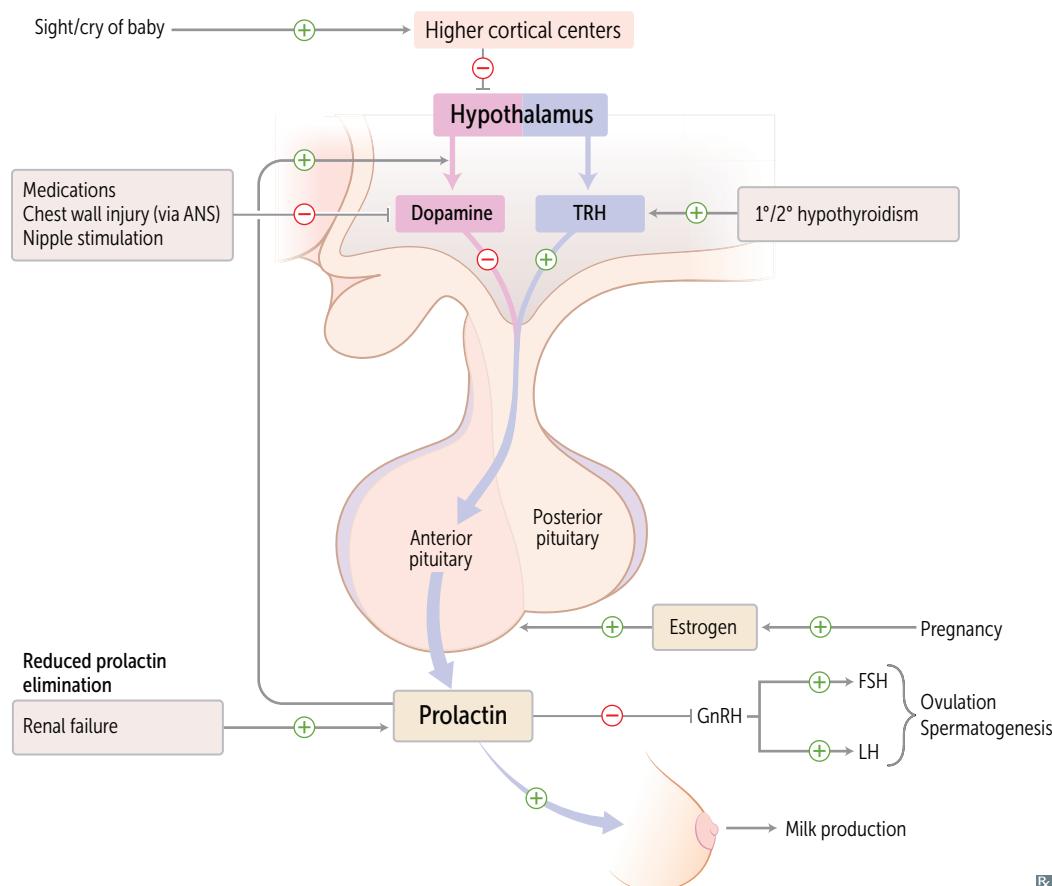
REGULATION

Plasma osmolality (1°); hypovolemia.



Prolactin

SOURCE	Secreted mainly by anterior pituitary.	Structurally homologous to growth hormone.
FUNCTION	Stimulates milk production in breast; inhibits ovulation in females and spermatogenesis in males by inhibiting GnRH synthesis and release.	Excessive amounts of prolactin associated with galactorrhea, amenorrhea, infertility, osteoporosis (in females); gynecomastia, infertility, decreased libido, impotence (in males).
REGULATION	Prolactin secretion from anterior pituitary is tonically inhibited by dopamine from tuberoinfundibular pathway of hypothalamus. Prolactin in turn inhibits its own secretion by ↑ dopamine synthesis and secretion from hypothalamus. TRH ↑ prolactin secretion (eg, in 1° or 2° hypothyroidism). Dopamine has stronger effect on prolactin regulation than TRH does.	Dopamine agonists (eg, bromocriptine, cabergoline) inhibit prolactin secretion and can be used in treatment of prolactinoma. Dopamine antagonists (eg, most antipsychotics, metoclopramide) and estrogens (eg, OCPs, pregnancy) stimulate prolactin secretion.



Thyroid hormones

Thyroid produces triiodothyronine (T_3) and thyroxine (T_4), iodine-containing hormones that control the body's metabolic rate.

SOURCE

Follicles of thyroid. $5'$ -deiodinase converts T_4 (the major thyroid product) to T_3 in peripheral tissue (5, 4, 3). Peripheral conversion is inhibited by glucocorticoids, β -blockers, and propylthiouracil (PTU). Reverse T_3 (rT_3) is a metabolically inactive byproduct of the peripheral conversion of T_4 and its production is increased by growth hormone and glucocorticoids. Functions of thyroid peroxidase include oxidation, organification of iodine, and coupling of monoiodotyrosine (MIT) and diiodotyrosine (DIT). Inhibited by PTU and methimazole. $DIT + DIT = T_4$. $DIT + MIT = T_3$. Wolff-Chaikoff effect—protective autoregulation; sudden exposure to excess iodine temporarily turns off thyroid peroxidase $\rightarrow \downarrow T_3/T_4$ production.

FUNCTION

Only free hormone is active. T_3 binds nuclear receptor with greater affinity than T_4 . T_3 functions —7 B's:

- Brain maturation
- Bone growth (synergism with GH and IGF-1)
- β -adrenergic effects. $\uparrow \beta_1$ receptors in heart $\rightarrow \uparrow CO, HR, SV$, contractility; β -blockers alleviate adrenergic symptoms in thyrotoxicosis
- Basal metabolic rate \uparrow (via $\uparrow Na^+/K^+$ -ATPase $\rightarrow \uparrow O_2$ consumption, RR, body temperature)
- Blood sugar (\uparrow glycogenolysis, gluconeogenesis)
- Break down lipids (\uparrow lipolysis)
- Stimulates surfactant synthesis in Babies

REGULATION

TRH $\rightarrow \oplus$ TSH release $\rightarrow \oplus$ follicular cells. Thyroid-stimulating immunoglobulin (TSI) may \oplus follicular cells in Graves disease.

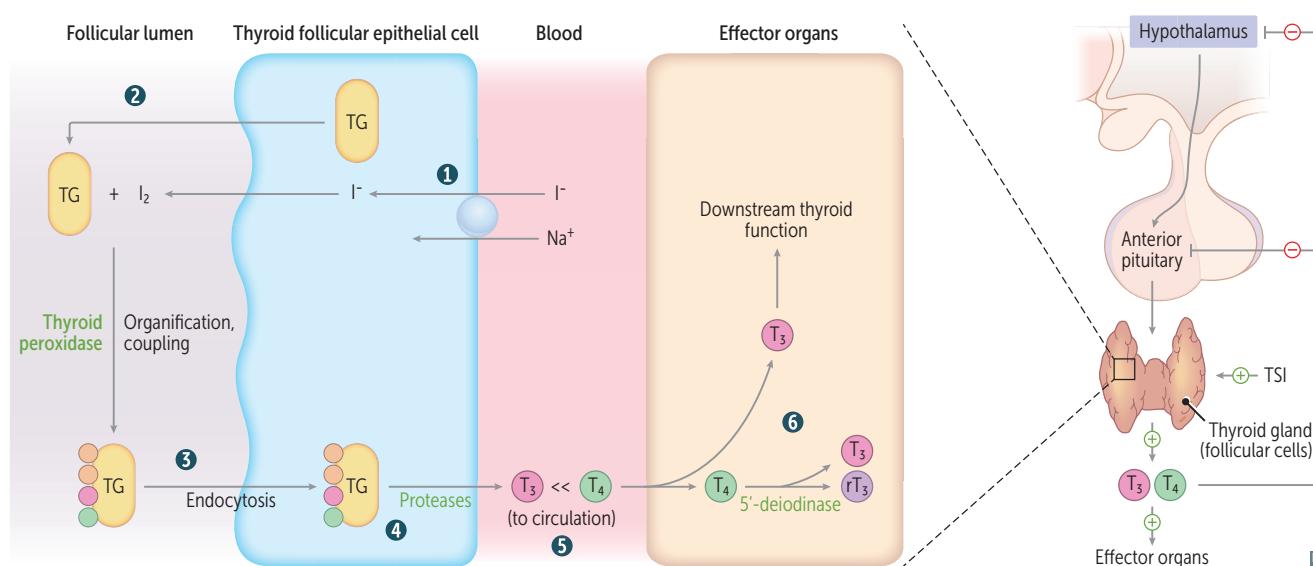
Negative feedback primarily by free T_3/T_4 :

- Anterior pituitary $\rightarrow \downarrow$ sensitivity to TRH
- Hypothalamus $\rightarrow \downarrow$ TRH secretion

Thyroxine-binding globulin (TBG) binds most T_3/T_4 in blood. Bound T_3/T_4 = inactive.

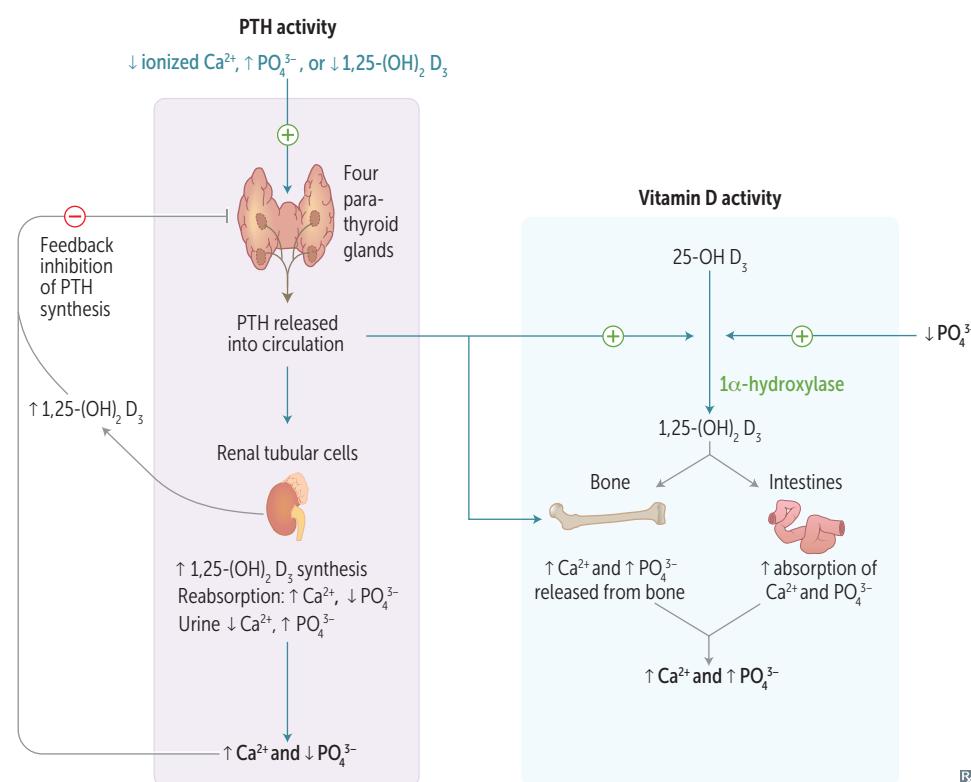
- \uparrow TBG in pregnancy, OCP use (estrogen $\rightarrow \uparrow$ TBG) $\rightarrow \uparrow$ total T_3/T_4
- \downarrow TBG in steroid use, nephrotic syndrome

T_3 and T_4 are the only lipophilic hormones with charged amino acids and require specific transporters to diffuse into the cell (facilitated diffusion).



Parathyroid hormone

SOURCE	Chief cells of parathyroid	
FUNCTION	<ul style="list-style-type: none"> ↑ free Ca^{2+} in the blood (1° function) ↑ Ca^{2+} and PO_4^{3-} absorption in GI system ↑ Ca^{2+} and PO_4^{3-} from bone resorption ↑ Ca^{2+} reabsorption from DCT ↓ PO_4^{3-} reabsorption in PCT ↑ $1,25\text{-}(\text{OH})_2\text{D}_3$ (calcitriol) production by activating 1α-hydroxylase in PCT (tri to make D_3 in the PCT) 	<ul style="list-style-type: none"> PTH ↑ serum Ca^{2+}, ↓ serum PO_4^{3-}, ↑ urine PO_4^{3-}, ↑ urine cAMP ↑ RANK-L (receptor activator of NF-κB ligand) secreted by osteoblasts and osteocytes; binds RANK (receptor) on osteoclasts and their precursors to stimulate osteoclasts and ↑ Ca^{2+} → bone resorption (intermittent PTH release can also stimulate bone formation) <p>PTH = Phosphate-Trashing Hormone</p> <p>PTH-related peptide (PTHRP) functions like PTH and is commonly increased in malignancies (eg, squamous cell carcinoma of the lung, renal cell carcinoma)</p>
REGULATION	<ul style="list-style-type: none"> ↓ serum Ca^{2+} → ↑ PTH secretion ↑ serum PO_4^{3-} → ↑ PTH secretion ↓ serum Mg^{2+} → ↑ PTH secretion ↓↓ serum Mg^{2+} → ↓ PTH secretion <p>Common causes of ↓ Mg^{2+} include diarrhea, aminoglycosides, diuretics, alcohol use disorder</p>	<ul style="list-style-type: none"> Ca^{2+} is the major regulator of PTH release



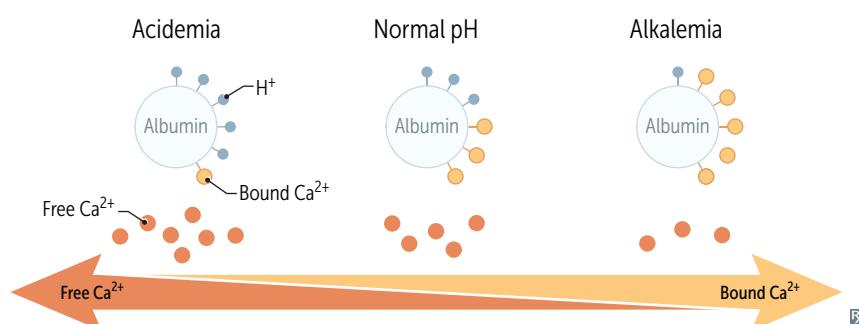
Calcium homeostasis

Plasma Ca^{2+} exists in three forms:

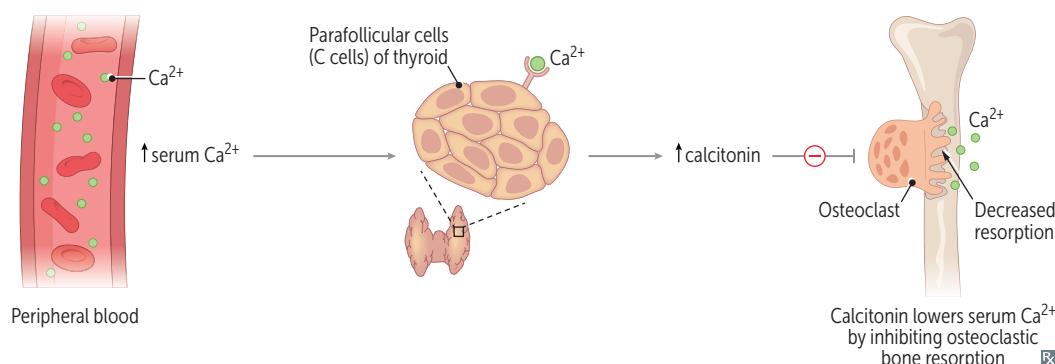
- Ionized/free (~ 45%, active form)
- Bound to albumin (~ 40%)
- Bound to anions (~ 15%)

Ionized/free Ca^{2+} is 1° regulator of PTH; changes in pH alter PTH secretion, whereas changes in albumin concentration do not

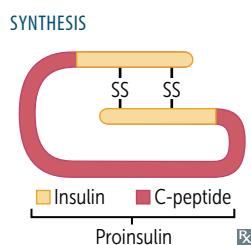
Ca^{2+} competes with H^+ to bind to albumin
 $\uparrow \text{pH}$ (less H^+) \rightarrow albumin binds more Ca^{2+}
 $\downarrow \text{pH}$ (more H^+) \rightarrow albumin binds less Ca^{2+}
 $\rightarrow \uparrow \text{ionized } \text{Ca}^{2+} \rightarrow \downarrow \text{PTH}$

**Calcitonin**

SOURCE	Parafollicular cells (C cells) of thyroid.	Calcitonin opposes actions of PTH. Not important in normal Ca^{2+} homeostasis Calcitonin tones down serum Ca^{2+} levels and keeps it in bones
FUNCTION	\downarrow bone resorption.	
REGULATION	\uparrow serum $\text{Ca}^{2+} \rightarrow$ \uparrow calcitonin secretion.	

**Glucagon**

SOURCE	Made by α cells of pancreas.
FUNCTION	Promotes glycogenolysis, gluconeogenesis, lipolysis, ketogenesis. Elevates blood sugar levels to maintain homeostasis when bloodstream glucose levels fall too low (ie, fasting state).
REGULATION	Secreted in response to hypoglycemia. Inhibited by insulin, amylin, somatostatin, hyperglycemia.

Insulin

Preproinsulin (synthesized in RER of pancreatic β cells) \rightarrow cleavage of “presignal” \rightarrow proinsulin (stored in secretory granules) \rightarrow cleavage of proinsulin \rightarrow exocytosis of insulin and C-peptide equally. Both insulin and C-peptide are \uparrow in endogenous insulin secretion (eg, type 2 DM, insulin secretagogues, insulinoma), whereas exogenous insulin lacks C-peptide (helps differentiate factitious hypoglycemia).

Insulin is synthesized in pancreas and cleared by both liver and kidneys.

FUNCTION

Binds insulin receptors (tyrosine kinase activity ①), inducing glucose uptake (carrier-mediated transport) into insulin-dependent tissue ② and gene transcription.

Anabolic effects of insulin:

- \uparrow glucose transport in skeletal muscle and adipose tissue
- \uparrow glycogen synthesis and storage
- \uparrow triglyceride synthesis
- \uparrow Na^+ retention (kidneys)
- \uparrow protein synthesis (muscles)
- \uparrow cellular uptake of K^+ and amino acids
- \downarrow glucagon release
- \downarrow lipolysis in adipose tissue

Unlike glucose, insulin does not cross placenta.

In mothers with diabetes, excess glucose can cross placenta and $\uparrow\uparrow$ fetal insulin.

Insulin-dependent glucose transporters:

- GLUT4: adipose tissue, striated muscle (exercise can also \uparrow GLUT4 expression)

Insulin-independent transporters:

- GLUT1: RBCs, brain, cornea, placenta
- GLUT2 (bidirectional): β islet cells, liver, kidney, GI tract (think 2-way street)
- GLUT3: brain, placenta
- GLUT5 (fructose): spermatocytes, GI tract
- SGLT1/SGLT2 (Na^+ -glucose cotransporters): kidney, small intestine

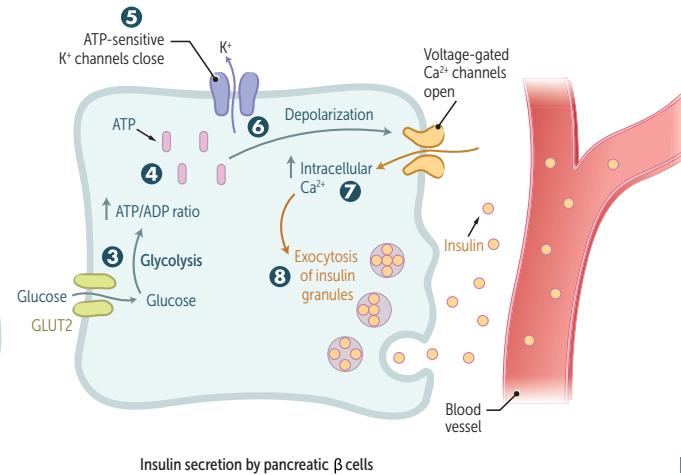
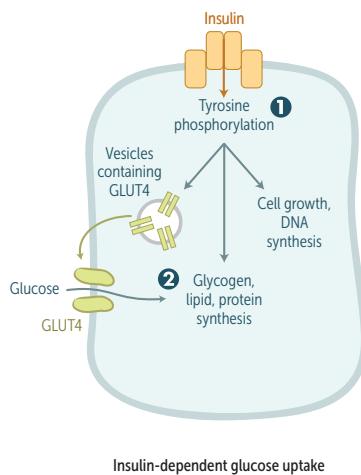
Brain prefers glucose, but may use ketone bodies during starvation. RBCs utilize only glucose, as they lack mitochondria for aerobic metabolism.

BRICK LIPS (insulin-independent glucose uptake): Brain, RBCs, Intestine, Cornea, Kidney, Liver, Islet (β) cells, Placenta, Spermatocytes.

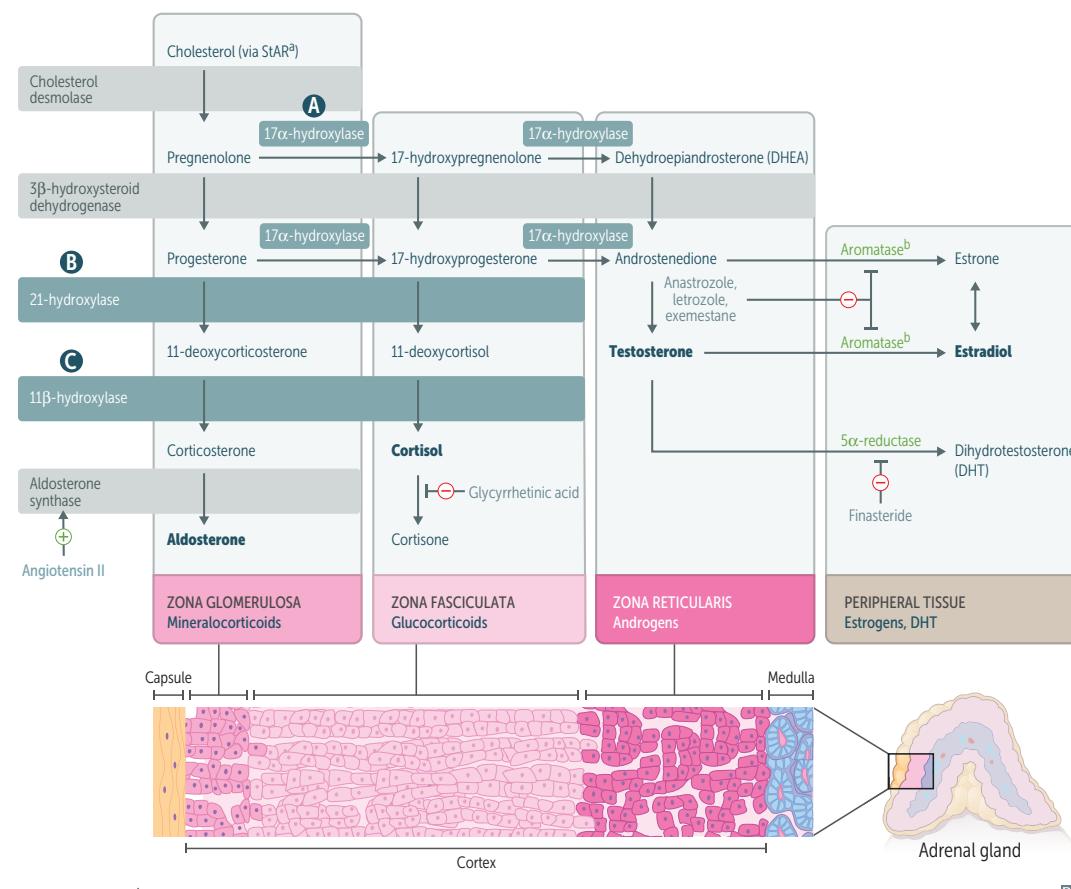
REGULATION

Glucose is the major regulator of insulin release. \uparrow insulin response with oral vs IV glucose due to incretins (eg, glucagonlike peptide 1 [GLP-1], glucose-dependent insulinotropic polypeptide [GIP]), which are released after meals and \uparrow β cell sensitivity to glucose. Release \downarrow by α_2 , \uparrow by β_2 stimulation (2 = regulates insulin).

Glucose enters β cells ③ \rightarrow \uparrow ATP generated from glucose metabolism ④ closes K^+ channels (target of sulfonylureas) ⑤ and depolarizes β cell membrane ⑥. Voltage-gated Ca^{2+} channels open \rightarrow Ca^{2+} influx ⑦ and stimulation of insulin exocytosis ⑧.



Adrenal steroids and congenital adrenal hyperplasias



^a Rate-limiting step, ^b Mostly in peripheral tissues.



ENZYME DEFICIENCY	MINERALOCORTICOIDS	[K ⁺]	BP	CORTISOL	SEX HORMONES	LABS	PRESENTATION
A 17α-hydroxylase^a	↓ aldosterone ↑ 11-deoxycorti- costerone ^b	↓	↑	↓	↓	↓ androstenedione	XY: atypical genitalia, undescended testes XX: lacks 2° sexual development
B 21-hydroxylase^a	↓		↑	↓	↓	↑ renin activity ↑ 17-hydroxy- progesterone	Most common Presents in infancy (salt wasting) or childhood (precocious puberty) XX: virilization
C 11β-hydroxylase^a	↓ aldosterone ↑ 11-deoxycorti- costerone ^b	↓	↑	↓	↑	↓ renin activity	Presents in infancy (severe hypertension) or childhood (precocious puberty) XX: virilization

^aAll congenital adrenal enzyme deficiencies are autosomal recessive disorders and most are characterized by skin hyperpigmentation (due to ↑ MSH production, which is coproduced and secreted with ACTH) and bilateral adrenal gland enlargement (due to ↑ ACTH stimulation).

^bResults in ↑ BP.

If deficient enzyme starts with 1, it causes hypertension; if deficient enzyme ends with 1, it causes virilization in females.

Cortisol

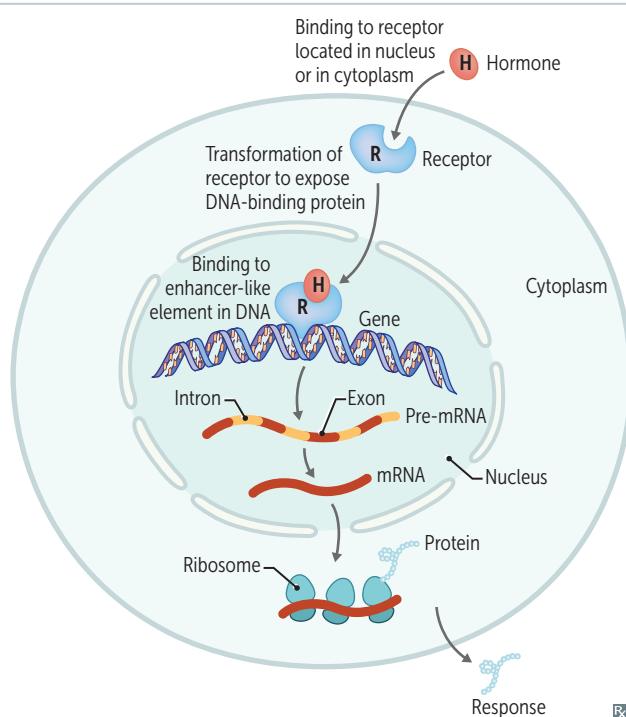
SOURCE	Adrenal zona fasciculata.	Bound to corticosteroid-binding globulin.
FUNCTION	<ul style="list-style-type: none"> ↑ Appetite ↑ Blood pressure: <ul style="list-style-type: none"> ▪ Uregulates α_1-receptors on arterioles → ↑ sensitivity to norepinephrine and epinephrine (permissive action) ▪ At high concentrations, can bind to mineralocorticoid (aldosterone) receptors ↑ Insulin resistance (diabetogenic) ↑ Gluconeogenesis, lipolysis, and proteolysis (↓ glucose utilization) ↓ Fibroblast activity (poor wound healing, ↓ collagen synthesis, ↑ striae) ↓ Inflammatory and Immune responses: <ul style="list-style-type: none"> ▪ Inhibits production of leukotrienes and prostaglandins ▪ Inhibits WBC adhesion → neutrophilia ▪ Blocks histamine release from mast cells ▪ Eosinopenia, lymphopenia ▪ Blocks IL-2 production ↓ Bone formation (↓ osteoblast activity) 	Cortisol is A BIG FIB . Exogenous glucocorticoids can cause reactivation of TB and candidiasis (blocks IL-2 production).
REGULATION	CRH (hypothalamus) stimulates ACTH release (pituitary) → cortisol production in adrenal zona fasciculata. Excess cortisol ↓ CRH, ACTH, and cortisol secretion.	<p>Chronic stress may induce prolonged cortisol secretion, cortisol resistance, impaired immunocompetency, and dysregulation of HPA axis.</p>

Appetite regulation

Ghrelin	Stimulates hunger (orexigenic effect) and GH release (via GH secretagog receptor). Produced by stomach. Sleep deprivation, fasting, or Prader-Willi syndrome → ↑ ghrelin production. Ghrelin makes you <i>ghrow hungry</i>. Acts on lateral area of hypothalamus (hunger center) to ↑ appetite.
Leptin	Satiety hormone. Produced by adipose tissue. Mutation of leptin gene → severe obesity. Obese people have ↑ leptin due to ↑ adipose tissue but are tolerant or resistant to leptin's anorexigenic effect. Sleep deprivation or starvation → ↓ leptin production. Leptin keeps you thin. Acts on ventromedial area of hypothalamus (satiety center) to ↓ appetite.
Endocannabinoids	Act at cannabinoid receptors in hypothalamus and nucleus accumbens, two key brain areas for the homeostatic and hedonic control of food intake → ↑ appetite. Exogenous cannabinoids cause "the munchies."

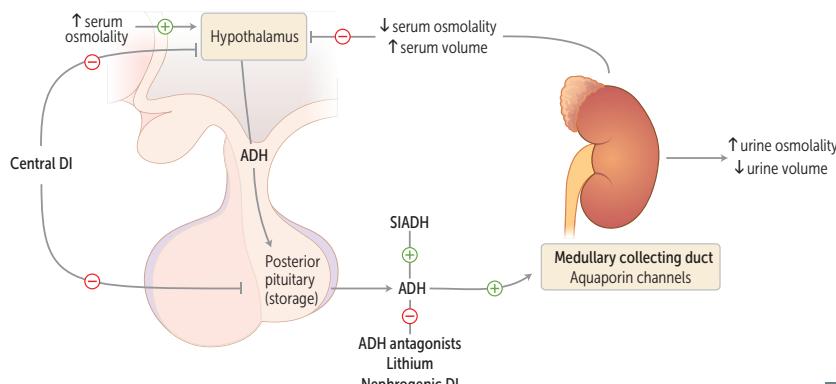
Signaling pathways of endocrine hormones

cAMP	FSH, LH, ACTH, TSH, CRH, hCG, ADH (V ₂ -receptor), MSH, PTH, Calcitonin, Histamine (H ₂ -receptor), Glucagon, GHRH	FLAT ChAMPs CHuGG
cGMP	BNP, ANP, EDRF (NO)	BAD GraMPa Think vasodilation and diuresis
IP ₃	GnRH, Oxytocin, ADH (V ₁ -receptor), TRH, Histamine (H ₁ -receptor), Angiotensin II, Gastrin	GOAT HAG
Intracellular receptor	Progesterone, Estrogen, Testosterone, Cortisol, Aldosterone, T ₃ /T ₄ , Vitamin D	PET CAT in TV
Receptor tyrosine kinase	IGF-1, FGF, PDGF, EGF, Insulin	MAP kinase pathway Get Found In the MAP
Nonreceptor tyrosine kinase	G-CSF, Erythropoietin, Thrombopoietin, Prolactin, Immunomodulators (eg, cytokines IL-2, IL-6, IFN), GH	JAK/STAT pathway Think acidophils and cytokines GET a JAKed PIG

Signaling pathways of steroid hormones

Steroid hormones are lipophilic and therefore must circulate bound to specific binding globulins, which ↑ their solubility.
 In males, ↑ sex hormone-binding globulin (SHBG) lowers free testosterone → gynecomastia.
 In females, ↓ SHBG raises free testosterone → hirsutism.
 ↑ estrogen (eg, OCPs, pregnancy) → ↑ SHBG.

▶ ENDOCRINE—PATHOLOGY

Syndrome of inappropriate antidiuretic hormone secretion

Characterized by excessive free water retention, euvolemic hyponatremia with continued urinary Na^+ excretion, urine osmolality $>$ serum osmolality.

Body responds to water retention with ↓ aldosterone and ↑ ANP and BNP \rightarrow ↑ urinary Na^+ secretion \rightarrow normalization of extracellular fluid volume \rightarrow euvolemic hyponatremia.

Treatment: fluid restriction (first line), salt tablets, IV hypertonic saline, diuretics, ADH antagonists (eg, conivaptan, tolvaptan, demeclocycline).

SIADH causes include (**HEED**-up water):

- Head trauma/CNS disorders
- Ectopic ADH (eg, small cell lung cancer)
- Exogenous hormones (eg, vasopressin, desmopressin, oxytocin)
- Lung disease
- Drugs (eg, SSRIs, carbamazepine, cyclophosphamide)

Primary polydipsia and diabetes insipidus

Characterized by the production of large amounts of dilute urine $+/-$ thirst. Urine specific gravity < 1.006 . Urine osmolality usually $< 300 \text{ mOsm/kg}$. Central DI may be transient if damage is below hypothalamic median eminence or in the posterior pituitary (ADH in hypothalamus can still be secreted systemically via portal capillaries in median eminence). Central DI, also known as arginine vasopressin deficiency; nephrogenic DI, also known as arginine vasopressin resistance.

	Primary polydipsia	Central DI	Nephrogenic DI
DEFINITION	Excessive water intake	↓ ADH release	ADH resistance
CAUSES	Psychiatric illnesses, hypothalamic lesions affecting thirst center	Idiopathic, brain injury (trauma, hypoxia, tumor, surgery, infiltrative diseases)	Hereditary (V_2 -receptor mutation), drugs (eg, lithium, demeclocycline), hypercalcemia, hypokalemia
SERUM OSMOLALITY	↓	↑	↑
ADH LEVEL	↓ or normal	↓	Normal or ↑
WATER RESTRICTION^a	Significant ↑ in urine osmolality ($> 700 \text{ mOsm/kg}$)	No change or slight ↑ in urine osmolality	No change or slight ↑ in urine osmolality
DESMOPRESSIN ADMINISTRATION^b	—	Significant ↑ in urine osmolality ($> 50\%$)	Minimal change in urine osmolality
TREATMENT	Water restriction	Desmopressin (DDAVP)	Manage the underlying cause; low-solute diet, HCTZ, amiloride, indomethacin

^aNo water intake for 2–3 hours followed by hourly measurements of urine volume and osmolality as well as plasma Na^+ concentration and osmolality.

^bDesmopressin (ADH analog) is administered if serum osmolality > 295 – 300 mOsm/kg , plasma $\text{Na}^+ \geq 145 \text{ mEq/L}$, or urine osmolality does not increase despite ↑ plasma osmolality.

Hypopituitarism

Undersecretion of pituitary hormones due to:

- Hypothalamic disease (ie, mass lesion, radiation, infiltrative lesions)
- Pituitary surgery
- Pituitary disorders (eg, mass effect due to nonsecreting pituitary adenoma, craniopharyngioma)
- Empty sella
- **Sheehan syndrome**—ischemic infarct of pituitary following severe postpartum hemorrhage; pregnancy-induced pituitary growth → ↑ susceptibility to hypoperfusion. Usually presents with failure to lactate, amenorrhea, cold intolerance (anterior pituitary hormones mainly affected). Treatment: hormone replacement therapy (glucocorticoids, thyroxine, sex steroids, human growth hormone)

Acromegaly

Excess GH in adults. Typically caused by pituitary adenoma.

FINDINGS

Large tongue with deep furrows, frontal bossing, coarsening of facial features with aging **A**, deep voice, diaphoresis (excessive sweating), hypertrophic arthropathy, impaired glucose tolerance (insulin resistance), HTN, LVH, HFpEF (most common cause of death).

↑ GH in children → gigantism (↑ linear bone growth due to unfused epiphysis).

Acromegaly in adults, gigantism in **j(g)uniors**.

DIAGNOSIS

↑ serum IGF-1 (GH levels unreliable as they fluctuate throughout the day); failure to suppress serum GH following oral glucose tolerance test; pituitary mass seen on brain MRI.



TREATMENT

Pituitary adenoma resection. If not cured, treat with octreotide (somatostatin analog), pegvisomant (GH receptor antagonist), or dopamine agonists (eg, cabergoline).

Hypothyroidism vs hyperthyroidism

	Hypothyroidism	Hyperthyroidism
METABOLIC	Cold intolerance, ↓ sweating, weight gain (↓ basal metabolic rate → ↓ calorigenesis), hyponatremia (↓ free water clearance)	Heat intolerance, ↑ sweating, weight loss (↑ synthesis of Na ⁺ /K ⁺ -ATPase → ↑ basal metabolic rate → ↑ calorigenesis)
SKIN/HAIR	Dry, cool skin (due to ↓ blood flow); coarse, brittle hair; diffuse alopecia; brittle nails; puffy facies and generalized nonpitting edema (myxedema) due to ↑ GAGs in interstitial spaces → ↑ osmotic pressure → water retention	Warm, moist skin (due to vasodilation); fine hair; onycholysis (A); pretibial myxedema in Graves disease (B)
OCULAR	Periorbital edema (C)	Ophthalmopathy in Graves disease (including periorbital edema, exophthalmos), lid lag/retraction (↑ sympathetic stimulation of superior tarsal muscle)
GASTROINTESTINAL	Constipation (↓ GI motility), ↓ appetite	Hyperdefecation/diarrhea (↑ GI motility), ↑ appetite
MUSCULOSKELETAL	Hypothyroid myopathy (proximal weakness, ↑ CK), carpal tunnel syndrome, myoedema (small lump rising on the surface of a muscle when struck with a hammer)	Thyrotoxic myopathy (proximal weakness, normal CK), osteoporosis/↑ fracture rate (T ₃ stimulates osteoclast differentiation, ↑ bone resorption, and release of calcium; may also affect osteoblasts)
REPRODUCTIVE	Abnormal uterine bleeding, ↓ libido, infertility	Abnormal uterine bleeding, gynecomastia, ↓ libido, infertility
NEUROPSYCHIATRIC	Hypoactivity, lethargy, fatigue, weakness, depressed mood, ↓ reflexes (delayed/slow relaxing)	Hyperactivity, restlessness, anxiety, insomnia, fine tremors (due to ↑ β-adrenergic activity), ↑ reflexes (brisk)
CARDIOVASCULAR	Bradycardia, dyspnea on exertion (↓ cardiac output)	Tachycardia, palpitations, dyspnea, arrhythmias (eg, atrial fibrillation), chest pain and systolic HTN due to ↑ number and sensitivity of β-adrenergic receptors, ↑ expression of cardiac sarcolemmal ATPase and ↓ expression of phospholamban
LABS	↑ TSH (if 1°) ↓ free T ₄ Hypercholesterolemia (due to ↓ LDL receptor expression)	↓ TSH (if 1°) ↑ free T ₃ and T ₄ ↓ LDL, HDL, and total cholesterol



Hypothyroidism**Hashimoto thyroiditis**

Also called chronic autoimmune thyroiditis. Most common cause of hypothyroidism in iodine-sufficient regions. Associated with HLA-DR3 (differs by ethnicity), ↑ risk of primary thyroid lymphoma (typically diffuse large B-cell lymphoma).
 Findings: moderately enlarged, **nontender** thyroid. May be preceded by transient hyperthyroid state (“Hashitoxicosis”) due to follicular rupture and thyroid hormone release.
 Serology: ⊕ antithyroid peroxidase (antimicrosomal) and antithyroglobulin antibodies.
 Histology: Hürthle cells **A**, lymphoid aggregates with germinal centers **B**.
Postpartum thyroiditis—mild, self-limited variant of Hashimoto thyroiditis arising < 1 year after delivery. Natural history: hyperthyroidism (within 3 months of birth) → hypothyroidism → recovery/euthyroid state.

Subacute granulomatous thyroiditis

Also called de Quervain thyroiditis. Usually, a self-limited disease. Natural history: transient hyperthyroidism → euthyroid state → hypothyroidism → euthyroid state. Often preceded by viral infection.
 Findings: ↑ ESR, jaw pain, very **tender** thyroid (de Quervain is associated with **pain**).
 Histology: granulomatous inflammation **C**.

Riedel thyroiditis

Also called invasive fibrous thyroiditis. May occur as part of IgG₄-related disease spectrum (eg, autoimmune pancreatitis, retroperitoneal fibrosis, noninfectious aortitis). Hypothyroidism occurs in ⅓ of patients. Fibrosis may extend to local structures (eg, trachea, esophagus), mimicking anaplastic carcinoma.
 Findings: slowly enlarging, hard (rocklike), fixed, **nontender** thyroid.
 Histology: thyroid replaced by fibrous tissue and inflammatory infiltrate **D**.

Congenital hypothyroidism

Formerly called cretinism. Most commonly caused by thyroid dysgenesis (abnormal thyroid gland development; eg, agenesis, hypoplasia, ectopy) or dyshormonogenesis (abnormal thyroid hormone synthesis; eg, mutations in thyroid peroxidase) in iodine-sufficient regions.
 Findings (**6 P's**): **pot-bellied**, **pale**, **puffy-faced** child **E** with protruding umbilicus, **protuberant tongue** **F**, and **poor brain development**.

Other causes

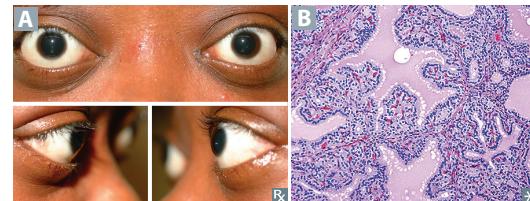
Iodine deficiency (most common cause worldwide; typically presents with goiter **G**), iodine excess (Wolff-Chaikoff effect), drugs (eg, amiodarone, lithium), nonthyroidal illness syndrome (also called euthyroid sick syndrome; ↓ T₃ with normal/↓ T₄ and TSH in critically ill patients).



Hyperthyroidism**Graves disease**

Most common cause of hyperthyroidism. Thyroid-stimulating immunoglobulin (IgG, can cause transient neonatal hyperthyroidism; type II hypersensitivity) stimulates TSH receptors on thyroid (hyperthyroidism, diffuse goiter), dermal fibroblasts (pretibial myxedema), and orbital fibroblasts (Graves orbitopathy; treat with glucocorticoids). Activation of T-cells → lymphocytic infiltration of retroorbital space → ↑ cytokines (eg, TNF- α , IFN- γ) → ↑ fibroblast secretion of hydrophilic GAGs → ↑ osmotic muscle swelling, muscle inflammation, and adipocyte count → exophthalmos **A**. Often presents during stress (eg, pregnancy). Associated with HLA-DR3 and HLA-B8.

Histology: tall, crowded follicular epithelial cells; scalloped colloid **B**.

**Toxic multinodular goiter**

Focal patches of hyperfunctioning follicular cells distended with colloid working independently of TSH (due to TSH receptor mutations in 60% of cases). ↑ release of T₃ and T₄. Hot nodules (hyperfunctioning nodules visualized on radioactive iodine scan) are rarely malignant.

Thyroid storm

Uncommon but serious complication that occurs when hyperthyroidism is incompletely treated/untreated and then significantly worsens in the setting of acute stress such as infection, trauma, surgery. Presents with agitation, delirium, fever, diarrhea, coma, and tachyarrhythmia (cause of death). May see ↑ LFTs. Treat with the **4 P's**: β -blockers (eg, propranolol), propylthiouracil, glucocorticoids (eg, prednisolone), potassium iodide (Lugol iodine). Iodide load → ↓ T₄ synthesis → Wolff-Chaikoff effect.

Other causes

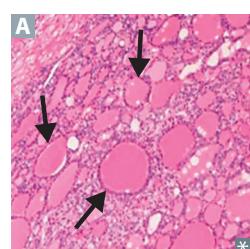
Exogenous thyrotoxicosis (excessive intake of thyroid hormone; suspect in patient trying to lose weight), ectopic thyroid production (struma ovarii), contrast-induced thyroiditis (Jod-Basedow phenomenon), drug-induced thyroiditis (amiodarone, lithium).

Causes of goiter

Smooth/diffuse: Graves disease, Hashimoto thyroiditis, iodine deficiency, TSH-secreting pituitary adenoma.
Nodular: toxic multinodular goiter, thyroid adenoma, thyroid cancer, thyroid cyst.

Thyroid adenoma

Benign solitary growth of the thyroid. Most are nonfunctional (“cold” on radioactive iodine scan), can rarely cause hyperthyroidism via autonomous thyroid hormone production (“hot” or “toxic”). Most common histology is follicular (arrows in **A**); absence of capsular or vascular invasion (unlike follicular carcinoma).



Thyroid cancer

Typically diagnosed with fine needle aspiration; treated with thyroidectomy. Complications of surgery include hypocalcemia (due to removal of parathyroid glands), transection of recurrent laryngeal nerve during ligation of inferior thyroid artery (leads to dysphagia and dysphonia [hoarseness]), and injury to the external branch of the superior laryngeal nerve during ligation of superior thyroid vascular pedicle (may lead to loss of tenor usually noticeable in professional voice users).

Papillary carcinoma

Most common. Empty-appearing nuclei with central clearing (“**Orphan Annie**” eyes) **A**, psammoma bodies, nuclear grooves (**Papi** and **Moma** adopted **Orphan Annie**). ↑ risk with RET/PTC rearrangements and BRAF mutations, childhood irradiation.

Papillary carcinoma: most prevalent, palpable lymph nodes. Good prognosis.

Follicular carcinoma

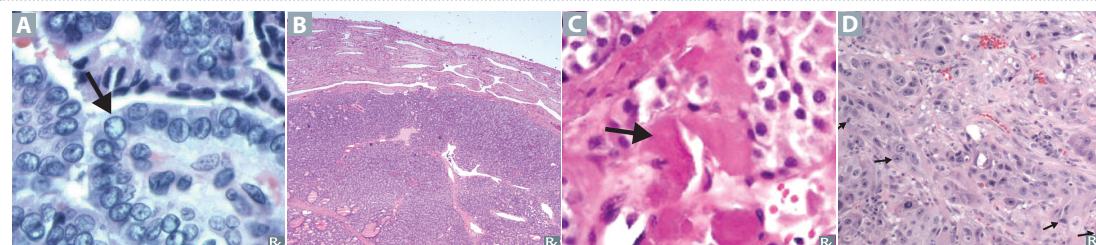
Good prognosis. Invades tumor capsule and vasculature (unlike follicular adenoma), uniform follicles **B**; hematogenous spread is common. Associated with RAS mutation and PAX8-PPAR-γ translocations. Fine needle aspiration cytology may not be able to distinguish between follicular adenoma and carcinoma.

Medullary carcinoma

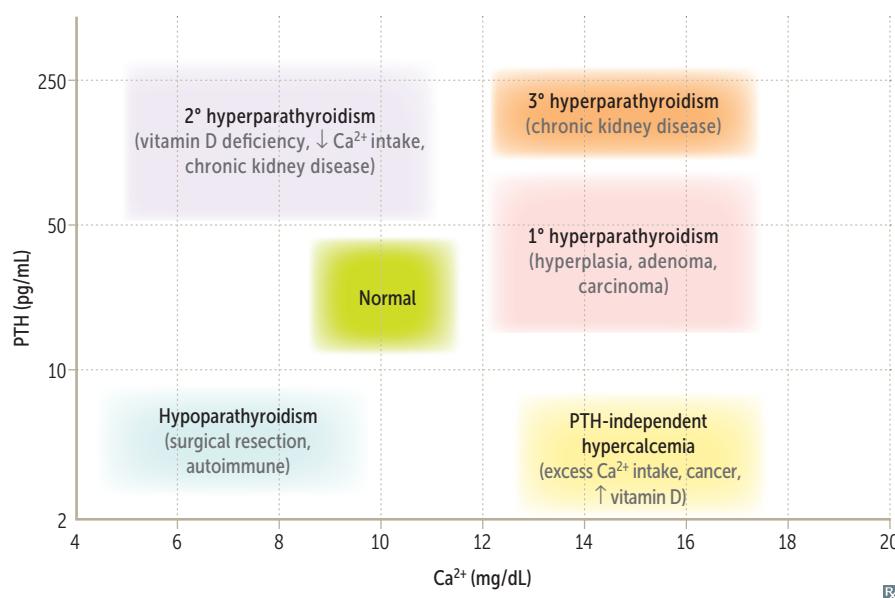
From parafollicular “**C** cells”; produces calcitonin, sheets of polygonal cells in an amyloid stroma **C** (stains with **Congo red**). Associated with **MEN 2A** and **2B** (RET mutations; **MEN2**llary carcinoma).

Undifferentiated/anaplastic carcinoma

Older patients; presents with rapidly enlarging neck mass → compressive symptoms (eg, dyspnea, dysphagia, hoarseness); very poor prognosis. Typically composed of pleomorphic cells with frequent mitoses **D**. May arise de novo, but most often arises from dedifferentiation of a preexisting follicular or papillary thyroid carcinoma.



Diagnosing parathyroid disease



Hypoparathyroidism



Due to injury to parathyroid glands or their blood supply (usually during thyroid surgery), autoimmune destruction, or DiGeorge syndrome. Findings: tetany, hypocalcemia, hyperphosphatemia.

Chvostek sign—tapping of facial nerve (tap the **Cheek**) → contraction of facial muscles.

Trousseau sign—occlusion of brachial artery with BP cuff (cuff the **Triceps**) → carpal spasm.

Pseudohypoparathyroidism type 1A—autosomal dominant, maternally transmitted mutations (imprinted GNAS gene). GNAS1-inactivating mutation (coupled to PTH receptor) that encodes the G_s protein α subunit → inactivation of adenylate cyclase when PTH binds to its receptor → end-organ resistance (kidney and bone) to PTH.

Physical findings: Albright hereditary osteodystrophy (shortened 4th/5th digits **A**, short stature, round face, subcutaneous calcifications, developmental delay).

Labs: ↑ PTH, ↓ Ca²⁺, ↑ PO₄³⁻.

Pseudopseudohypoparathyroidism—autosomal dominant, paternally transmitted mutations (imprinted GNAS gene) but without end-organ resistance to PTH due to normal maternal allele maintaining renal responsiveness to PTH.

Physical findings: same as Albright hereditary osteodystrophy.

Labs: normal PTH, Ca²⁺, PO₄³⁻.

Lab values in hypocalcemic disorders

DISORDER	Ca ²⁺	PO ₄ ³⁻	PTH	ALP	25(OH) VITAMIN D	1,25(OH) ₂ VITAMIN D
Vitamin D deficiency	—/↓	—/↓	↑	↑	↓	—/↑
2° hyperparathyroidism (CKD)	↓	↑	↑	↑	—	↓
Hypoparathyroidism	↓	↑	↓	—	—	—/↓
Pseudohypo-parathyroidism	↓	↑	↑	↑	—	—/↓

Hyperparathyroidism

Primary hyperparathyroidism



Usually due to parathyroid adenoma or hyperplasia. **Hypercalcemia**, hypercalciuria (renal **stones**), polyuria (**thrones**), hypophosphatemia, ↑ PTH, ↑ ALP, ↑ urinary cAMP. Most often asymptomatic. May present with **bone** pain, weakness, constipation (“**groans**”), abdominal/flank pain (kidney stones, acute pancreatitis), neuropsychiatric disturbances (“**psychiatric overtones**”).

Secondary hyperparathyroidism

2° hyperplasia due to ↓ Ca²⁺ absorption and/or ↑ PO₄³⁻, most often in chronic kidney disease (causes hypovitaminosis D and hyperphosphatemia → ↓ Ca²⁺). **Hypocalcemia**, hyperphosphatemia in chronic kidney disease (vs hypophosphatemia with most other causes), ↑ ALP, ↑ PTH.

Tertiary hyperparathyroidism

Refractory (autonomous) hyperparathyroidism resulting from end-stage renal disease. ↑↑ PTH, ↑ Ca²⁺.

Familial hypocalciuric hypercalcemia

Autosomal dominant. Defective G-coupled Ca²⁺-sensing receptors in multiple tissues (eg, parathyroids, kidneys). Higher than normal Ca²⁺ levels required to suppress PTH. Excessive renal Ca²⁺ reabsorption → mild hypercalcemia and hypocalciuria with normal to ↑ PTH levels.

Osteitis fibrosa cystica

cystic **bone** spaces filled with brown fibrous tissue **A** (“brown tumor” consisting of osteoclasts and deposited hemosiderin from hemorrhages; causes bone pain). Due to ↑ PTH, classically associated with 1° (but also seen with 2°) hyperparathyroidism.

“**Stones, thrones, bones, groans**, and **psychiatric overtones**.”

Renal osteodystrophy

renal disease → 2° and 3° hyperparathyroidism → bone lesions.

Diabetes mellitus

ACUTE MANIFESTATIONS

Polydipsia, polyuria, polyphagia (3 P's), weight loss, DKA (type 1), hyperosmolar hyperglycemic state (type 2).

Rarely, can be caused by unopposed secretion of GH and epinephrine. Also seen in patients on glucocorticoid therapy (steroid diabetes).

CHRONIC COMPLICATIONS

Nonenzymatic glycation:

- Small vessel disease (hyaline arteriolosclerosis) → retinopathy, neuropathy, nephropathy.
- Large vessel disease (atherosclerosis) → CAD, cerebrovascular disease, peripheral vascular disease. MI is the most common cause of death.

Osmotic damage (sorbitol accumulation in organs with aldose reductase and ↓ or absent sorbitol dehydrogenase):

- Neuropathy: motor, sensory (glove and stocking distribution), autonomic degeneration (eg, GERD, gastroparesis, diabetic diarrhea).
- Cataracts.

DIAGNOSIS

TEST

HbA_{1c}

DIAGNOSTIC CUTOFF

≥ 6.5%

NOTES

Reflects average blood glucose over prior 3 months (influenced by RBC turnover)

Fasting plasma glucose

≥ 126 mg/dL

Fasting for > 8 hours

2-hour oral glucose tolerance test

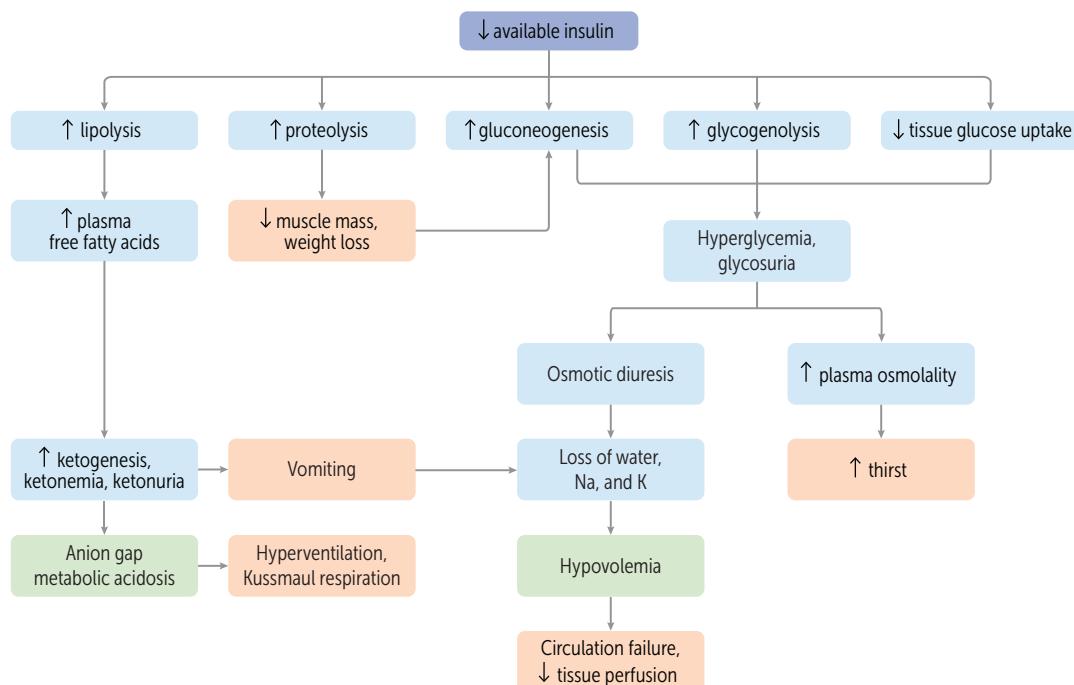
≥ 200 mg/dL

2 hours after consumption of 75 g of glucose in water

Random plasma glucose

≥ 200 mg/dL

Presence of hyperglycemic symptoms is required



Type 1 vs type 2 diabetes mellitus

	Type 1	Type 2
1° DEFECT	Autoimmune T-cell-mediated destruction of β cells (islet cell cytoplasmic +/- antiglutamic acid decarboxylase +/- insulin autoantibodies often present)	↑ resistance to insulin, progressive pancreatic β-cell failure
INSULIN NECESSARY IN TREATMENT	Always	Sometimes
AGE (EXCEPTIONS COMMON)	< 30 yr	> 40 yr
ASSOCIATION WITH OBESITY	No	Yes
GENETIC PREDISPOSITION	Relatively weak (50% concordance in identical twins), polygenic	Relatively strong (90% concordance in identical twins), polygenic
ASSOCIATION WITH HLA SYSTEM	Yes, HLA-DR4 and -DR3 (4 – 3 = type 1)	No
GLUCOSE INTOLERANCE	Severe	Mild to moderate
INSULIN SENSITIVITY	High	Low
KETOACIDOSIS	Common	Rare
β-CELL NUMBERS IN THE ISLETS	↓	Variable (with amyloid deposits)
SERUM INSULIN LEVEL	↓	↑ initially, but ↓ in advanced disease
CLASSIC SYMPTOMS ^a	Common	Sometimes
HISTOLOGY	Islet leukocytic infiltrate	Islet amyloid polypeptide deposits

^aPolydipsia, polyuria, polyphagia, weight loss

Hyperglycemic emergencies

	Diabetic ketoacidosis	Hyperosmolar hyperglycemic state
PATHOGENESIS	Insulin noncompliance or ↑ requirements due to ↑ stress (eg, infection) → lipolysis and oxidation of free fatty acids → ↑ ketone bodies (β-hydroxybutyrate > acetoacetate). Insulin deficient, ketones present.	Profound hyperglycemia → excessive osmotic diuresis → dehydration and ↑ serum osmolality → HHS. Classically seen in older patients with type 2 DM and limited ability to drink. Insulin present, ketones deficient.
SIGNS/SYMPOTMS	DKA is Deadly: Delirium/psychosis, Kussmaul respirations (rapid, deep breathing), Abdominal pain-nausea/vomiting, Dehydration. Fruity breath odor due to exhaled acetone.	Thirst, polyuria, lethargy, focal neurologic deficits, seizures.
LABS	Hyperglycemia, ↑ H ⁺ , ↓ HCO ₃ ⁻ (↑ anion gap metabolic acidosis), ↑ urine and blood ketone levels, leukocytosis. Normal/↑ serum K ⁺ , but depleted intracellular K ⁺ due to transcellular shift from ↓ insulin and acidosis. Osmotic diuresis → ↑ K ⁺ loss in urine → total body K ⁺ depletion.	Hyperglycemia (often > 600 mg/dL), ↑ serum osmolality (> 320 mOsm/kg), normal pH (no acidosis), no ketones. Normal/↑ serum K ⁺ , ↓ intracellular K ⁺ .
COMPLICATIONS	Life-threatening mucormycosis, cerebral edema, cardiac arrhythmias.	Can progress to coma and death if untreated.
TREATMENT	IV fluids, IV insulin, and K ⁺ (to replete intracellular stores). Glucose may be required to prevent hypoglycemia from insulin therapy.	

Hypoglycemia in diabetes mellitus

Usually occurs in patients treated with insulin or insulin secretagogues (eg, sulfonylureas, meglitinides) in the setting of high-dose treatment, inadequate food intake, and/or exercise.

- Neurogenic (autonomic) symptoms: diaphoresis, tachycardia, tremor, anxiety, hunger. Allow perception of ↓ glucose (hypoglycemia awareness).
- Neuroglycopenic symptoms: altered mental status, seizures, death due to insufficient glucose in CNS. May occur in the absence of preceding neurogenic symptoms in patients with attenuated autonomic response, eg, β-blocker use (ie, hypoglycemia unawareness).

Treatment: simple carbohydrates (eg, glucose tablets, fruit juice), IM glucagon, IV dextrose.

Cushing syndrome

ETIOLOGY

↑ cortisol due to a variety of causes:

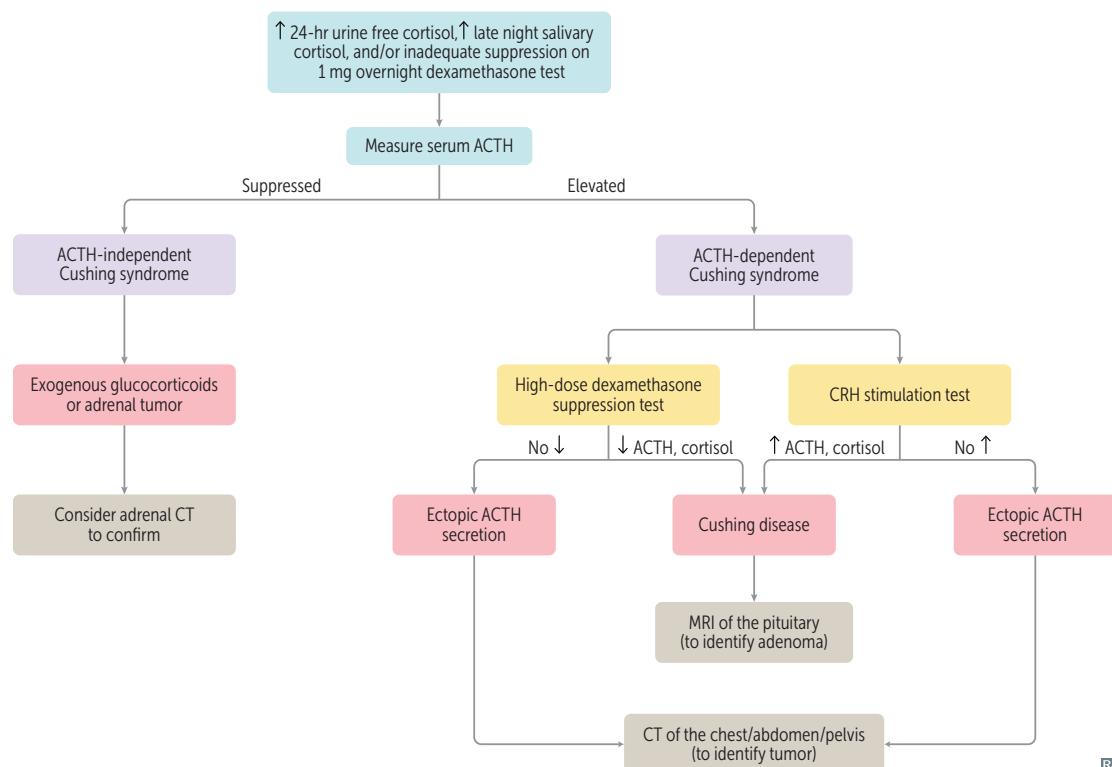
- Exogenous glucocorticoids → ↓ ACTH → bilateral adrenal atrophy. Most common cause.
- Primary adrenal adenoma, hyperplasia, or carcinoma → ↓ ACTH → atrophy of uninvolved adrenal gland.
- ACTH-secreting pituitary adenoma (Cushing disease); paraneoplastic ACTH secretion (eg, small cell lung cancer, bronchial carcinoids) → bilateral adrenal hyperplasia. Cushing disease is responsible for the majority of endogenous cases of Cushing syndrome.

FINDINGS

MOON FACIES: Metabolic syndrome (hypertension, hyperglycemia, hyperlipidemia), **O**besity (truncal weight gain with wasting of extremities, round “moon” facies **A**, dorsocervical fat pad “buffalo hump”), **O**steoporosis, **N**euro-psychiatric (depression, anxiety, irritability), **F**acial plethora, **A**ndrogen excess (acne, hirsutism), **C**ataract, **I**mmunosuppression, **E**cchymoses (easy bruising), **S**kin changes (thinning, striae **B**, hyperpigmentation).

DIAGNOSIS

Screening tests include: ↑ free cortisol on 24-hr urinalysis, ↑ late night salivary cortisol, and no suppression with overnight low-dose dexamethasone test.



Adrenal insufficiency

Inability of adrenal glands to generate enough glucocorticoids +/- mineralocorticoids for the body's needs. Can be acute or chronic. Symptoms include weakness, fatigue, orthostatic hypotension, muscle aches, weight loss, GI disturbances, sugar and/or salt cravings.

Treatment: glucocorticoid +/- mineralocorticoid replacement.

Primary adrenal insufficiency**Secondary and tertiary adrenal insufficiency**

↓ gland function → ↓ cortisol, ↓ aldosterone → hypotension (hyponatremic volume contraction), hyperkalemia, metabolic acidosis, skin/mucosal (pressure areas and buccal mucosa) hyperpigmentation **A**. ↓ cortisol → ↓ negative feedback effect on the pituitary → ↑ production of POMC derivatives (β -endorphin, ACTH, MSH) → ↑ melanin synthesis due to ↑ MSH. Primary pigments the skin/mucosa.

Addison disease—chronic 1° adrenal insufficiency; caused by adrenal atrophy or destruction. Most commonly due to autoimmune adrenalitis (high-income countries) or TB (low-income countries).

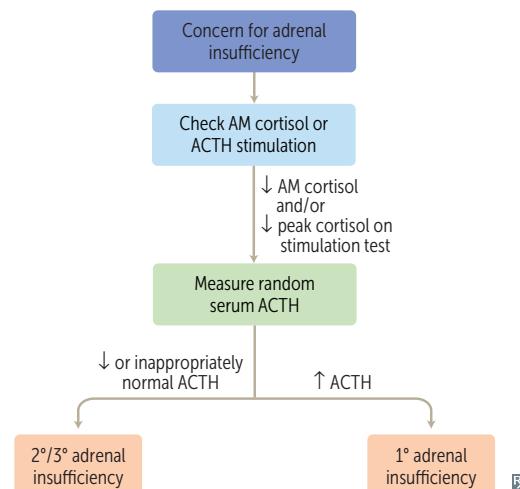
Acute adrenal insufficiency

↓ pituitary ACTH secretion (secondary) or ↓ hypothalamic CRH secretion (tertiary). No hyperkalemia (aldosterone synthesis preserved due to functioning adrenal gland, intact RAAS), no hyperpigmentation.

2° adrenal insufficiency is due to pituitary pathologies, 3° adrenal insufficiency is most commonly due to abrupt cessation of chronic glucocorticoid therapy (HPA suppression). **Tertiary** from treatment.

Also called adrenal (addisonian) crisis; often precipitated by acute stressors that ↑ glucocorticoid requirements (eg, infection) in patients with pre-existing adrenal insufficiency or on glucocorticoid therapy. May present with acute abdominal pain, nausea, vomiting, altered mental status, shock.

Waterhouse-Friderichsen syndrome—bilateral adrenal hemorrhage in the setting of sepsis (eg, meningococcemia) → acute 1° adrenal insufficiency.



Hyperaldosteronism

Increased secretion of aldosterone from adrenal gland. Clinical features include hypertension, ↓ or normal K⁺, metabolic alkalosis. 1° hyperaldosteronism does not directly cause edema due to aldosterone escape mechanism. However, certain 2° causes of hyperaldosteronism (eg, heart failure) impair the aldosterone escape mechanism, leading to worsening of edema.

Primary hyperaldosteronism

Seen in patients with bilateral adrenal hyperplasia or adrenal adenoma (Conn syndrome). ↑ aldosterone, ↓ renin. Leads to treatment-resistant hypertension.

Secondary hyperaldosteronism

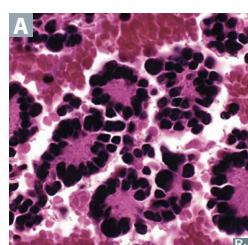
Seen in patients with renovascular hypertension, juxtaglomerular cell tumors (renin-producing), and edema (eg, cirrhosis, heart failure, nephrotic syndrome). ↑ aldosterone, ↑ renin.

Neuroendocrine tumors

Heterogeneous group of neoplasms originating from neuroendocrine cells (which have traits similar to nerve cells and hormone-producing cells).

Most neoplasms occur in the GI system (eg, carcinoid, gastrinoma), pancreas (eg, insulinoma, glucagonoma), and lungs (eg, small cell carcinoma). Also in thyroid (eg, medullary carcinoma) and adrenals (eg, pheochromocytoma).

Neuroendocrine cells (eg, pancreatic β cells, enterochromaffin cells) share a common biologic function through amine precursor uptake decarboxylase (APUD) despite differences in embryologic origin, anatomic site, and secretory products (eg, chromogranin A, neuron-specific enolase [NSE], synaptophysin, serotonin, histamine, calcitonin). Treatment: surgical resection, somatostatin analogs.

Neuroblastoma

Most common solid extracranial tumor in children (typically < 4 years old). Usually arises in adrenal medulla, but may occur anywhere along the sympathetic chain. Originates from neural crest cells.

Most common presentation is abdominal distension and a firm, irregular mass that can cross the midline (vs Wilms tumor, which is smooth and unilateral). Less likely to develop hypertension than with pheochromocytoma (neuroblastoma is normotensive). Can also present with opsoclonus-myoclonus syndrome ("dancing eyes-dancing feet").

↑ HVA and VMA (catecholamine metabolites) in urine. Homer-Wright rosettes (neuroblasts surrounding a central area of neuropil **A**) characteristic of neuroblastoma and medulloblastoma. Bombesin and NSE \oplus . Associated with amplification of **N-myc** oncogene.

Pheochromocytoma

ETIOLOGY



Most common tumor of the adrenal medulla in adults (black arrow in A; red arrow points to bone metastases). Derived from chromaffin cells (arise from neural crest). Rare. May be associated with germline mutations (eg, NF-1, VHL, RET [MEN 2A, 2B]).

SYMPTOMS

Most tumors secrete epinephrine, norepinephrine, and dopamine, which can cause episodic hypertension. May also secrete EPO → polycythemia. Symptoms occur in “spells”—relapse and remit.

FINDINGS

↑ catecholamines and metanephhrines (eg, homovanillic acid, vanillylmandelic acid) in urine and plasma; episodic hyperglycemia may be an uncommon finding.

TREATMENT

Irreversible α -antagonists (eg, phenoxybenzamine) followed by β -blockers prior to tumor resection. α -blockade must be achieved before giving β -blockers to avoid a hypertensive crisis. A before B.

Rule of 10's:

- 10% malignant
- 10% bilateral
- 10% extra-adrenal (paraganglioma; eg, bladder wall, organ of Zuckerkandl)
- 10% calcify
- 10% kids

Episodic hyperadrenergic symptoms (5 P's):

- P**ressure (\uparrow BP)
- P**ain (headache)
- P**erspiration
- P**alpitations (tachycardia)
- P**allor

Chromogranin, synaptophysin and NSE \oplus .

Phenoxybenzamine for **phe**ochromocytoma.

Multiple endocrine neoplasias

All **MEN** syndromes have autosomal **dominant** inheritance.

The X-MEN are **dominant** over villains.

SUBTYPE

CHARACTERISTICS

MEN1

Pituitary tumors (prolactin or GH)

Pancreatic endocrine tumors—Zollinger-Ellison syndrome, insulinomas, VIPomas, glucagonomas (rare)

Parathyroid adenomas

Associated with mutation of *MEN1* (tumor suppressor, codes for menin, chromosome 11), angiofibromas, collagenomas, meningiomas

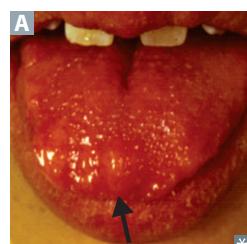
MEN2A

Parathyroid hyperplasia

Medullary thyroid carcinoma—neoplasm of parafollicular C cells; secretes calcitonin; prophylactic thyroidectomy required

Pheochromocytoma (secretes catecholamines)

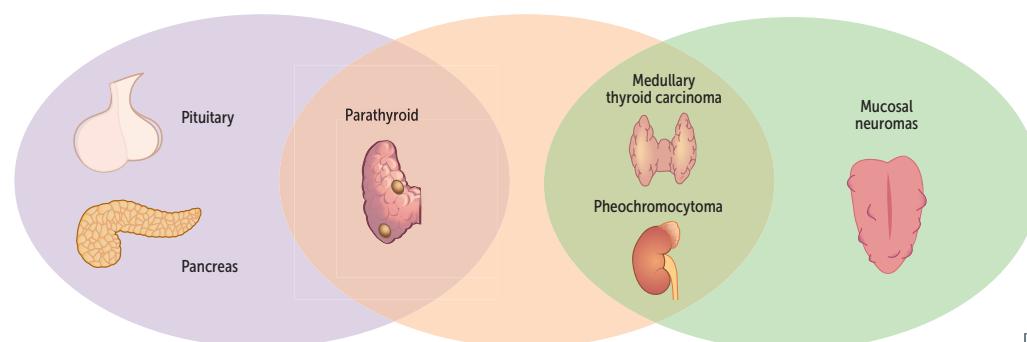
Associated with mutation in *RET* (protooncogene, codes for receptor tyrosine kinase, chromosome 10)

MEN2B

MEN1 = 3 P's

MEN2A = 2 P's, 1 M

MEN2B = 1 P, 2 M's



Pancreatic islet cell tumors**Insulinoma**

Tumor of pancreatic β cells \rightarrow overproduction of insulin \rightarrow hypoglycemia. May see Whipple triad: low blood glucose, symptoms of hypoglycemia (eg, lethargy, syncope, diplopia), and resolution of symptoms after normalization of plasma glucose levels. Symptomatic patients have \downarrow blood glucose and \uparrow C-peptide levels (vs exogenous insulin use). $\sim 10\%$ of cases associated with MEN1 syndrome.

Treatment: surgical resection.

Glucagonoma

Tumor of pancreatic α cells \rightarrow overproduction of glucagon. Presents with **6 D's**: dermatitis (necrolytic migratory erythema), diabetes (hyperglycemia), DVT, declining weight, depression, diarrhea.

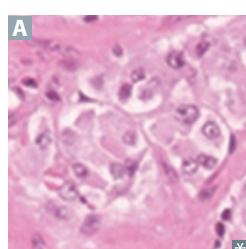
Treatment: octreotide, surgical resection.

Somatostatinoma

Tumor of pancreatic δ cells \rightarrow overproduction of somatostatin \rightarrow \downarrow secretion of secretin, cholecystokinin, glucagon, insulin, gastrin, gastric inhibitory peptide (GIP).

May present with diabetes/glucose intolerance, steatorrhea, gallstones, achlorhydria.

Treatment: surgical resection; somatostatin analogs (eg, octreotide) for symptom control.

Carcinoid tumors

Carcinoid tumors arise from neuroendocrine cells, most commonly in the intestine or lung.

Neuroendocrine cells secrete 5-HT, which undergoes hepatic first-pass metabolism and enzymatic breakdown by MAO in the lung. If 5-HT reaches the systemic circulation (eg, after liver metastasis), carcinoid tumor may present with **carcinoid syndrome**—episodic flushing, diarrhea, wheezing, right-sided valvular heart disease (eg, tricuspid regurgitation, pulmonic stenosis), \uparrow urinary 5-HIAA. Excess 5-HT production depletes tryptophan stores, leading to niacin deficiency (pellagra).

Histology: rosettes **A**, chromogranin A \oplus , synaptophysin \oplus .

Diagnosis: \uparrow 24-hour urinary excretion of 5-HIAA. Octreotide scintigraphy \rightarrow tumor localization and staging.

Treatment: surgical resection, somatostatin analog (eg, octreotide) or tryptophan hydroxylase inhibitor (eg, telotristat) for symptom control.

Rule of thirds:

1/3 metastasize

1/3 present with 2nd malignancy

1/3 are multiple

Zollinger-Ellison syndrome

Constellation of symptoms resulting in acid hypersecretion from gastrin-secreting tumor (gastrinomas) in duodenum (most common) or pancreas \rightarrow single or multiple, recurrent ulcers in the duodenum/jejunum (often refractory to proton pump inhibitors) with resulting malabsorption (acid inactivation of pancreatic enzymes secreted into the small bowel). Presents with abdominal pain, heartburn, diarrhea/steatorrhea, weight loss. Positive secretin stimulation test (\uparrow gastrin levels after secretin administration, which normally inhibits gastrin release). Chromogranin A \oplus . May be associated with MEN1.

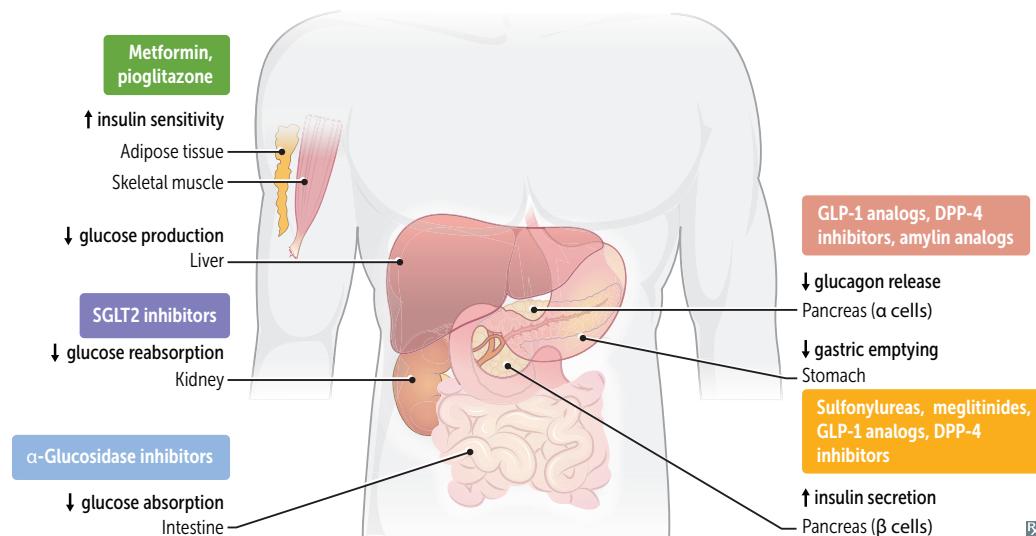
▶ ENDOCRINE—PHARMACOLOGY

Diabetes mellitus therapy

All patients with diabetes mellitus should receive education on diet, exercise, blood glucose monitoring, and complication management. Treatment differs based on the type of diabetes and glycemic control:

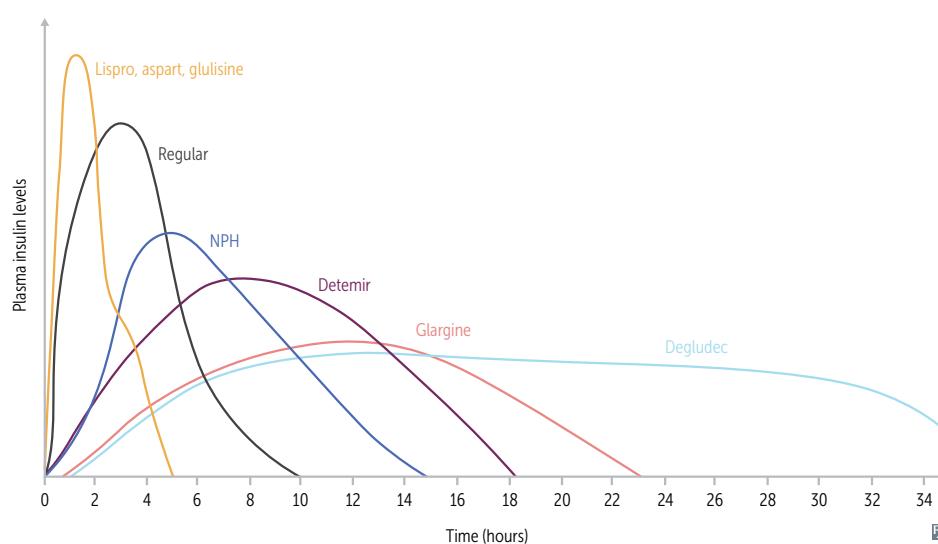
- Type 1 DM—insulin replacement
- Type 2 DM—oral agents (metformin is first line), non-insulin injectables, insulin replacement; weight loss particularly helpful in lowering blood glucose
- Gestational DM—insulin replacement if nutrition therapy and exercise alone fail

Regular (short-acting) insulin is preferred for DKA (via IV), hyperkalemia (with glucose to prevent concomitant hypoglycemia), and stress hyperglycemia.



DRUG	MECHANISM	ADVERSE EFFECTS
Insulin preparations		

Rapid acting (no lag): lispro, aspart, glulisine	Bind insulin receptor (tyrosine kinase activity). Liver: ↑ glucose storage as glycogen.	Hypoglycemia, lipodystrophy, hypersensitivity reactions (rare), weight gain.
Short acting: regular	Muscle: ↑ glycogen, protein synthesis. Fat: ↑ TG storage.	
Intermediate acting: NPH	Cell membrane: ↑ K ⁺ uptake.	
Long acting: detemir, glargine		
Very long acting: degludec		



Diabetes mellitus therapy (continued)

DRUG	MECHANISM	ADVERSE EFFECTS
Increase insulin sensitivity		
Metformin	Inhibits mitochondrial glycerol-3-phosphate dehydrogenase (mGPD) → inhibition of hepatic gluconeogenesis and the action of glucagon. ↑ glycolysis, peripheral glucose uptake (↑ insulin sensitivity).	GI upset, lactic acidosis (in patients with renal insufficiency, cirrhosis, sepsis, or hypoperfusion), vitamin B ₁₂ deficiency. Weight loss (often desired).
Pioglitazone	Activate PPAR-γ (a nuclear receptor) → ↑ insulin sensitivity and levels of adiponectin → regulation of glucose metabolism and fatty acid storage.	Weight gain, edema, HF, ↑ risk of fractures. Delayed onset of action (several weeks).
Increase insulin secretion		
Sulfonylureas (1st gen) Chlorpropamide, tolbutamide		Disulfiram-like reaction with first-generation sulfonylureas only (rarely used).
Sulfonylureas (2nd gen) Glipizide, glyburide	Close K ⁺ channels in pancreatic B cell membrane → cell depolarizes → insulin release via ↑ Ca ²⁺ influx.	Hypoglycemia (↑ risk in renal insufficiency), weight gain.
Meglitinides Nateglinide, repaglinide		
Increase glucose-induced insulin secretion		
GLP-1 analogs Exenatide, liraglutide, semaglutide	↓ glucagon release, ↓ gastric emptying, ↑ glucose-dependent insulin release.	Nausea, vomiting, pancreatitis. Weight loss (often desired). ↑ satiety (often desired).
DPP-4 inhibitors Linagliptin, saxagliptin, sitagliptin	Inhibit DPP-4 enzyme that deactivates GLP-1 → ↓ glucagon release, ↓ gastric emptying. ↑ glucose-dependent insulin release.	Respiratory and urinary infections, weight neutral. ↑ satiety (often desired).
Decrease glucose absorption		
Sodium-glucose co-transporter 2 inhibitors Canagliflozin, dapagliflozin, empagliflozin	Block reabsorption of glucose in proximal convoluted tubule (glucosuria). Also cause natriuresis, osmotic diuresis → ↓ blood glucose, ↓ serum Na ⁺ , ↓ ECF volume, ↓ blood pressure.	Glucosuria (UTIs, vulvovaginal candidiasis), dehydration (orthostatic hypotension), weight loss. Glucose flows in urine. Use with caution in renal insufficiency (↓ efficacy with ↓ GFR).
α-glucosidase inhibitors Acarbose, miglitol	Inhibit intestinal brush-border α-glucosidases → delayed carbohydrate hydrolysis and glucose absorption → ↓ postprandial hyperglycemia.	GI upset, bloating. Not recommended in renal insufficiency.
Others		
Amylin analogs Pramlintide	↓ glucagon release, ↓ gastric emptying.	Hypoglycemia, nausea. ↑ satiety (often desired).

Thionamides

Propylthiouracil, methimazole.

MECHANISM

Block thyroid peroxidase, inhibiting the oxidation of iodide as well as the organification and coupling of iodine → inhibition of thyroid hormone synthesis. PTU also blocks 5'-deiodinase → ↓ Peripheral conversion of T₄ to T₃.

CLINICAL USE

Hyperthyroidism. PTU used in Primary (first) trimester of pregnancy (due to methimazole teratogenicity); methimazole used in second and third trimesters of pregnancy (due to risk of PTU-induced hepatotoxicity). Not used to treat Graves ophthalmopathy (treated with glucocorticoids).

ADVERSE EFFECTS

Skin rash, agranulocytosis (rare), aplastic anemia, hepatotoxicity.

PTU use has been associated with ANCA-positive vasculitis.

Methimazole is a possible teratogen (can cause aplasia cutis).

Levothyroxine, liothyronine

MECHANISM

Hormone replacement for T₄ (levothyroxine; levo = 4 letters) or T₃ (liothyronine; lio = 3 letters). Avoid levothyroxine with antacids, bile acid resins, or ferrous sulfate (↓ absorption).

CLINICAL USE

Hypothyroidism, myxedema. May be misused for weight loss. Distinguish exogenous hyperthyroidism from endogenous hyperthyroidism by using a combination of TSH receptor antibodies, radioactive iodine uptake, and/or measurement of thyroid blood flow on ultrasound.

ADVERSE EFFECTS

Tachycardia, heat intolerance, tremors, arrhythmias.

Hypothalamic/pituitary drugs

DRUG

CLINICAL USE

Conivaptan, tolvaptan

ADH antagonists
SIADH (block action of ADH at V₂-receptor)

Demeclocycline

ADH antagonist, a tetracycline
SIADH (interferes with ADH signaling)

Desmopressin

ADH analog
Central DI, von Willebrand disease, sleep enuresis, hemophilia A

GH

GH deficiency, Turner syndrome

Oxytocin

Induction of labor (stimulates uterine contractions), control uterine hemorrhage

Octreotide

Somatostatin analog
Acromegaly, carcinoid syndrome, gastrinoma, glucagonoma, esophageal varices

Fludrocortisone

MECHANISM

Synthetic analog of aldosterone with glucocorticoid effects. Fludrocortisone retains fluid.

CLINICAL USE

Mineralocorticoid replacement in 1° adrenal insufficiency.

ADVERSE EFFECTS

Similar to glucocorticoids; also edema, exacerbation of heart failure, hyperpigmentation.

Cinacalcet

MECHANISM	Sensitizes calcium-sensing receptor (CaSR) in parathyroid gland to circulating Ca^{2+} \rightarrow ↓ PTH. Pronounce “Senacalcet.”
CLINICAL USE	2° hyperparathyroidism in patients with CKD receiving hemodialysis, hypercalcemia in 1° hyperparathyroidism (if parathyroidectomy fails), or in parathyroid carcinoma.
ADVERSE EFFECTS	Hypocalcemia.

Sevelamer

MECHANISM	Nonabsorbable phosphate binder that prevents phosphate absorption from the GI tract.
CLINICAL USE	Hyperphosphatemia in CKD.
ADVERSE EFFECTS	Hypophosphatemia, GI upset.

Cation exchange resins Patiromer, sodium polystyrene sulfonate, zirconium cyclosilicate.

MECHANISM	Bind K^+ in colon in exchange for other cations (eg, Na^+ , Ca^{2+}) \rightarrow K^+ excreted in feces.
CLINICAL USE	Hyperkalemia.
ADVERSE EFFECTS	Hypokalemia, GI upset.

▶ NOTES