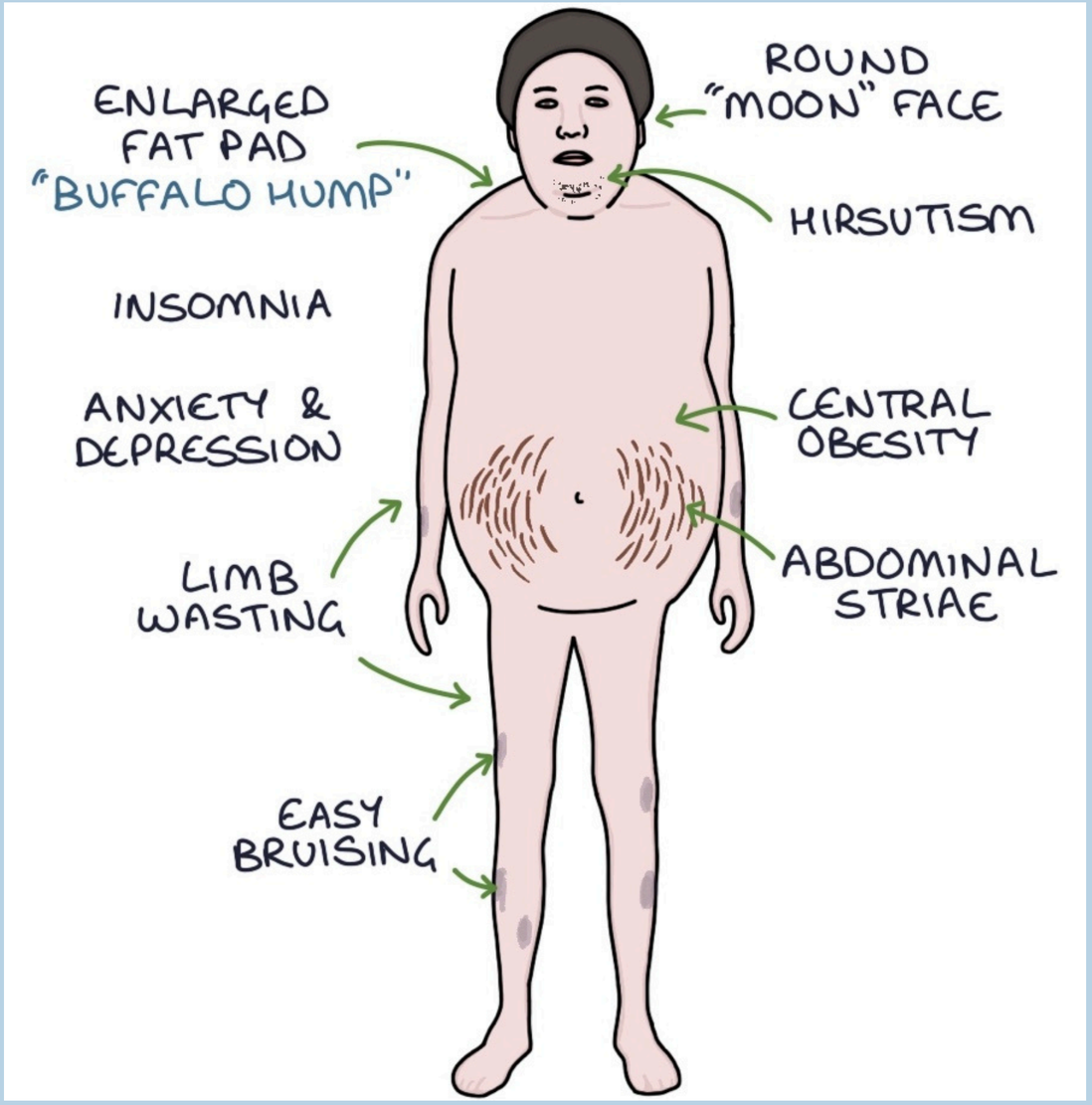
Cushing's syndrome

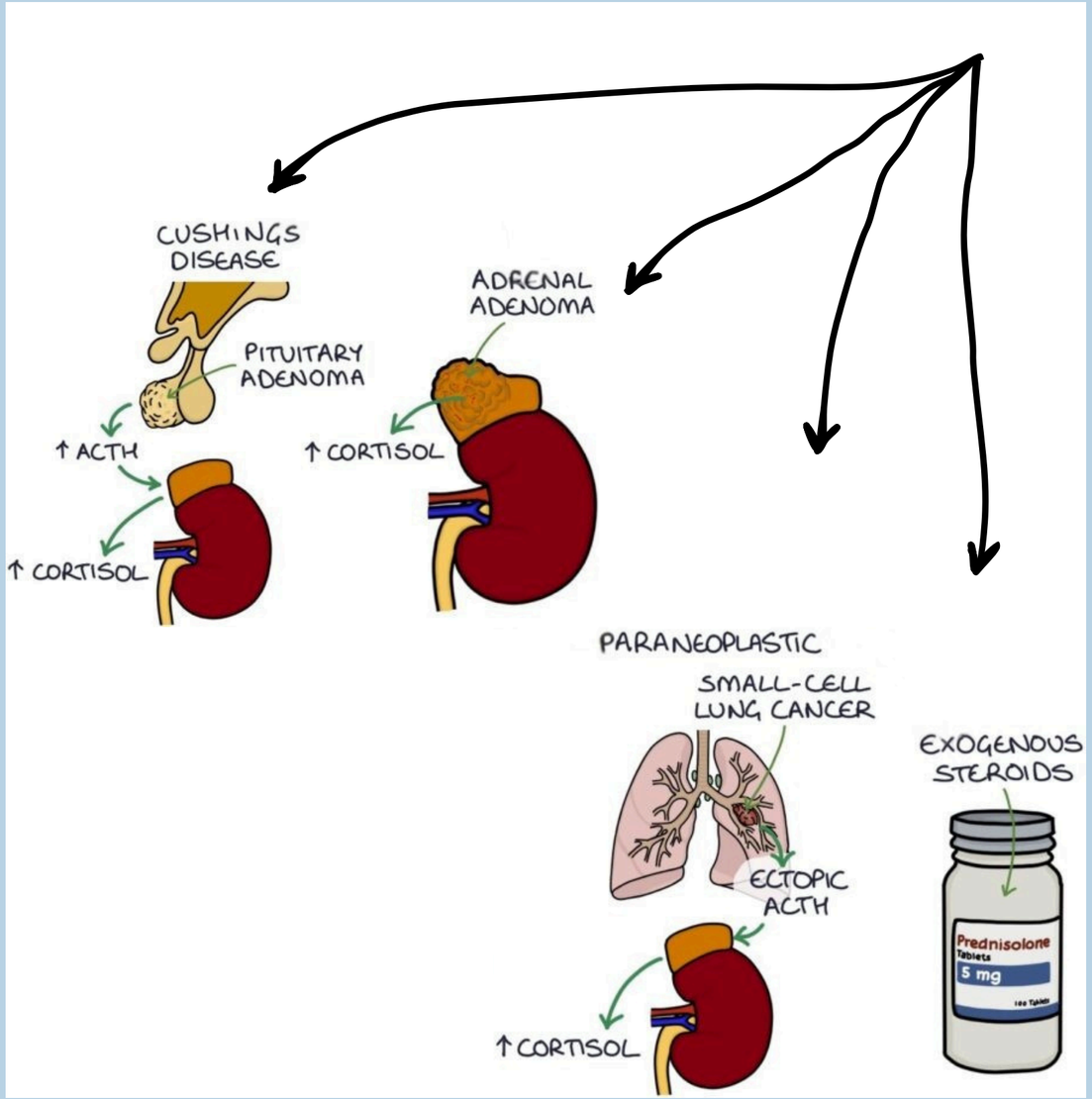
Rama Malkawi
Sara Rahahleh
Dana Manaseer



Contents:

Definition

is an endocrine disorder caused by hypercortisolism.



Note

- While the term "**Cushing syndrome**" can be applied to any cause of hypercortisolism, "**Cushing disease**" refers specifically to secondary hypercortisolism that results from excessive production of ACTH by pituitary adenomas.
- Secondary hypercortisolism is also called ACTH-dependent Cushing syndrome because hypercortisolism is the result of increased ACTH levels.

Etiology

1. Exogenous Cushing syndrome:
   - Prolonged glucocorticoid therapy→ hypercortisolism → decreased ACTH → bilateral adrenal atrophy.
   - Most common cause of hypercortisolism.
2. Endogenous Cushing syndrome:

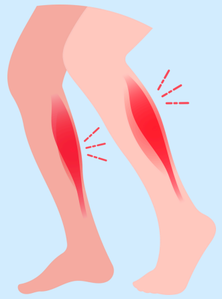
Types	Primary hypercortisolism (ACTH-independent Cushing syndrome)	Secondary hypercortisolism	
		Pituitary ACTH production (Cushing disease)	Ectopic ACTH production
Relative frequency	5-10%	~75%	15%
Sex	M<F (1:4)	M<F (1:4)	M=F
Causes	Autonomous overproduction of cortisol by the adrenal gland ACTH suppression atrophy of the contralateral adrenal gland: • Adrenal adenomas • Adrenal carcinoma • Macronodular adrenal hyperplasia	Pituitary adenomas → ACTH secretion → bilateral adrenal gland hyperplasia	Paraneoplastic syndrome → ACTH secretion → bilateral adrenal gland hyperplasia Carcinomas: . Small cell lung cancer . Renal cell carcinoma . Pancreatic or bronchial carcinoid tumors . Pheochromocytoma Medullary thyroid carcinoma

Clinical features

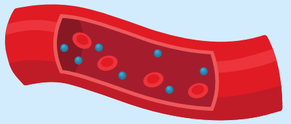
Skin

Neuropsychological

Musculoskeletal



Endocrine and metabolic



Skin

- Thin, easily bruisable skin with ecchymoses
- Stretch marks (classically purple abdominal striae)
- Hirsutism
- Acne
- If secondary hypercortisolism: often hyperpigmentation:
  - darkening of the skin due to an overproduction of melanin.
  - especially in areas that are not normally exposed to the sun (palm creases, oral cavity).
  - Caused by excessive ACTH production because melanocyte-stimulating hormone (MSH) is cleaved from the same precursor as ACTH called proopiomelanocortin (POMC) .
  - Not a feature of primary hypercortisolism.
- Delayed wound healing
- Flushing of the face

Neuropsychological & musculoskeletal

- Anxiety, irritability, fatigue, sleep disturbance, memory deficits, depression, psychosis.

- Osteopenia, osteoporosis, pathological fractures, avascular necrosis of the femoral head, muscle atrophy/weakness.

Endocrine & metabolic

- Insulin resistance hyperglycemia.
- Dyslipidemia
- Weight gain characterized by central obesity, moon facies, and a dorsocervical fat pad (buffalo hump)
- M: Decreased libido
- F: Decreased libido, virilization, and/or irregular menstrual cycles (e.g., amenorrhea)
- Growth delay (in children)

Other features

- Secondary hypertension (~90% of cases)
- Increased susceptibility to infections (due to immunosuppression)
- Peptic ulcer disease
- Cataracts

“CUSHINGOID”

is the acronym for side effects of corticosteroids:

Cataract

Ulcer (peptic)

Straie/**S**kin thinning

Hypertension/**H**irsutism/**H**yperglycemia

Infection

Necrosis (avascular head of the femur)

Glucose elevation

Osteoporosis/**O**besity

Immunosuppression

Depression/**D**iabetes

Note

- Patients with secondary hypercortisolism due to ectopic ACTH production may present with rapid onset of hypertension and hypokalemia without other typical features of Cushing syndrome.
- Consider a diagnosis of hypercortisolism in patients who present with proximal muscle weakness. central obesity, thinning skin, weight gain, sleep disturbance, and/or depression.

Diagnosis

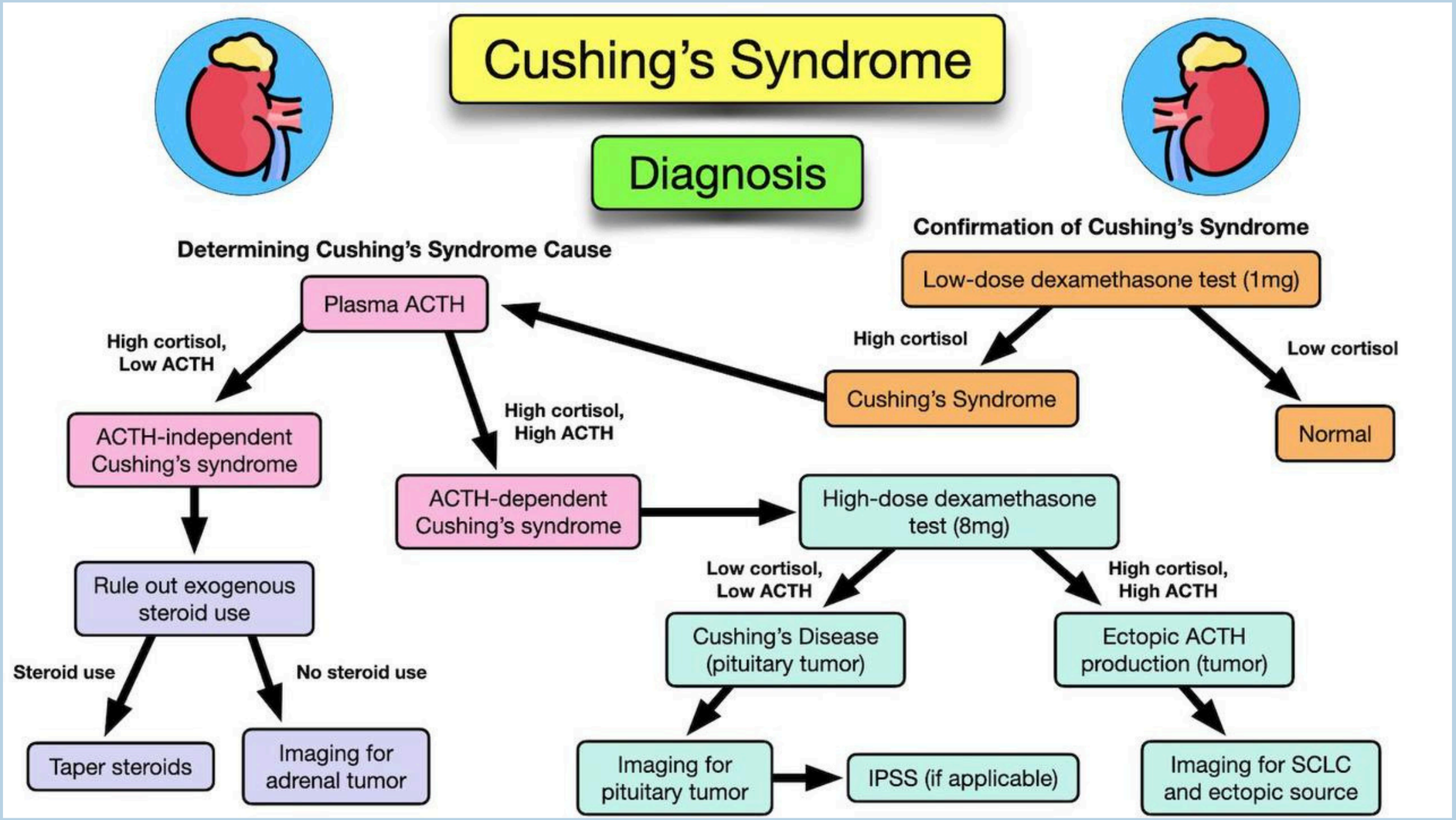
Prolonged glucocorticoid therapy is the most common cause of hypercortisolism (exogenous Cushing syndrome); further testing is not required in these patients.

- **Routine laboratory studies** : Not required to establish the diagnosis, but if performed, may show the following typical findings:

- Hypernatremia, hypokalemia, metabolic alkalosis .
- Hyperglycemia:

due to stimulation of gluconeogenic enzymes (e.g., glucose-6-phosphatase) and inhibition of glucose uptake in peripheral tissue.

- Hyperlipidemia (hypercholesterolemia and hypertriglyceridemia) .
- CBC: leukocytosis without left shift (predominantly neutrophilic), eosinopenia.


Cushing's Syndrome
Diagnosis
Determining Cushing's Syndrome Cause
Plasma ACTH
High cortisol, Low ACTH
High cortisol, High ACTH
ACTH-independent Cushing's syndrome
ACTH-dependent Cushing's syndrome
Rule out exogenous steroid use
Steroid use
No steroid use
Taper steroids
Imaging for adrenal tumor
Confirmation of Cushing's Syndrome
Low-dose dexamethasone test (1mg)
High cortisol
Low cortisol
Cushing's Syndrome
Normal
High-dose dexamethasone test (8mg)
Low cortisol, Low ACTH
High cortisol, High ACTH
Cushing's Disease (pituitary tumor)
Ectopic ACTH production (tumor)
Imaging for pituitary tumor
IPSS (if applicable)
Imaging for SCLC and ectopic source

Diagnosis

Testing for hypercortisolism :

❖ Any of the following tests can be used.

❖ The diagnosis is confirmed if at least two of the tests have abnormal results.

1. **Urine free cortisol :**

• Free cortisol is measured in a complete 24-hour urine collection.

• Supportive finding: ↑ urine free cortisol .

2. **Low-dose dexamethasone suppression test:**

• 1 mg of dexamethasone is administered between 11 pm and midnight and serum cortisol is measured the following morning between 8 and 9 am.

• Supportive finding: ↑ early morning serum cortisol level (> 50 nmol/L or > 1.8 mcg/dL) .

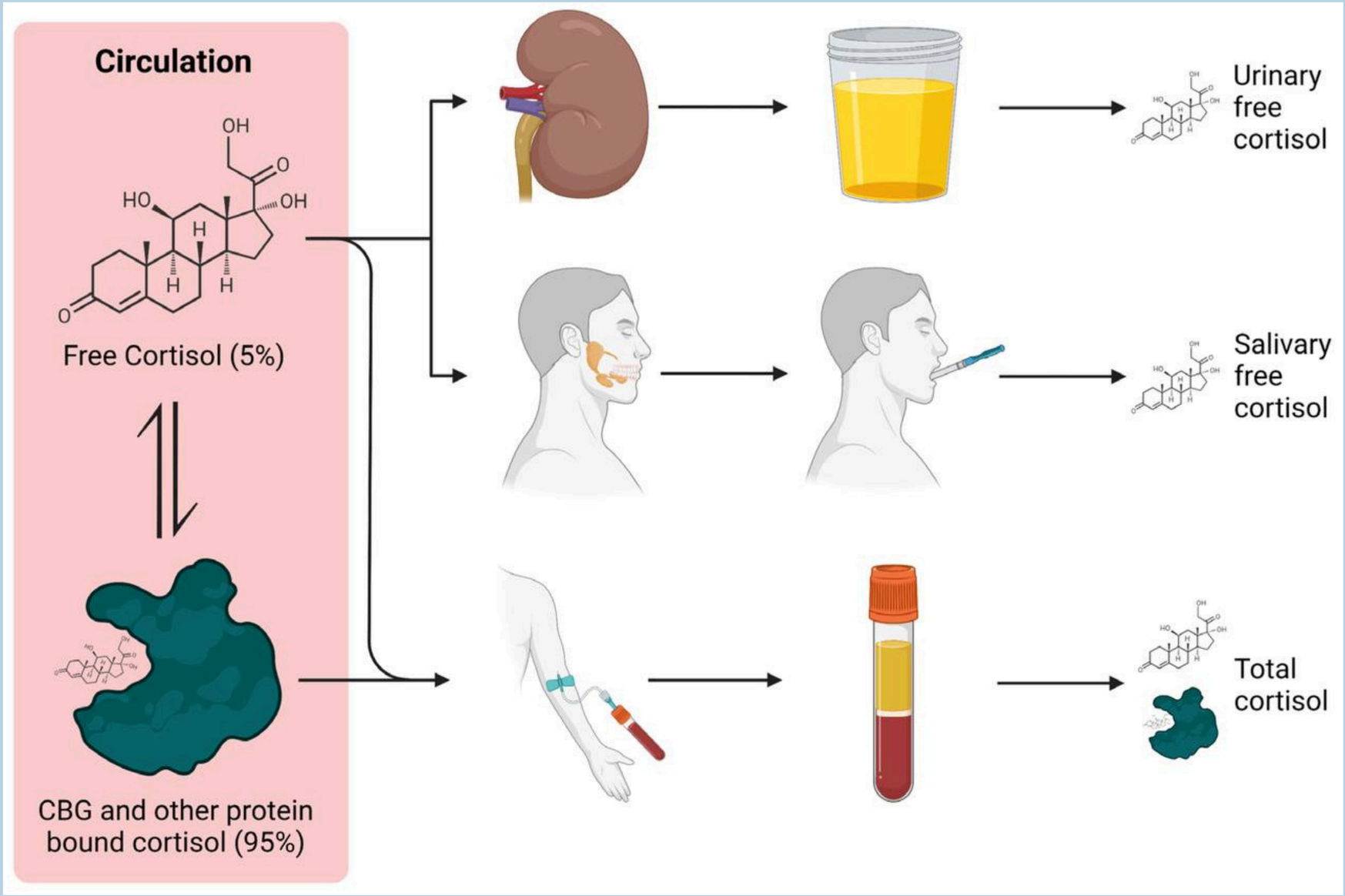
Diagnosis

3. **Late-night salivary cortisol:**

- A saliva sample is collected at the patient's usual bedtime.
- Supportive finding: ↑ salivary cortisol (> 4 nmol/L or > 145 ng/dL) .

4. **Late-night serum cortisol:**

- A serum sample is taken from the patient (awake or asleep).
- Supportive finding: ↑ serum cortisol (> 7.5 mcg/dL).


Circulation
Free Cortisol (5%)
CBG and other protein bound cortisol (95%)
Urinary free cortisol
Salivary free cortisol
Total cortisol

Identifying the cause:
Initial evaluation:

1) Consider nonneoplastic and physiological causes of hypercortisolism based on clinical features and patient history (e.g., depression, heavy alcohol use, obesity) and in pregnant patients.

2) Measure serum ACTH levels.
• Low (< 5 pg/mL):
Suspect primary hypercortisolism (ACTH-independent).
• Inappropriately normal OR elevated (> 20 pg/mL):
Suspect secondary hypercortisolism (ACTH-dependent).

3) Proceed based on the results.
•If ACTH-independent hypercortisolism is suspected: Obtain adrenal MRI and/or CT.
Assess for an adrenal tumor (e.g., adrenal adenoma, carcinoma, hyperplasia).
• If ACTH-dependent hypercortisolism is suspected: Obtain further testing.

Note

- Differentiating between Cushing syndrome and nonneoplastic-physiologic hypercortisolism can be very challenging. If there is any doubt, refer the patient to a specialized center.

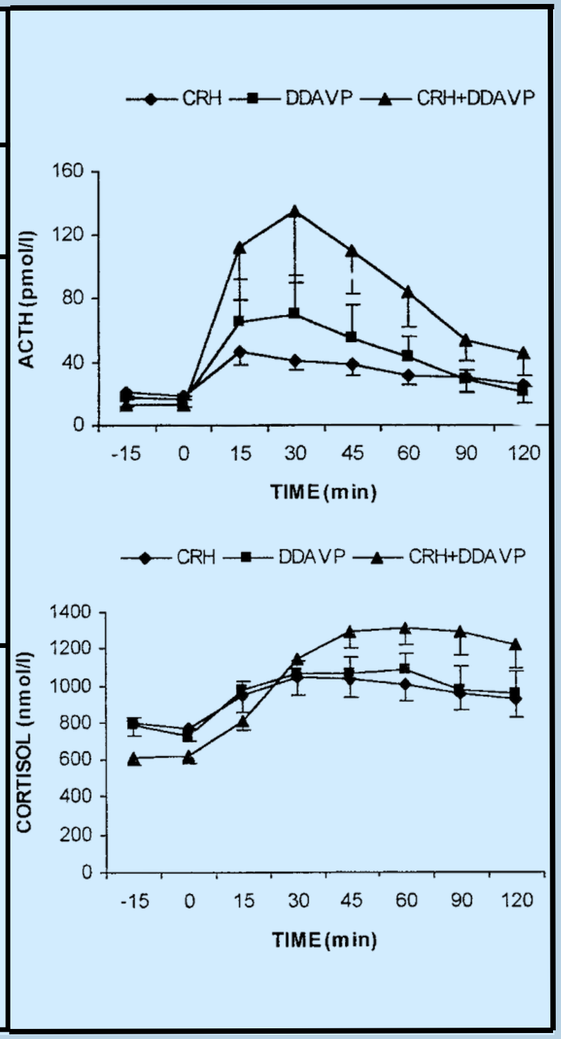
- Abdominal CT or MRI in a patient with Cushing disease will show bilateral hyperplasia of both the zona fasciculata and zona reticularis .

Further testing in patients with ACTH-dependent hypercortisolism:
The goal is to differentiate between Cushing disease and ectopic ACTH production. A combination of tests is often necessary.

❖ **Obtain a pituitary MRI to evaluate for Cushing disease**
1. Pituitary adenoma > 10 mm confirms Cushing disease.
2. If there is no evidence of a pituitary adenoma or findings are unclear, obtain either:
- Bilateral sampling of the inferior petrosal sinus
- Hormone testing in ACTH-dependent hypercortisolism

❖ **If ectopic ACTH production is suspected:**
imaging to locate the ACTH-producing primary malignancy (e.g., SCLC, RCC, carcinoid).

Hormone testing in ACTH-dependent hypercortisolism	
	Findings
CRH stimulation test	•ACTH and cortisol levels increase further: Cushing disease is likely. • No increase in ACTH or cortisol levels: Ectopic ACTH production is likely.
Desmopressin stimulation test	
High-dose dexamethasone suppression test	•Adequate suppression, i.e., 1 cortisol (< 50% of baseline): Cushing disease is likely. • No or inadequate suppression: Ectopic ACTH production is likely.



Differential diagnosis :

	Normal	Primary hypercortisolism	Ectopic ACTH secretion	Cushing disease
ACTH levels	↔	↓	↑	
Low-dose dexamethasone suppression test	↓ cortisol	↔ cortisol		
High-dose dexamethasone suppression test	↓ cortisol	↔ cortisol		↓ cortisol
CRH and desmopressin stimulation tests	↑ ACTH, ↑ cortisol	↔ ACTH, ↔ cortisol		↑ ACTH, cortisol

Treatment

The following section applies to endogenous Cushing syndrome. For patients with exogenous
Cushing syndrome, consider lowering the dose of glucocorticoids or replacing them.

Approach:

- Manage with a multidisciplinary team including an endocrinologist
- First-line treatment: tumor resection
- Second-line or adjunctive therapy: pharmacological treatment
- Patients who develop adrenal insufficiency after surgery require lifelong glucocorticoid replacement therapy
- Enzyme inhibitors (e.g., metyrapone, ketoconazole) suppress cortisol synthesis, while glucocorticoid antagonists block the action of cortisol in peripheral tissues

Treatment

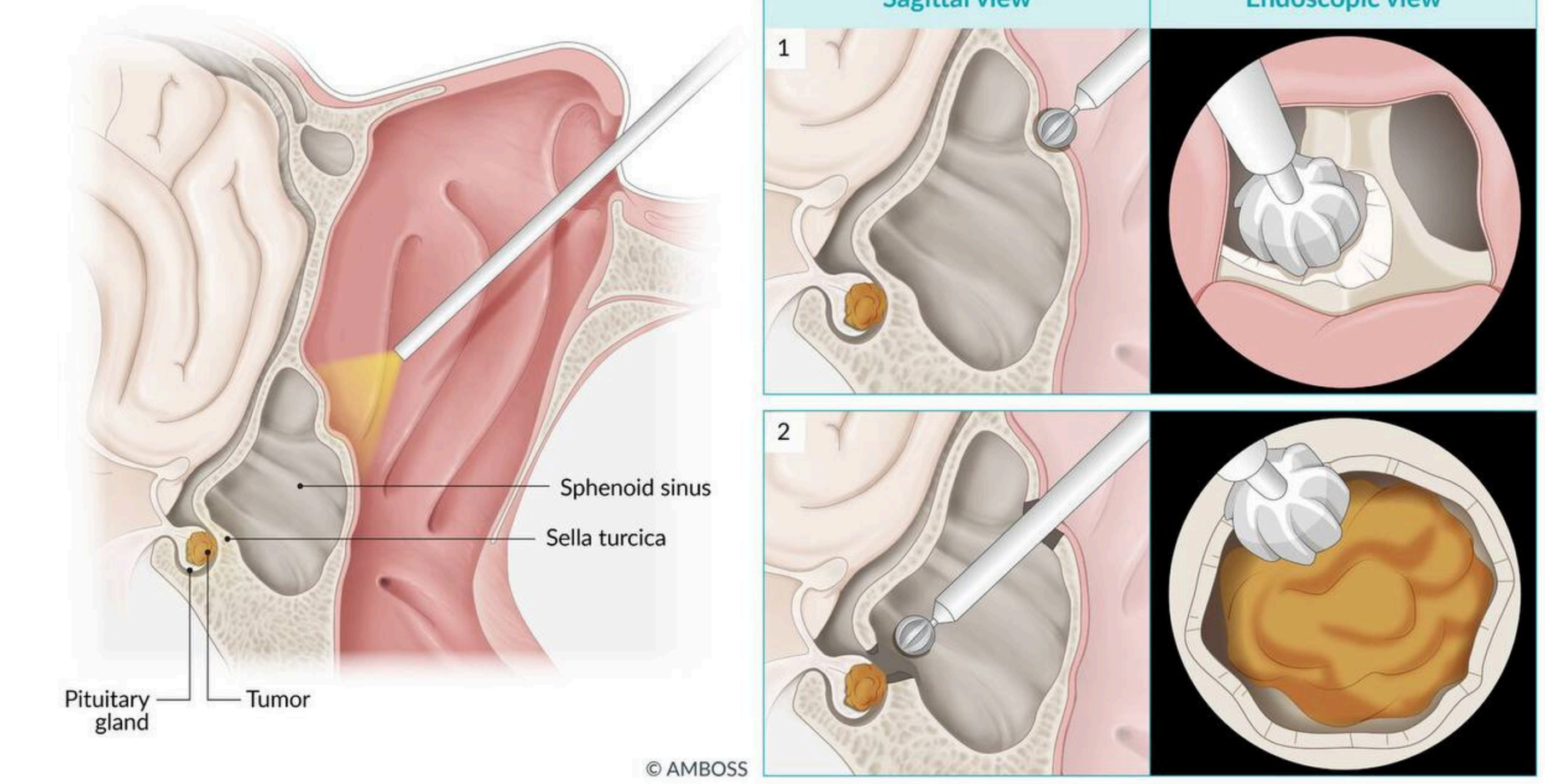
First line: curative surgery:

1. Primary hypercortisolism: unilateral or bilateral laparoscopic or open adrenalectomy for adrenocortical tumors.
2. Cushing disease: transsphenoidal hypophysectomy.
3. Ectopic ACTH production: tumor resection with node dissection.

Follow up:

- Patients should receive lifelong monitoring for recurrence.
- Glucocorticoid replacement therapy is often necessary after surgery.

Transsphenoidal hypophysectomy



Treatment

Bilateral adrenalectomy:

• Indications:

1. Primary hypercortisolism caused by bilateral adrenal disease (recommended curative treatment)
2. Emergency treatment in severe ACTH-dependent hypercortisolism that cannot be controlled pharmacologically
3. Symptomatic treatment for metastatic or occult ectopic tumors.

• **Complication**: Nelson syndrome (post adrenalectomy syndrome)

• **Etiology**:

bilateral adrenalectomy in patients with a previously undetected pituitary adenoma

• **Pathophysiology**:

bilateral adrenalectomy - no endogenous cortisol production - no negative feedback from cortisol on the hypothalamus - 1 CRH production uncontrolled - enlargement of preexisting but undetected ACTH-secreting pituitary adenoma - T secretion of ACTH and MSH - manifestation of symptoms due to pituitary adenoma and T MSH

• **Clinical features**:

headache, bitemporal hemianopia (mass effect), cutaneous hyperpigmentation

• **Diagnostics**:

- High levels of B-MSH and ACTH.
- Pituitary adenoma on MRI confirms the diagnosis.

• **Treatment**:

surgery (e.g., transsphenoidal resection) and/or pituitary radiation therapy (e.g., if the tumor cannot be fully resected).

Thank you!