Adrenal Insufficency

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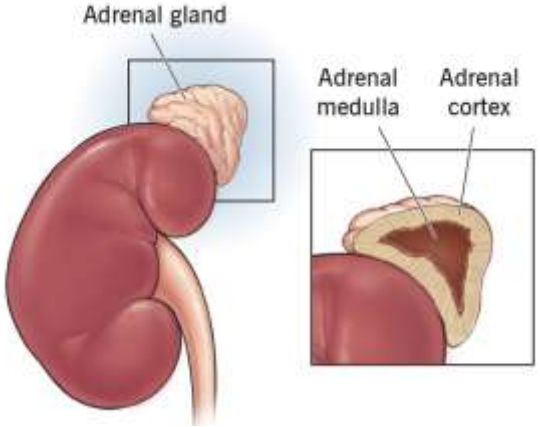

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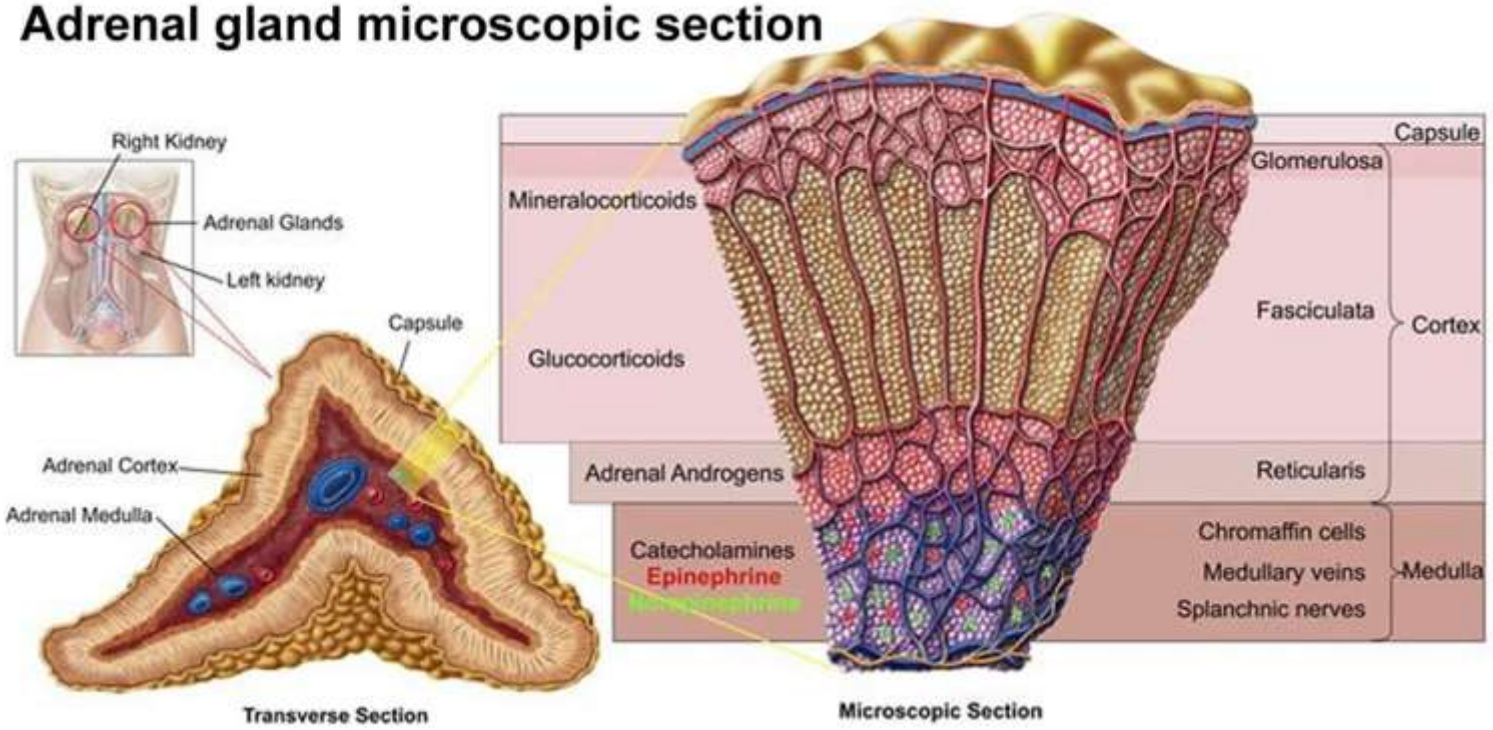
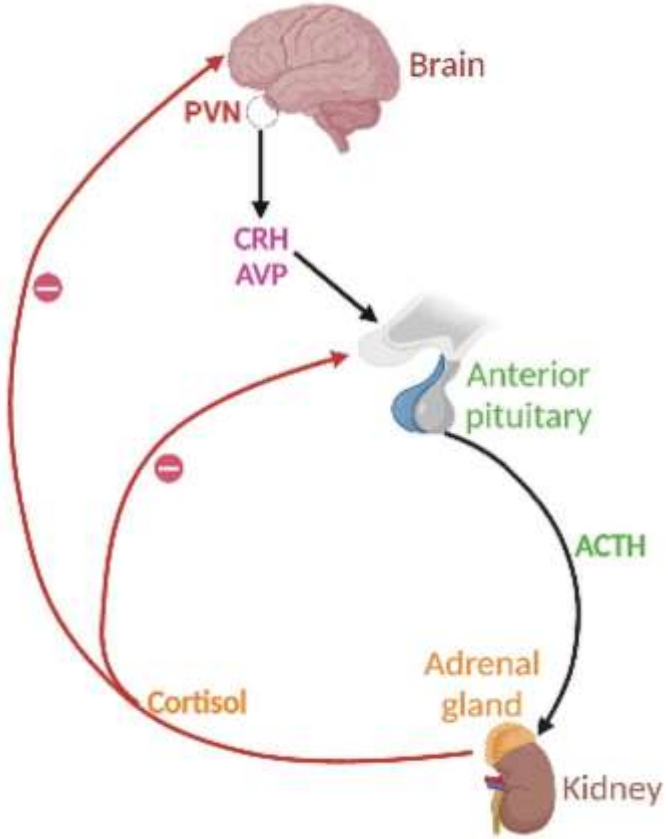
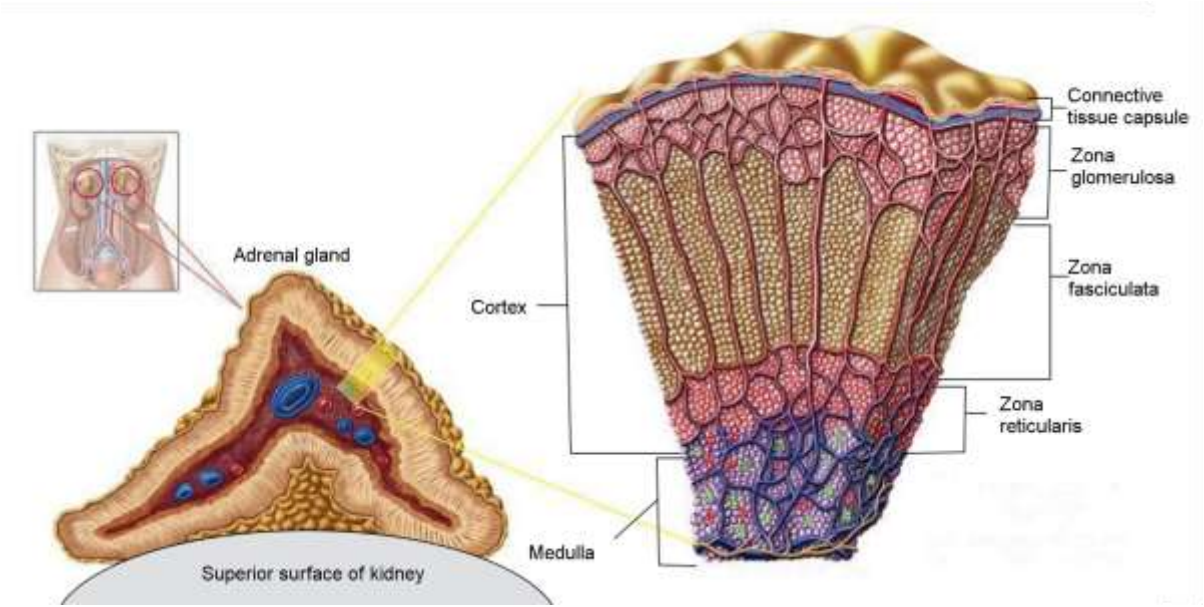
Adrenal gland



hypothalamic pituitary adrenal axis



Adrenal insufficiency is the decreased production of adrenocortical hormones (glucocorticoids, mineralocorticoids, and adrenal androgens) and is classified as primary, secondary, or tertiary.



Etiology

Primary adrenal insufficiency :

Primary adrenal insufficiency can be caused by abrupt destruction of the adrenal gland (acute adrenal insufficiency; e.g., due to massive adrenal hemorrhage) or by its gradual progressive destruction or atrophy (chronic adrenal insufficiency; e.g., due to autoimmune conditions, infection).

- **Autoimmune adrenalitis (Addison disease)**
  - **Most common cause in the US (~ 80–90% of all cases of primary adrenal insufficiency)**
  - **Caused by autoimmune destruction of both adrenal cortices, Antibodies that react with several steroidogenic**

enzymes (most often 21-hydroxylase)

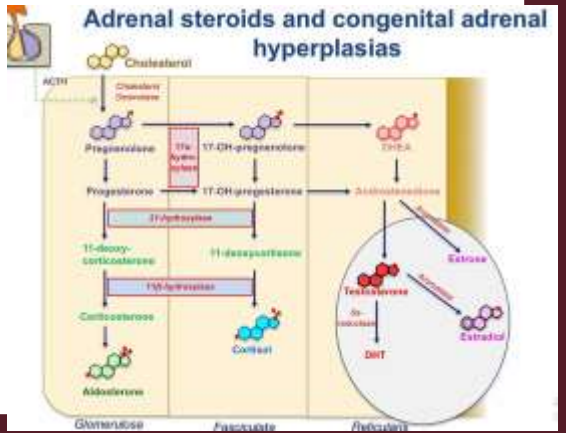
- **Which might be isolated or part of APS**

- Autoimmune polyendocrine syndrome type I

(Addison's disease, chronic mucocutaneous candidiasis, hypoparathyroidism, dental enamel hypoplasia)

- Autoimmune polyendocrine syndrome type II (schmidt's syndrome) :

Addison's disease + primary hypothyroidism, or insulin-dependent diabetes.



Etiology

Primary adrenal insufficiency (Addison disease) :

- **Infectious adrenalitis**
  - **Tuberculosis: most common cause worldwide, but rare in the US(adrenal glands are usually enlarged by inflammatory cell infiltration of the cortex and granulomas early in the disease, Adrenal calcifications can be seen radiographically in 50 percent of patients.**
  - **CMV disease in immunosuppressed states (especially AIDS)**
  - **Disseminated fungal infections :Histoplasmosis**
- **Adrenal hemorrhage**
  - **Sepsis: especially meningococcal sepsis (endotoxic shock) → hemorrhagic necrosis (Waterhouse-Friderichsen syndrome)**
  - **Disseminated intravascular coagulation (DIC)**
  - **Anticoagulation: especially heparin (heparin-induced thrombocytopenia)**
  - **Venous thromboembolism, especially in antiphospholipid syndrome (APS) Recurrent thromboses are a typical manifestation of APS.**

Etiology

Primary adrenal insufficiency (Addison disease) :

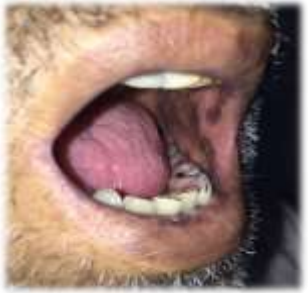
- **Infiltration of the adrenal glands**
  - **Tumors (adrenocortical tumors, lymphomas, metastatic carcinoma)**
  - **Amyloidosis**
  - **Hemochromatosis**
- **Bilatral Adrenalectomy**
- **Trauma (mostly blunt trauma, can also occur postoperatively)**
- **congenital adrenal hypoplasia .**

Pathophysiology

Primary adrenal insufficiency (Addison disease)

Damage to the adrenal gland leads to the deficiency in all three hormones produced by the adrenal cortex: androgen, cortisol, and aldosterone.

- **Hypoandrogenism**
  - Loss of libido(females)
- **Hypocortisolism leads to:**
  - ↑ ACTH → ↑ production of POMC (in order to increase ACTH production) → ↑ melanocyte-stimulating hormone (MSH) → hyperpigmentation of the skin (bronze skin)
  - ↑ ADH level → retention of free water → dilutional hyponatremia
  - ↓ Expression of enzymes involved in gluconeogenesis → ↓ rate of gluconeogenesis → hypoglycemia
  - Lack of potentiation of catecholamines action → hypotension
- **Hypoaldosteronism** → hypotension (hypotonic hyponatremia and volume contraction), hyperkalemia, metabolic acidosis



Etiology

Secondary adrenal insufficiency:

Secondary adrenal insufficiency is caused by conditions that decrease ACTH production (impaired hypothalamic-pituitary-adrenal axis).

- Sudden discontinuation of chronic glucocorticoid therapy during prolonged glucocorticoid therapy
  - Prolonged iatrogenic suppression of the hypothalamic-pituitary-adrenal axis
- Hypopituitarism: ↓ ACTH → ↓ endogenous cortisol
  - Pituitary apoplexy
  - Granulomatous disease (tuberculosis, sarcoid, eosinophilic granuloma)
  - Secondary tumor deposits (breast, bronchus)
  - Postpartum pituitary infarction (sheehan's syndrome)
  - Pituitary irradiation (effect usually delayed for several years)
  - Isolated ACTH deficiency
  - Idiopathic

Pathophysiology

Secondary adrenal insufficiency

● ↓ ACTH → hypoandrogenism and hypocortisolism

● Aldosterone synthesis is not affected (mineralocorticoid production is controlled by RAAS and angiotensin II, not by ACTH).

- Signs of aldosterone deficiency can help differentiate primary adrenal insufficiency from secondary and tertiary adrenal insufficiency

Clinical features

The sign and symptoms of AI are rather nonspecific such as :

O weakness, fatigue

O musculoskeletal pain

O weight loss, depression, and anxiety.

O abdominal pain, nausea , vomiting

As a result, the diagnosis is frequently delayed, resulting in a clinical presentation with an acute life-threatening adrenal crisis .

Clinical features

Hormonal changes	Clinical features	Laboratory findings	Primary adrenal insufficiency	Secondary adrenal insufficiency	Tertiary adrenal insufficiency
Hypoaldosteronism	- Hypotension - Salt craving	- Hyponatremia - Hyperkalemia - Normal anion gap metabolic acidosis	✓	● Absent	● Absent
Hypocortisolism	- Weight loss, anorexia - Fatigue, lethargy, depression - Muscle aches - Weakness - GI complaints (nausea, vomiting, diarrhea) - Sugar cravings - (Orthostatic) hypotension	- Hypoglycemia - Hyponatremia	✓	✓	✓
Hypoandrogenism	- Loss of libido - Loss of axillary and pubic hair	● ↓ DHEA-S	✓	✓	✓
Elevated ACTH	- Hyperpigmentation of palmar creases, oral mucosa	● ↑ MSH	✓	● Absent	● Absent

Diagnostic approach

Step 1: Confirm Cortisol Deficiency

- Use basal morning serum cortisol and/or ACTH stimulation tests.
- >15Mg/dl : RULE OUT AI
- <3 Mg/dl : CONFIRM AI
- 3-15 : GO TO STEP 2

Step 2 : Perform a **short ACTH stimulation test (Tetracosactide/Synacthen test)**:

- Administer **250 µg ACTH (1–24) IM/IV** at any time of day.
- Measure plasma cortisol at **0 and 30 minutes**.

Interpretation:

- **Normal response**: cortisol ≥ **18–20 µg/dL** at 30 minutes.
- **Adrenal insufficiency**: cortisol < **18 µg/dL**

Step 3: Localize the Defect (Primary vs. Central)

- Measure **early morning ACTH** with concurrent serum cortisol.

Interpretation:

- ↑ **ACTH → Primary adrenal insufficiency** (adrenal gland defect).
- ↓ **or inappropriately normal ACTH → Central adrenal insufficiency** (pituitary/hypothalamic defect).
- **ACTH in upper half of reference range → Indeterminate** 🡪 check **aldosterone & renin.**

-Low aldosterone + high renin → Primary.

-Normal aldosterone/renin → Central (may be partial)

Step 4: If Primary Adrenal Insufficiency Is Diagnosed

Clinical history:

- Autoimmunity, infections, malignancy, bleeding/thrombosis risk, neurologic symptoms , medications.

- **First test**: **21-hydroxylase antibodies** (positive → autoimmune adrenalitis).

- **Adrenal CT :CT findings guide further workup**:

Bilateral enlargement → infection/infiltration.
Hemorrhage/infarction → coagulopathy workup.
Masses → metastasis evaluation.

- **If all tests negative**:

Consider antibody-negative autoimmune or idiopathic causes.

Step 5: If Central Adrenal Insufficiency Is Diagnosed

- **Assess exogenous glucocorticoid use**:

Recent supraphysiologic steroids → likely cause.

- **Evaluate other causes**:

History: trauma, surgery, tumors, opioids, checkpoint inhibitors.
Symptoms: headaches, visual changes, polyuria.

- **Test other pituitary hormones**:

TSH, free T4, LH, FSH, testosterone/estradiol, prolactin, IGF-1.

- **Pituitary MRI**:

Look for tumors, hypophysitis, infarction.

- **If MRI negative**:

Consider undiagnosed trauma or genetic causes (rare)

Other investigations

CBC: eosinophilia, lymphocytosis

Kidney function &electrolytes: hypoglycemia, hyponatremia and hyperkalemia. High creatinine and urea (prerenal).

Thyroid function abnormalities

Treatment

Glucocorticoid Replacement

- **Preferred: Hydrocortisone** (short-acting)

Total daily dose: **10–12 mg/m²/day** in **2–3 divided doses** (largest dose in morning).

- **Alternatives** (long-acting):

Prednisone
Dexamethasone

Mineralocorticoid Replacement (Primary Adrenal Insufficiency Only)

- **Fludrocortisone:** 0.1 mg daily orally (range 0.05–0.2 mg).

Liberal salt intake.
Monitoring: Blood pressure, serum potassium, plasma renin activity

Androgen Replacement (Consider in Some Women)

- **Dehydroepiandrosterone (DHEA):**

Consider in **women** with impaired mood/well-being despite optimal glucocorticoid/mineralocorticoid therapy.
Dose: 25–50 mg daily.
Trial for 3–6 months; discontinue if no benefit or if androgenic side effects occur.

Treatment of Secondary & Tertiary Adrenal Insufficiency

- **Glucocorticoid Replacement is Required.**
- **Mineralocorticoid Replacement is NOT Needed** (aldosterone production is preserved).
- **Same Glucocorticoid Regimens** as for primary adrenal insufficiency

Monitor: Clinical symptoms; **ACTH levels are not useful** for monitoring (expected to be low).

Also: Assess and replace **other pituitary hormone deficiencies** (e.g., thyroid, gonadal, growth hormone)

Stress Dose

1. Minor Illness/Stress ("3 x 3 Rule")

- **Double or triple** the daily glucocorticoid dose for **3 days**.
- Example: If on hydrocortisone 20 mg/day → take 40–60 mg/day for 3 days.
- **No change** in mineralocorticoid dose.

2. Surgery/Procedures

- According if it is minor or major surgery

Then quickly **taper back to maintenance dose**.

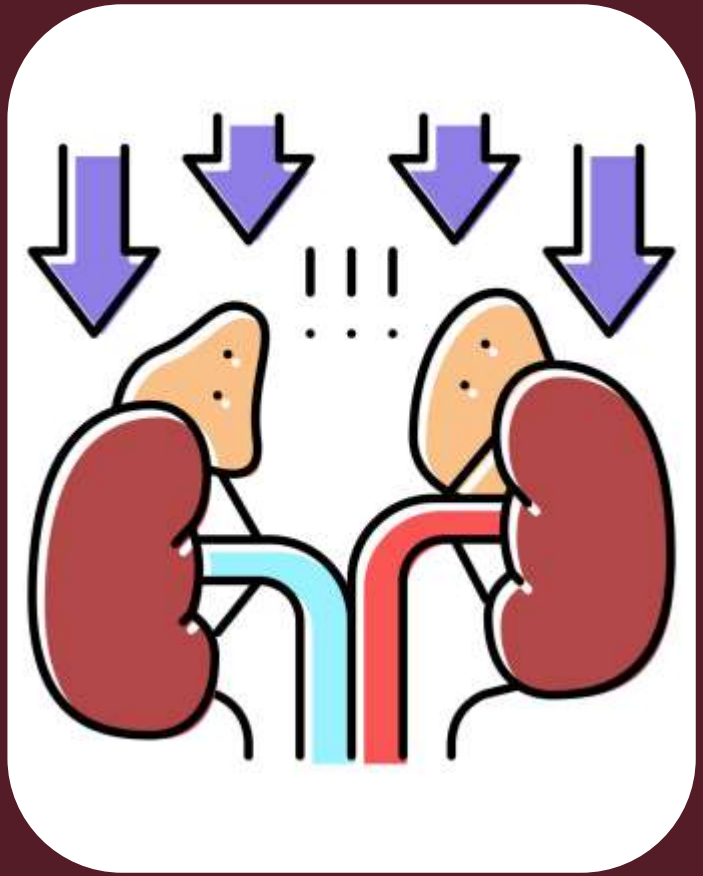
3. Severe Stress/Trauma/Emergency

- **Injectable glucocorticoid** (e.g., hydrocortisone 100 mg or dexamethasone 4 mg) should be available at home

Then seek immediate medical help.

4. Fasting (e.g., Ramadan)

- High-risk patients should avoid prolonged fasting.
- Consider switching to **once-daily prednisone** during fasting period.



Adrenal crisis

Life-threatening emergency!!

Triggered by anything that increases the person's normal stress level,
The body is unable to release sufficient cortisol to respond appropriately
May lead to shock & vascular collapse

- Typically resistant to catecholamine and IVF resuscitation

Main Clinical Features

- The predominant manifestation of adrenal crisis is **shock** (hypotension <90/50, cardiovascular collapse). Patients often present with a constellation of nonspecific symptoms:
- Anorexia
- Nausea and vomiting
- Abdominal pain (may be diffuse, mimicking an acute surgical abdomen)
- Weakness, fatigue, lethargy
- Fever (typically indicates infection and must be investigated)
- Confusion, delirium, stupor, or coma

TREATMENT:

Life-threatening emergency; treat immediately.

- Immediate steps:

- **IV fluids:** 1–3 liters 0.9% saline or 5% dextrose in saline over 12–24h.
- **IV glucocorticoid:Hydrocortisone:** 100 mg IV bolus → then 50 mg IV q6h (or 200 mg/24h continuous infusion).

Alternatives: methylprednisolone, dexamethasone if hydrocortisone unavailable.

- **Draw labs first** (cortisol, ACTH, electrolytes) but **do not delay treatment**.

- **Mineralocorticoid not needed acutely.**

Thank You