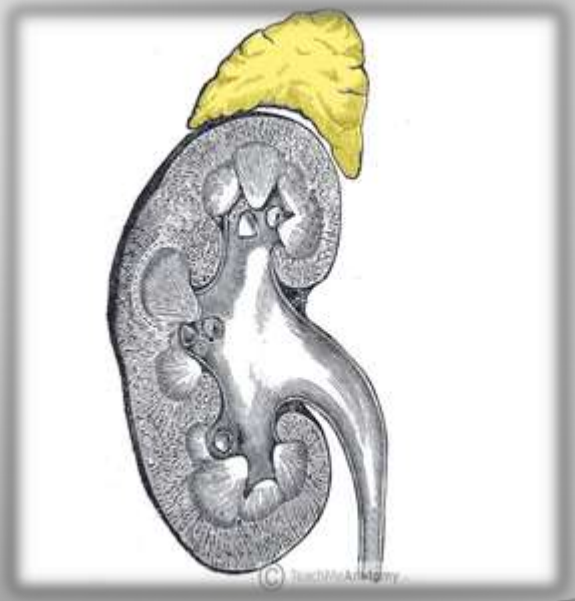
ADRENAL INSUFFECINCY



Aya Almazydeh

Naher Alqtaitat

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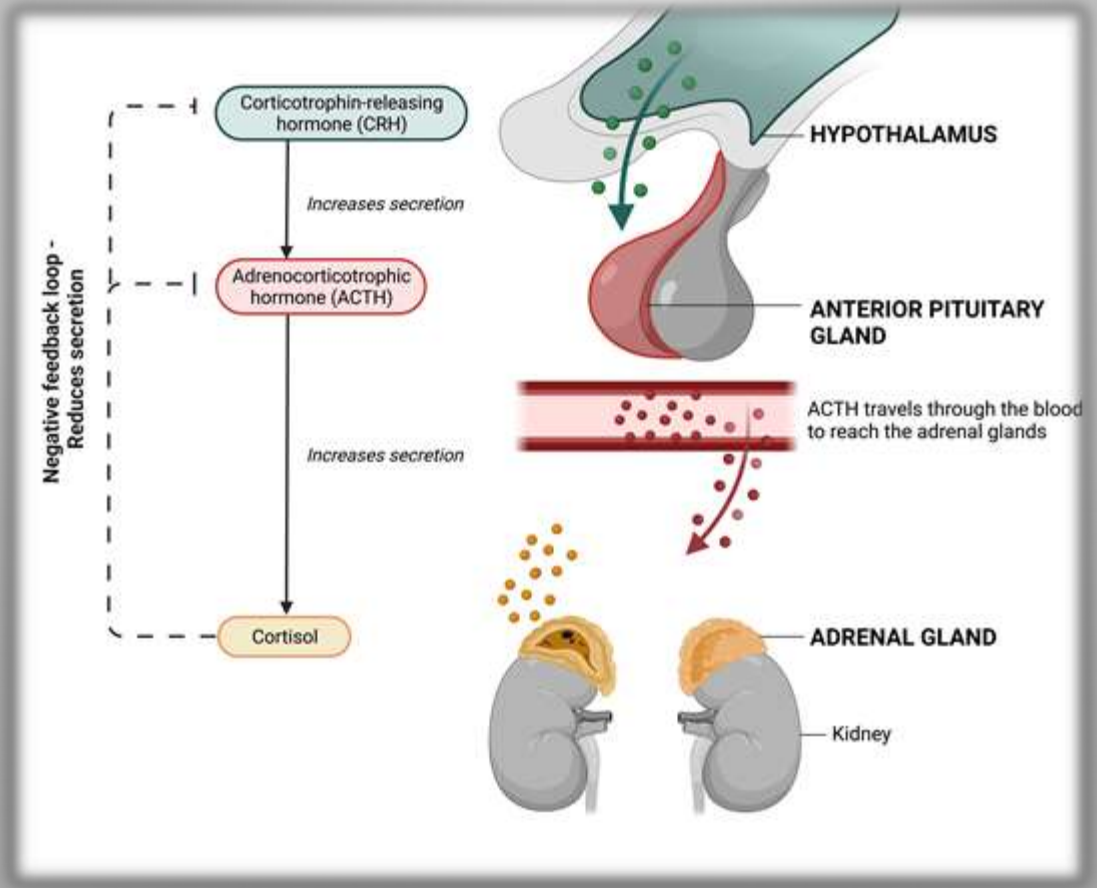
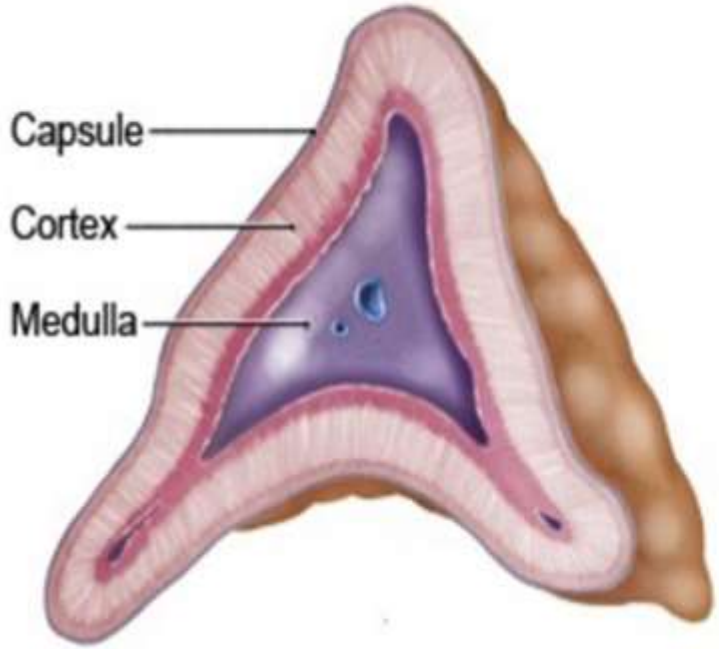
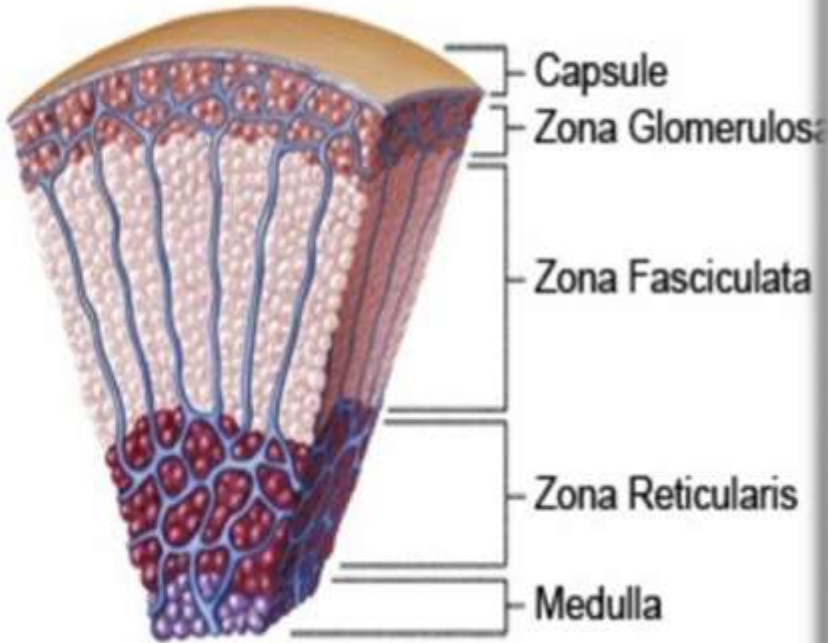

Corticotrophin-releasing hormone (CRH)
Increases secretion
Adrenocorticotrophic hormone (ACTH)
Increases secretion
Cortisol
Negative feedback loop - Reduces secretion
HYPOTHALAMUS
ANTERIOR PITUITARY GLAND
ACTH travels through the blood to reach the adrenal glands
ADRENAL GLAND
Kidney

Transverse Section



Microscopic Section



ZONA GLUMERULOSA → MINERALOCORTICOID

ZONA FASICULATA → CORTISOL

ZONA RETICULARIS → ANDROGEN

PATHOPHYSIOLOGY

CORTICOTROPHIN- RELEASING HORMONE (CRH) IS SECRETED IN THE HYPOTHALAMUS IN RESPONSE TO CIRCADIAN RHYTHM, STRESS AND OTHER STIMULI.

CRH TRAVELS DOWN THE PORTAL SYSTEM TO STIMULATE ADRENOCORTICOTROPHIN (ACTH) RELEASE FROM THE ANTERIOR PITUITARY.

ACTH IS DERIVED FROM THE PROHORMONE PRO-OPIOMELANOCORTIN (POMC), WHICH UNDERGOES PROCESSING WITHIN THE PITUITARY TO PRODUCE ACTH AND A NUMBER OF PEPTIDES LIKE MSH AND OTHERS. CIRCULATING ACTH STIMULATES CORTISOL PRODUCTION IN THE ADRENAL.

THE SECRETED CORTISOL (OR ANY OTHER SYNTHETIC CORTICOSTEROID ADMINISTERED TO THE PATIENT) CAUSES NEGATIVE FEEDBACK ON THE HYPOTHALAMUS AND PITUITARY TO INHIBIT FURTHER CRH/ACTH RELEASE.

UNLIKE CORTISOL, MINERALOCORTICOIDS AND SEX STEROIDS DO NOT CAUSE NEGATIVE FEEDBACK ON THE CRH/ACTH AXIS.

MINERALOCORTICOID SECRETION IS MAINLY CONTROLLED BY THE RENIN–ANGIOTENSIN SYSTEM

ANDROGENS PRODUCED BY THE ADRENALS MAKES THE MAJORITY OF ANDROGENS IN FEMALE BUT ARE NEGLIGIBLE IN MALES (PRODUCED MAINLY IN THE TESTICLES)

FOLLOWING ADRENALECTOMY OR OTHER ADRENAL DAMAGE (E.G. ADDISON'S DISEASE), CORTISOL SECRETION IS ABSENT OR REDUCED; ACTH LEVELS WILL THEREFORE RISE

INTRODUCTION

Adrenal insufficiency is defined by the inability of the adrenal cortex to produce sufficient amounts of glucocorticoids and/or mineralocorticoids.

Adrenal insufficiency may be caused by disease of the adrenal glands (primary) or Disorders of the pituitary gland (secondary).

Primary disease (eg. Addison disease) results in loss of cortisol, aldosterone, and adrenal androgens; while secondary insufficiency causes only cortisol and adrenal androgen deficiencies (aldosterone synthesis is not acth-dependent ➔ it's controlled by the RAS system).

In primary adrenal insufficiency there is destruction of the entire adrenal cortex.

→ Glucocorticoid, mineralocorticoid and sex steroid production are therefore all reduced.

→ This differs from hypothalamic–pituitary disease, in which mineralocorticoid secretion remains largely intact, being predominantly stimulated by angiotensin ii.

CAUSES

☐ Primary hypoadreneralisim cause

1. Autoimmune (addison's disease) >> most common causes of primary adrenal insufficiency in developed countries .

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.

2. Infections (tuberculosis, fungal infections, CMV, HIV)
3. Metastatic tumor
4. Infiltrations (amyloid, hemochromatosis)
5. Intra-adrenal hemorrhage (waterhouse-friderichsen syndrome) after meningococcal septicemia
6. Congenital adrenal hypolasia
7. Bilateral adrenalectomy

SECONDARY HYPOADRENALISIM

1. Exogenous glucocorticoid therapy >> most common cause of secondary adrenal insufficiency .

Look for patients who recently discontinued glucocorticoid
Therapy or did not increase their glucocorticoid dose in times of stress.

2. Hypopituitarism
3. Pituitary apoplexy
4. Granulomatous disease (tuberculosis, sarcoid, eosinophilic granuloma)
5. Secondary tumor deposits (breast, bronchus)
6. Postpartum pituitary infarction (sheehan's syndrome)
7. Pituitary irradiation (effect usually delayed for several years)
8. Isolated ACTH deficiency
9. Idiopathic

☐ CLINICAL FEATURES

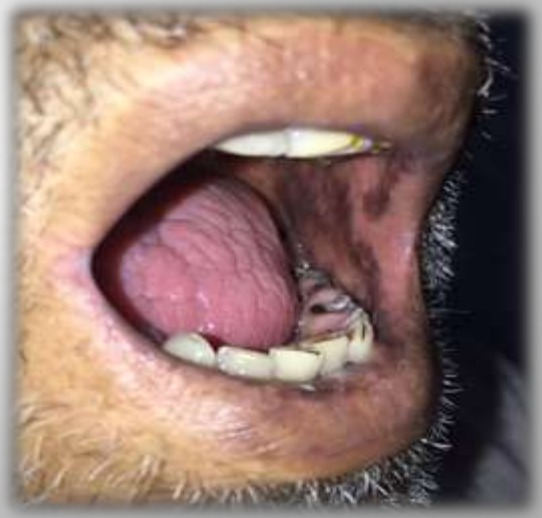
The sign and symptoms of AI are rather nonspecific such as :

- **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 .

Or sign and symptoms related to hormonal changes .....

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 • **Gastrointestinal complaints** (e.g., 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 areas that are not normally exposed to sunlight (e.g., palmar creases, mucous membrane of the oral cavity)	• ↑ MSH	✓	• **Absent**	• **Absent**



Primary adrenal insufficiency **P**igments the skin. **S**econdary adrenal insufficiency **S**pares the skin. **T**ertiary adrenal insufficiency is due to **T**reatment (cortisol).

Most cases of adrenal insufficiency are subclinical and only become apparent during periods of stress (e.g., surgery, trauma, infections), when the cortisol requirement is higher!

INVESTIGATIONS:

- **ROUTINE LABS INCLUDING :**

CBC Anemia lymphocytosis eosinophilia

KIDNEY FUNCTION Azotemia

ELECTROLYTES Hyponatremia hyperkalemia hypercalcemia

Normal anion gap metabolic acidosis

Hypoglycemia

- 8:00 am serum cortisol level , if <3 microg/dl diagnoses cortisol deficiency and values >15 microg/dl exclude the diagnosis.

(3-15) INDETEMINANT CORTISOL LEVEL

- Cosyntropin stimulation test
  serum cortisol >18 mg/dl excludes adrenal insufficiency , values < 18 confirms the diagnosis .

- morning ACTH level can help distinguish primary from secondary adrenal insufficiency

Endocrine testing for adrenal insufficiency [17]			
	Morning cortisol	Morning ACTH	ACTH stimulation test
Primary adrenal insufficiency	↓	↑	No increase in serum cortisol after stimulation
Secondary/tertiary adrenal insufficiency		↓	Increase in serum cortisol after stimulation
Longstanding secondary/tertiary adrenal insufficiency [18]		↓	No (or very little) increase in serum cortisol after stimulation

☐ **IMAGING:**

☐ **If morning ACTH is elevated……primary ADRENAL INSUFFECINCY do adrenal CT**

☐ **if morning ACTH is suppressed or normal secondary ADRENAL INSUFFECINCY do pituitary MRI**

☐ **21 hydroxylase antibodies**

MANAGEMENT

ADRENAL CRISIS

Similar symptoms and signs of adrenal insufficiency but are more severe, Including :

- ☐ **Severe hypotension**
- ☐ **Severe abdominal pain**
- ☐ **Fever & decreased level of consciousness**
- ☐ **Hypoglycemia**
- ☐ **Hyperkalemia**
- ☐ **Hyponatremia**
- ☐ **Metabolic acidosis**

Adrenal crisis can be life-threatening, so treatment with high doses of hydrocortisone should be started immediately, without waiting for diagnostic confirmation of hypocortisolism!

☐ **a blood sample is taken for later measurement of plasma cortisol.**

The **5 S**'s of adrenal crisis treatment are **Salt** (0.9% saline), **Sugar** (50% dextrose), **Steroids** (100 mg hydrocortisone IV once, then 200 mg over 24 hours), **Support** (normal saline to correct hypotension and electrolyte abnormalities), and **Search** (for the underlying disorder).

Box 21.18 Management of acute hypoadrenalism

Clinical context

Hypotension, hyponatraemia, hyperkalaemia, hypoglycaemia, dehydration, pigmentation often with precipitating infection, infarction, trauma or operation. The major deficiencies are of salt, steroid and glucose.

Requirements

Assuming normal cardiovascular function, the following are required:

- 1 L of 0.9% saline should be given over 30–60 min with 100 mg of i.v. bolus hydrocortisone
- Subsequent requirements are several litres of saline within 24 h (assessing with central venous pressure line if necessary) plus hydrocortisone, 100 mg i.m., 6-hourly, until the patient is clinically stable
- Glucose should be infused if there is hypoglycaemia
- Oral replacement medication is then started, unless the patient is unable to take oral medication: initially, hydrocortisone 20 mg, 8-hourly, reducing to 20–30 mg in divided doses over a few days (see **Box 21.19**)
- Fludrocortisone is unnecessary acutely, as the high cortisol doses provide sufficient mineralocorticoid activity – it should be introduced before discharge

LONG TERM REPLACEMENT

☐ Glucocorticoid replacement

- Hydrocortisone 10 mg on awakening and 5 to 10 mg in early afternoon.
- Monitor clinical symptoms and morning plasma ACTH.

☐ Mineralocorticoid replacement

- Fludrocortisone 0.1 (0.05 to 0.2) mg orally.

- Monitor lying and standing blood pressure and pulse, edema, serum potassium, and plasma renin activity.

ANDROGEN REPLACEMENT

DHEAS (50 mg/day) is occasionally given to women with primary adrenal insufficiency who have symptoms of reduced libido and fatigue, but the evidence in support of this is not robust and treatment may be associated with side-effects such as acne and hirsutism

In order to prevent the development of secondary and tertiary adrenal insufficiency, prolonged steroid therapy should be tapered slowly rather than stopped abruptly.

Hyperpigmentation in Addison disease

Left: bronze-toned facial hyperpigmentation before treatment
Right: after treatment with glucocorticoid replacement therapy

THANK YOU