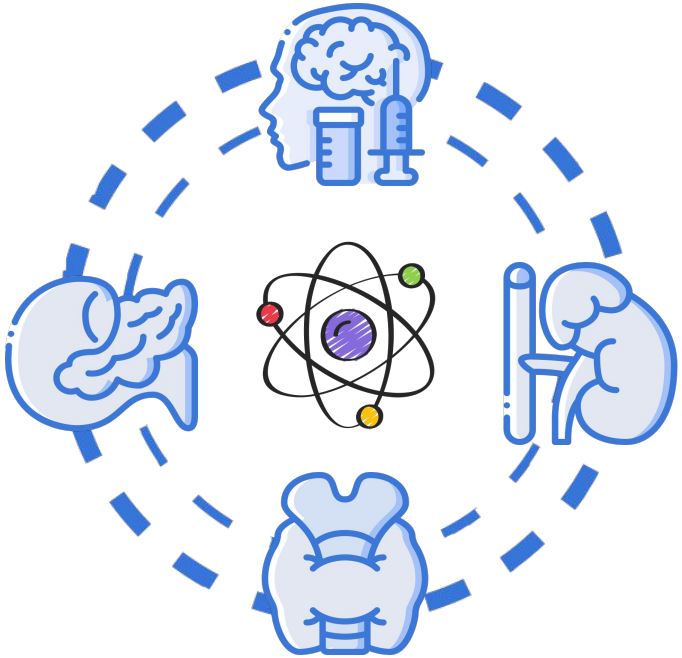
Addison's Disease



Color Index:

- Main Topic
- Main content
- Important
- Drs' notes
- Extra info

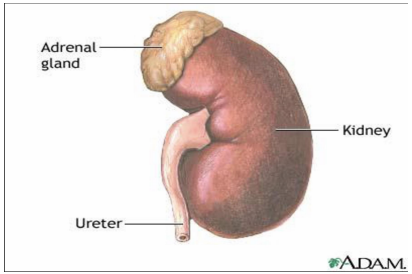
Editing File

Objectives:

- Identify different causes of primary adreno-cortical hypofunction(Addison's disease).
- Identify secondary causes of adreno-cortical hypofunction.
- Understand the diagnostic algorithm for adreno-cortical hypofunction.
- Understand the interpretation of laboratory tests of adreno-cortical hypofunction.

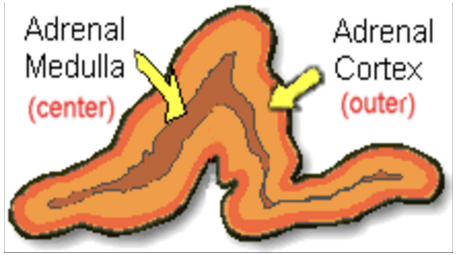
Adrenal gland

ANATOMY:



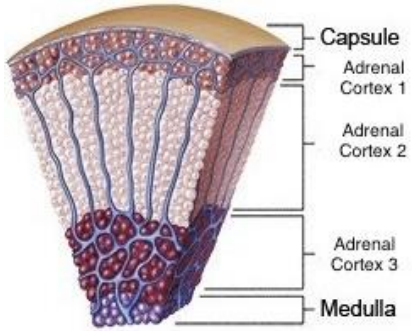
The adrenal gland is situated on the anterio-superior aspect of the kidney.

HISTOLOGY:



The adrenal gland consists of two distinct tissues of different embryological origin, the outer cortex and inner medulla.

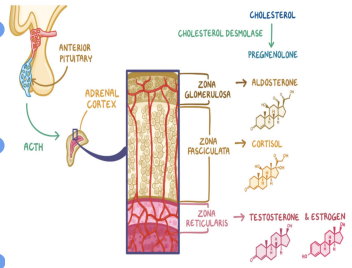
Adrenal cortex zones:



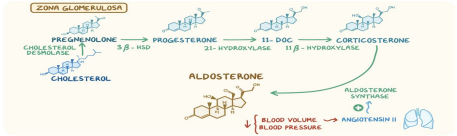
Zona Glomerulosa → **The outermost zone aldosterone (the principal mineralocorticoid).**

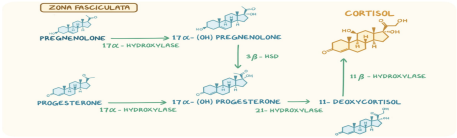
Zona Fasciculata → **Glucocorticoids – mainly cortisol (95%)**

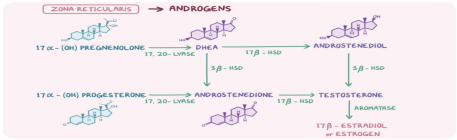
Zona Reticularis → **Sex hormones**



Steroid Hormone Synthesis







Cholesterol (27C)

Pregnenolone (21C)

3-β-Hydroxysteroid dehydrogenase

Progesterone (21C)

21-α-Hydroxylase

17-α-Hydroxylase

11-Deoxycorticosterone (21C)

17-α-Hydroxyprogesterone (21C)

Androstenedione (19C)

11-β-Hydroxylase

21-α-Hydroxylase

Corticosterone

11-Deoxycortisol (21C)

Testosterone (19C)

11-β-Hydroxylase

Aldosterone (21C)

Cortisol (21C)

Estradiol (18C)

Peripheral Tissue

Aldosterone Hormone

The principal physiological function of aldosterone is:
to conserve Na+,mainly by facilitating **Na+ reabsorption** and reciprocal **K+** or **H+ secretion** in the distal renal tubule.

Is a major regulator of water and electrolyte balance, as well as blood pressure.

By acting on the distal convoluted tubule of kidney, leads to:

- ➔ ↑↑ potassium excretion
- ➔ ↑↑ sodium and water reabsorption

Renin-Angiotensin system is the most important regulatory mechanism controlling aldosterone secretion.

The Renin-Angiotensin System

controls aldosterone secretion.

involved in blood pressure regulation.

Renin

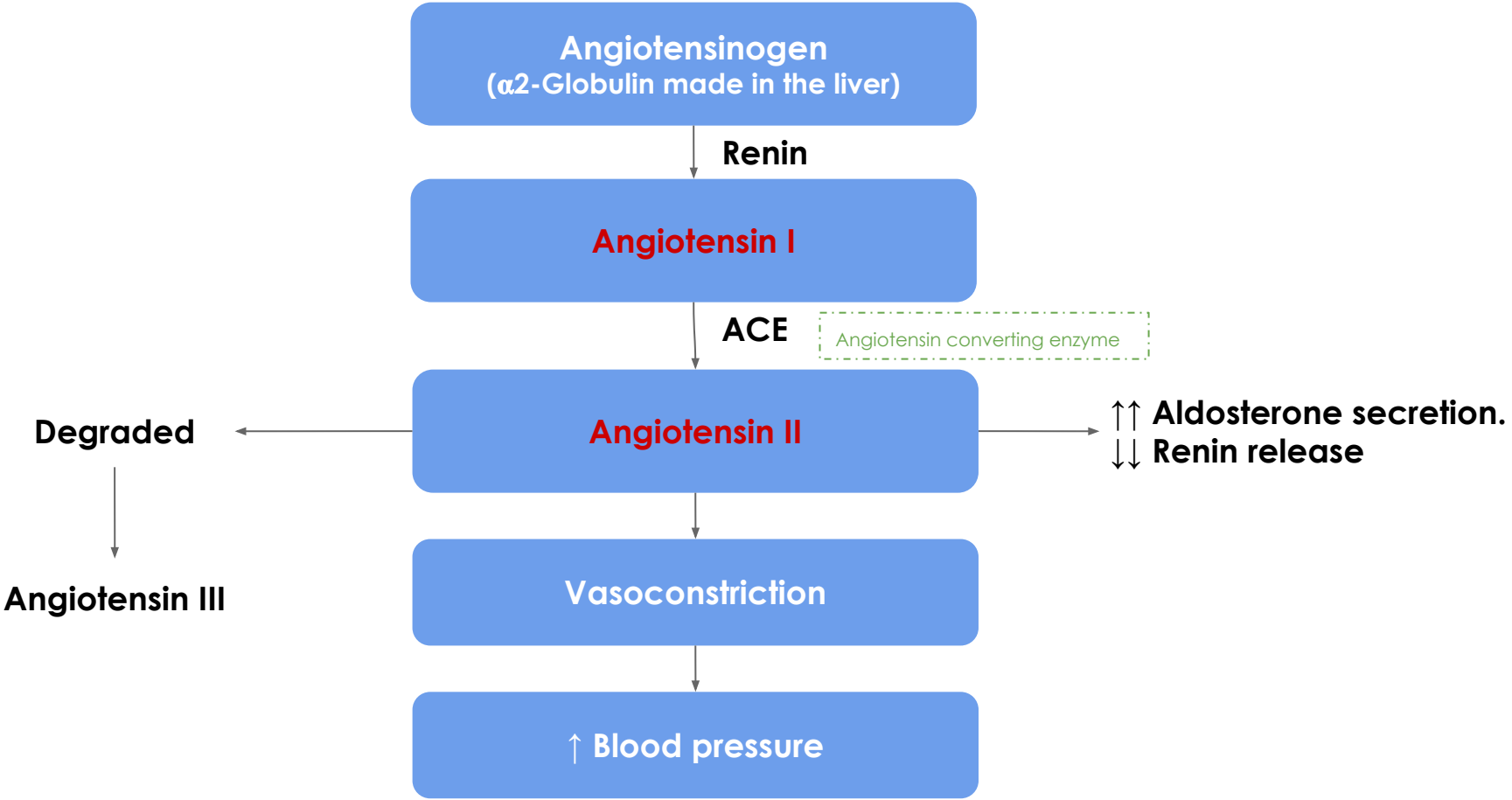
A proteolytic enzyme produced by the juxtaglomerular cells of the afferent renal arteriole.

Sensitive to blood pressure changes through baroreceptors.

released into the circulation in response to:

- fall in circulating blood volume.
- fall in renal perfusion pressure.
- loss of Na+.

Aldosterone and Renin-Angiotensin system



1 Primary Adrenocortical Hypofunction (AC)

Primary AC hypofunction: (destruction of adrenal gland, Addison's disease)

Causes:

- Autoimmune
- Infection, e.g., tuberculosis
- Infiltrative lesions, e.g., amylodosis

Helpful video for Addison

Signs and symptoms:

of primary adrenal failure (Addison's disease):
(The symptoms are precipitated by trauma, infection or surgery)

- Lethargy, weakness, nausea & weight loss.
- Hypotension especially on standing (postural)
- Hyperpigmentation (buccal mucosa, skin creases, scars)
- Deficiency of both glucocorticoids and mineralocorticoids
- Hypoglycemia, ↓Na+, ↑K+ and raised urea
- Life threatening and need urgent care.

Signs and symptoms:

of Hyperpigmentation

- occurs because melanocyte- stimulating hormone (MSH) and (ACTH) share the same precursor molecule, Pro- opiomelanocortin (POMC).
- The anterior pituitary POMC is cleaved into ACTH, γ-MSH, and β-lipotropin.
- The subunit ACTH undergoes further cleavage to produce α-MSH, the most important MSH for skin pigmentation.

2 Secondary Adrenocortical Hypofunction (AC)

Causes:

- Pituitary tumors
- Vascular lesions
- Head trauma
- Hypothalamic diseases
- Iatrogenic (steroid therapy, surgery or radiotherapy)

Signs and symptoms:

of Hyperpigmentation

- In secondary adrenocortical insufficiency, skin darkening does not occur.

Investigation of Addison's disease (AD)

The patient should be hospitalized

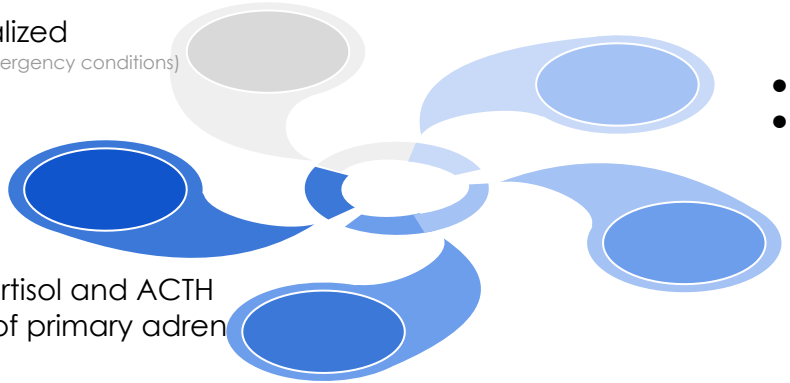
Because they have hypoglycemia (one of the emergency conditions)

Normal serum cortisol and UFC does not exclude AD.

Simultaneous[1] measurement of cortisol and ACTH improves the accuracy of diagnosis of primary adren failure:

Low serum cortisol (<200 nmol/L) and

High plasma ACTH (>200 ng/L)



Basal measurement of:

- Serum urea, Na+, K+ & glucose
- Serum cortisol and plasma ACTH

Definitive diagnosis and confirmatory tests should be done later after crisis.

1.Performing the test more than once

Confirmatory Tests

1. Short tetracosactrin (Synacthen) test (Short ACTH stimulation test):

- Measure basal S. cortisol
- Stimulate with I.M. synthetic ACTH (0.25 mg)
- Measure S. cortisol 30 min after I.M injection
- Normal: ↑ of S. cortisol to >500 nmol/L
- Failure of S. cortisol to respond to stimulation, confirm AD.
- **Abnormal results:**
- emotional stress
- glucocorticoid therapy
- estrogen contraceptives.

2. Adrenal antibodies

- Detection of adrenal antibodies in serum of patients with autoimmune Addison's disease

3. Imaging (Ultrasound/CT)

- Ultrasound or CT for adrenal glands for identifying the cause of primary adrenal failure

Investigation of Secondary AC Insufficiency

- Low serum cortisol with low plasma ACTH
- No response to short synacthen test: Adrenocortical cells fail to respond to short ACTH stimulation
- Depot Synacthen test (confirmatory test)

Depot Synacthen test (confirmatory test)

" Prolonged synacthen test "

1. Measure basal S. cortisol
2. Stimulate with I.M. synthetic ACTH (1.0 mg) on each of three consecutive days
3. Measure S. cortisol at 5 hours after I.M. injection on each of the three days

Other Investigations

- MRI for pituitary gland
- Insulin-induced hypoglycemia: Adrenal failure secondary to pituitary causes

Interpretation of results:

- **Addison's disease**: No rise of S. cortisol >600 nmol/L at 5 h after 3rd injection.
- **Secondary AC**: Stepwise increase in the S. cortisol after successive injections
- **Limitations**:
  - Hypothyroidism: Thyroid deficiency must be corrected before testing of adrenocortical functions
  - Prolonged steroid therapy

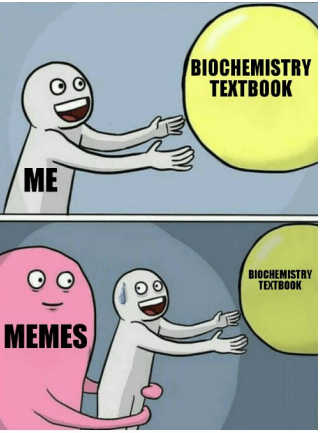
Investigations Summary

Very important slide!

	Investigation for Addison's disease	Investigation for Secondary AC Insufficiency
Screening	• Basal plasma ACTH and basal serum cortisol, glucose, urea and electrolytes Screening • High ACTH and Low cortisol	• Low ACTH and Low cortisol
Confirmation	• Short ACTH stimulation test: No response	• Long ACTH stimulation test: Stepwise Confirmation increase in S. cortisol
Others	• Adrenal autoantibodies Others • Ultrasound/CT adrenal glands	• Insulin-induced hypoglycemia Others • MRI pituitary gland

Take Home Messages

- **Addison's disease is due to destruction of adrenals by autoimmune, infection, or infiltrative lesions.**
- **Adrenocortical hypofunction may occur secondary to pituitary disease, e.g., tumors, infection, trauma, or iatrogenic (surgery or radiation).**
- **Initial screening for Addison's disease by serum cortisol and ACTH. Other tests to support the diagnosis include serum urea, electrolytes and glucose.**
- **Confirmatory tests for Addison's disease by short Synacthen test.**
- **Diagnosis of secondary adrenocortical hypofunction by depot (long) Synacthen test.**



That really happens.....cant stop it

This really happens..
- Girls leader

Summary

1. Renin-Angiotensin system is the most important regulatory mechanism for aldosterone secretion
2. Causes of primary adrenal insufficiency Autoimmune, Infection, e.g., tuberculosis and Infiltrative lesions, e.g., amyloidosis
3. Causes of secondary adrenal insufficiency are Pituitary tumors, Vascular lesions ,Trauma,Hypothalamic diseases (tertiary) and Iatrogenic (steroid therapy, surgery or radiotherapy.
4. In secondary adrenocortical insufficiency, skin darkening does not occur.
5. In primary adrenal insufficiency Low serum cortisol, High plasma ACTH but in secondary Low serum cortisol with low plasma ACTH.
6. Short tetracosactrin (Synacthen) test (Short ACTH stimulation test) is confirmatory test for both primary and secondary adrenal insufficiency but in primary there is no rise in S.cortisol and in case of secondary there is Stepwise increase in the S. cortisol

Quiz

MCQs :

Q1: From which zone the Cortisol secreted?
a) Zona Glomerulosa **b)** Zona Fasciculata **c)** Zona Reticularis **d)** All cortex

Q2: Aldosterone by acting on the distal convoluted tubule of kidney, leads to:
a) ↓ Sodium reabsorption **b)** ↑ Potassium excretion
c) ↓ Water reabsorption **d)** A+C

Q3: Which of the following is not a symptom of Addison's Disease?
a) Weight loss **b)** Bronzing of the skin **c)** Craving for salty foods **d)** Weight gain

Q4: Which of the following is a confirmatory test for secondary AC insufficiency?
a) Adrenal autoantibodies **b)** Short ACTH stimulation test
c) Long ACTH stimulation test **d)** Basal plasma ACTH

Q5: Which of the following describes 2ry AC insufficiency?
a) ↑ S. cortisol & Normal Plasma ACTH **b)** ↓ S. cortisol & sky high Plasma ACTH
c) ↑ S. cortisol & ↑ Urinary cortisol **d)** ↓ S. cortisol with ↓ plasma ACTH

Q6: Normally in a Short tetracosactrin (Synacthen) test, there will be an ..... response to I.M injection of ACTH
a) Positive **b)** Negative **c)** Absent **d)** Mixed

SAQs :

Q1: What is the enzyme that convert 11-Deoxycortisol to cortisol?

Q2: What are the deficiencies and decreases that happen as signs and symptoms of Addison's disease

Q3: Name 3 tests that are used to confirm the diagnosis of Addison's disease.

Q4: What are the limitations to the Depot synacthen test?

★ **MCQs Answer key:**

1) B 2) B 3) D 4) C 5) D 6) A

★ **SAQs Answer key:**

1) 11-β-Hydroxylase

2) Deficiency of both glucocorticoids and mineralocorticoids, Hypoglycemia, ↓Na+

3) 1- Short Synacthen (tetracosactrin) test (Short ACTH stimulation test) 2-Adrenal Antibodies 3- Imaging (CT, Ultrasound) of the adrenal gland

4) 1- hypothyrodism 2- prolonged steroid therapy

Team members

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- Deema Almaziad
- Ghaliah Alnufaei
- Haifa Alwaily
- Leena Alnassar
- Lama Aldakhil
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- Naif Alsolais
- **Omar Alyabis**
- Omar Saeed
- Rayyan Almousa
- Yazen Bajeaifer

Team Leaders

Lina Alosaimi

Mohannad Alqarni

★ I won't let you down
- Note to self

438 BIOCHEMISTRY TEAM

We hear you