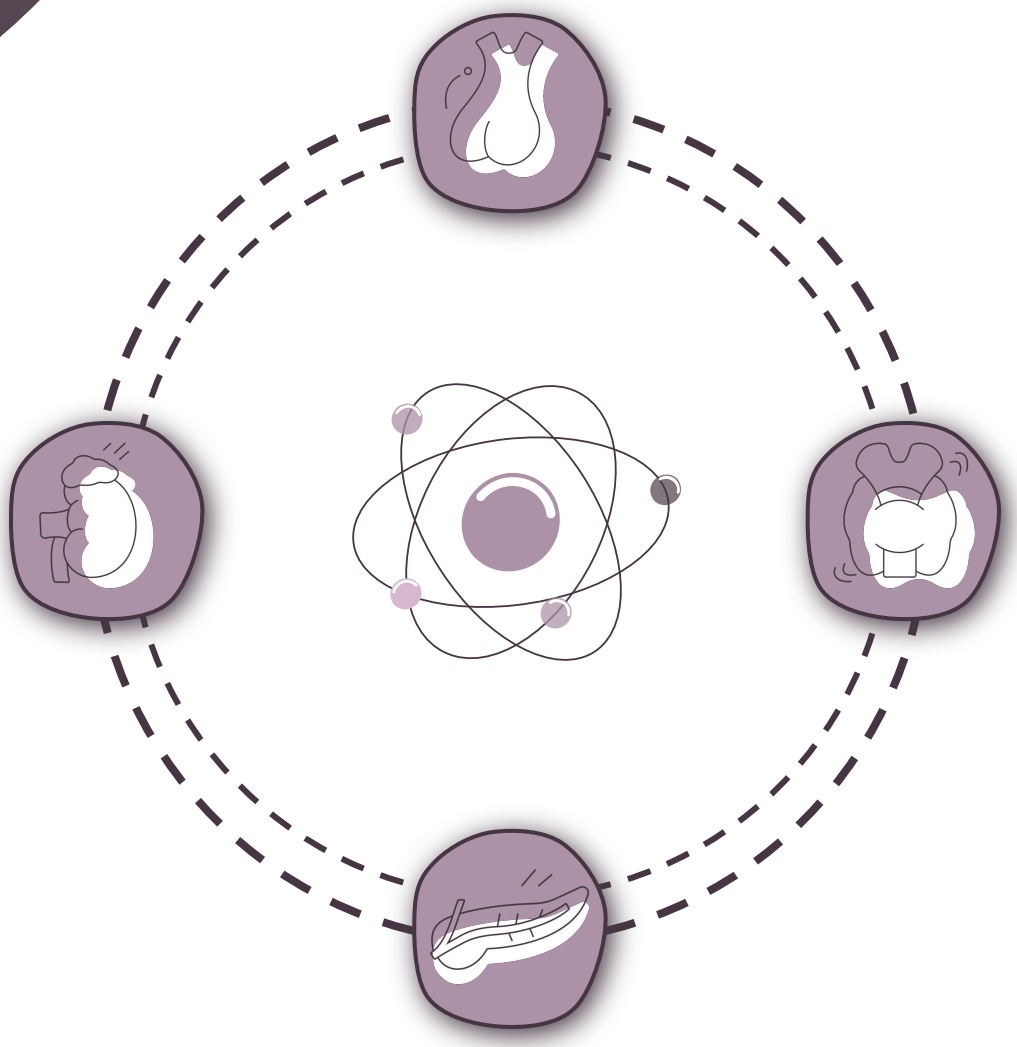

L5: Addison's disease

Color Index:
Main Text
Male's Slides
Female's Slides
Important
Doctor's Notes
Extra Info

Editing File link:

Objectives

1. To identify different causes of **primary** adrenocortical hypofunction **(Addison's disease) .**
2. To identify **secondary** causes of adrenocortical hypofunction.
3. To understand the **diagnostic algorithm** for adrenocortical hypofunction.
4. To understand the **interpretation** of laboratory tests of adrenocortical hypofunction.

To be in touch: click on the icons

Biochemistry 443 team channel:

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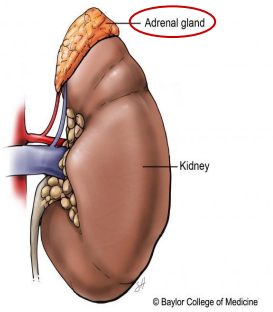
1

Adrenal gland

Anatomically

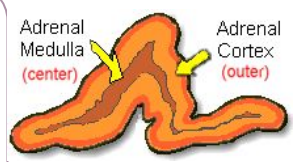
The adrenal gland is situated on the anterosuperior aspect of the kidney.



Histologically

The adrenal gland consists of two distinct tissues of different embryological origin:

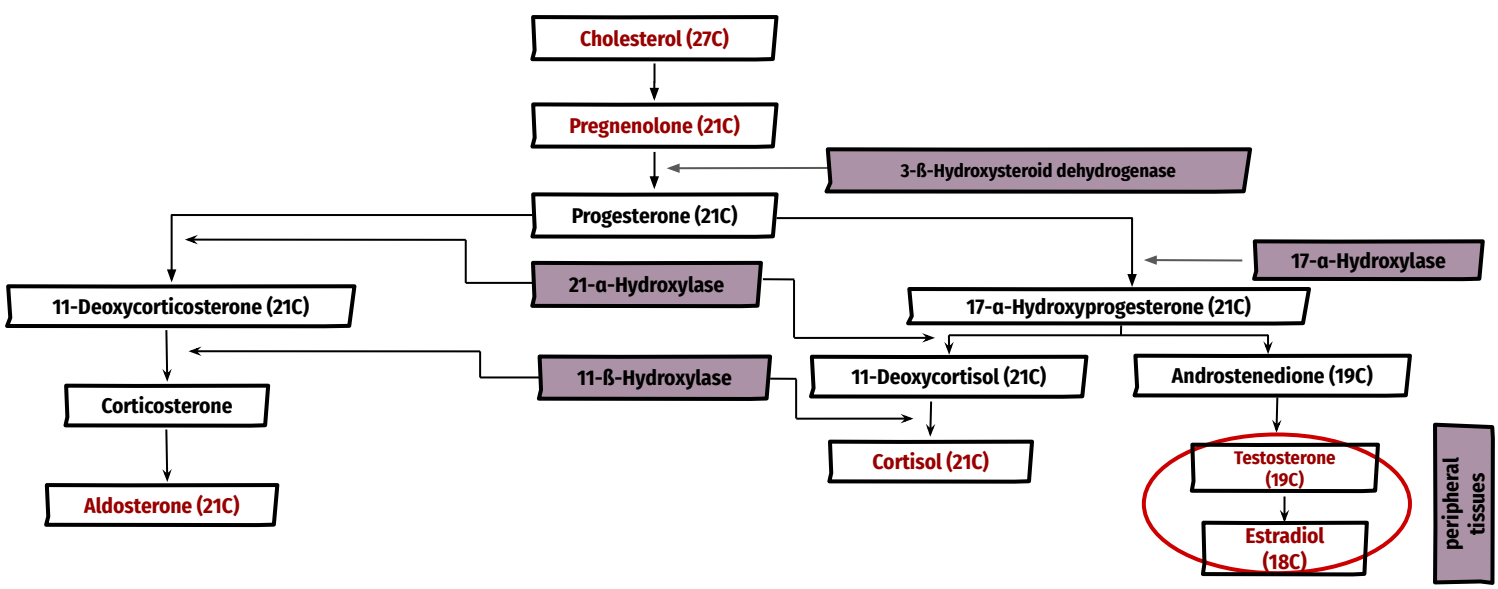
1-The outer cortex **2-inner medulla**



Adrenal Cortex

Layer	Zona Glomerulosa (Outermost layer)	Zona Fasciculata (The deeper layers of the cortex)	Zona Reticularis (The deeper layers of the cortex)
Secreted hormone	Aldosterone (the principal mineralocorticoid)	Glucocorticoids (mainly cortisol 95%)	Sex hormones

Steroid Hormone synthesis



2

Aldosterone Hormone

7:00

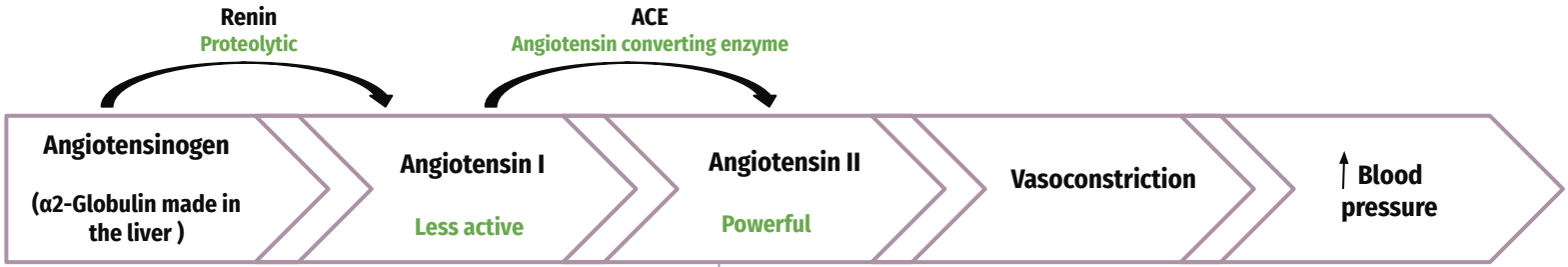
Aldosterone Hormone	overview	• Is a major regulator of water & electrolyte balance, as well as blood pressure.
	Function	• The principal physiological function of aldosterone is: to conserve Na+, mainly by facilitating Na+ reabsorption and reciprocal K+ or H+ secretion in the distal renal tubule.
	Actions	• By acting on the distal convoluted tubule of kidney, lead to: ➡ Potassium excretion or (dr.439 H+). ↑↑ ➡ Sodium and water reabsorption. ↑↑ Q* Where does it act ? on distal convoluted tubule. Q*What does it do ? 1- water & sodium reabsorption. 2- K+ or H+ excretion.

The Renin-Angiotensin system

- Renin-Angiotensin system is the most important regulatory mechanism controlling aldosterone secretion .
- Involved in blood pressure regulation.

Renin	
Overview	A proteolytic enzyme produced by the juxtaglomerular cells of the afferent renal arteriole.
Sensitivity	Sensitive to blood pressure changes through baroreceptors.
Release	Released into the circulation in response to : • Fall in circulating blood volume. • Fall in renal perfusion pressure. • Loss of Na+.

Aldosterone & Renin-Angiotensin system



Polypeptide and released in blood circulation.

- ↑↑ Aldosterone secretion.
- ↓↓ Renin release (Negative feedback).
- Degraded Angiotensin III.

-In CS : cortisol inhibit pituitary secretion.

3

Adrenocortical Hypofunction (AC)

1.Primary AC Hypofunction
Destruction of adrenal gland, Addison's disease

Causes	• Autoimmune • Infection, e.g., tuberculosis • Infiltrative lesions, e.g., amyloidosis	
Signs and symptoms	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) Due to High ACTH (occur in cushing's also) • Deficiency of both glucocorticoids and mineralocorticoids (in case of primary AC) • Hypoglycemia, ↓Na+, ↑K+ and raised urea (unlike cushing's remember? Hyperglycemia, normal Na+ , hypokalemia) • Life threatening and need urgent care Hypoglycemia because Cortisol is an Insulin Antagonist .	
Hyperpigmentation in Addison's disease	• 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 This occur in case of primary AC because the problem is in the adrenal gland (not respond to ACTH so cortisol level is low which will stimulate more ACTH production) so there will be increase ACTH which will go to another pathway that produce alpha MSH.	
Investigations	• The patient should be hospitalized (Because they have hypoglycemia (one of the emergency conditions) • Basal measurement of : 1- Serum urea, Na+, K+ & glucose 2- Serum cortisol and plasma ACTH • Definitive diagnosis and confirmatory tests should be done later after crisis. • Normal serum cortisol and UFC does not exclude AD • Simultaneous measurement of cortisol and ACTH improves the accuracy of diagnosis of primary adrenal failure: Low serum cortisol (<200 nmol/L) and High plasma ACTH (>200 ng/L).	
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.

4 Adrenocortical Hypofunction (AC)

	2.Secondary AC hypofunction Adrenal gland is Intact Treat the primary cause = Adrenal gland will work
Causes	• Pituitary tumors • Vascular lesions • Head trauma • Hypothalamic diseases • Iatrogenic (steroid therapy,surgery or radiotherapy) Will Inhibit Adrenal gland as -ve feedback
Signs and symptoms	• In secondary adrenocortical insufficiency, skin darkening does not occur. (because there is a little or no ACTH at all). No Hyperpigmentation
Investigations	• Low serum cortisol with low plasma ACTH (low cortisol is due to low ACTH not due to problem in adrenal gland) • No response to short synacthen test: Adrenocortical cells fail to respond to short ACTH stimulation • MRI for pituitary gland • Insulin induced hypoglycemia (Adrenal failure secondary to pituitary causes).(the patient must be hospitalized to do this test because hypoglycemia is abnormal condition and one of the emergency)
Confirmatory test	Depot synacthen test

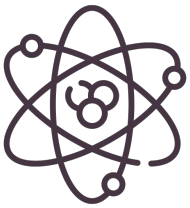
Depot Synacthen test

1	Measure basal S. cortisol.	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 (stepwise increase mean that the result in the second day is higher than the first day and the third day higher than second day) • Limitations: - Hypothyroidism: Thyroid deficiency must be corrected before testing of adrenocortical functions.(Thyroid hormones promote the effect of GH (permissiveness), GH go to every cell in the body so deficiency of thyroid hormones will decrease effect of GH which will cause decrease the number of adrenal cells leading to decrease release of cortisol from it). - Prolonged steroid therapy
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.	

Summary

Investigations summary from slides ★ The whole summary is important		
	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. • No need to Depot because ACTH is high which indicates AD.	• Long ACTH stimulation test: Stepwise increase in S.cortisol. • No response to short synacthen test .
Others	• Adrenal autoantibodies. • Ultrasound / CT adrenal glands.	• Insulin-induced hypoglycemia. • 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.

Test Yourself!

MCQs

Answers: B-C-A-C

Q1: Which of the following adrenocortical functional abnormalities can cause hyperpigmentation?
A. Functional adrenal carcinoma
B. Primary adrenocortical hypofunction
C. Secondary adrenocortical dysfunction
D. Steroid-induced cushing

Q2: From which zone is cortisol secreted?
A. Zona Glomerulosa
B. Zona Reticularis
C. Zona Fasiculata
D. All cortex

Q3: Which one of the following best describes renin ?
A. Proteolytic enzyme
B. Released in response to increased BP
C. Sensitive to blood PH
D. None of them

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

SAQs

Q1: what are the zones of the adrenal cortex and the hormones secreted from each zone?
Page 1

Q2: what are the investigations of the Secondary AC hypofunction ?
Page 4

Meet The Team!

Team Leaders

Abdullah AlDhuwaihy

Yazeed AlSulaim

Jouri Almaymoni

Deena Almahawas

Team Members

- Faisal AlShowier
- Mohammed AlRashed
- Abdulrahman AlOmar
- Mohammed AlEssa
- Mohammed AlSalamah
- Mohammed AlArfaj
- Hamad AlZomaia
- Talal AlGhadir
- Faisal AlZuhairy
- Abdulmalik AlShathri
- Abdulrahman AlOsleb
- Abo Owayed
- Yazan AlAhmari
- Fahad AlMughaiseeb
- Faris AlZahrani
- Khalid AlSobei
- Razan alsoteehi
- Razan Alaskar
- Haya Alzeer
- Dana A Alkheliwi
- Lama Hazzaa
- Afnan Alahmari
- Shaden Alhazzani
- Wasan Alanazi
- Salma Alsaadoun
- Remas Aljeaidi
- Jana Almutlaqah