Revised & Approved

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BIOCHEMISTRY TEAM
439

MED439
KING SAUD UNIVERSITY

Addison's Disease

Editing File

Color Index

- Main Text
- Important
- Extra
- Dr.'s Notes
- Girls slides
- Boys slides

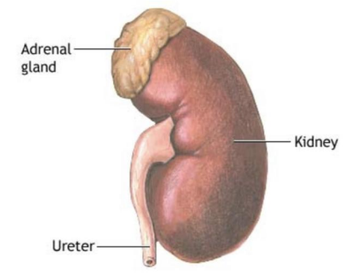
Objectives

- To identify different causes of primary adrenocortical hypofunction (Addison's disease)
- To identify secondary causes of adrenocortical hypofunction
- To understand the diagnostic algorithm for adrenocortical hypofunction
- To understand the interpretation of laboratory tests of adrenocortical hypofunction

Adrenal Gland

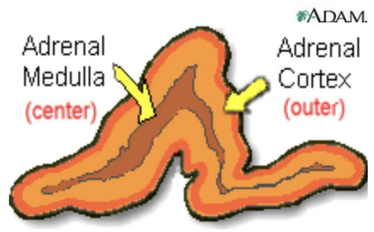
Anatomically

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

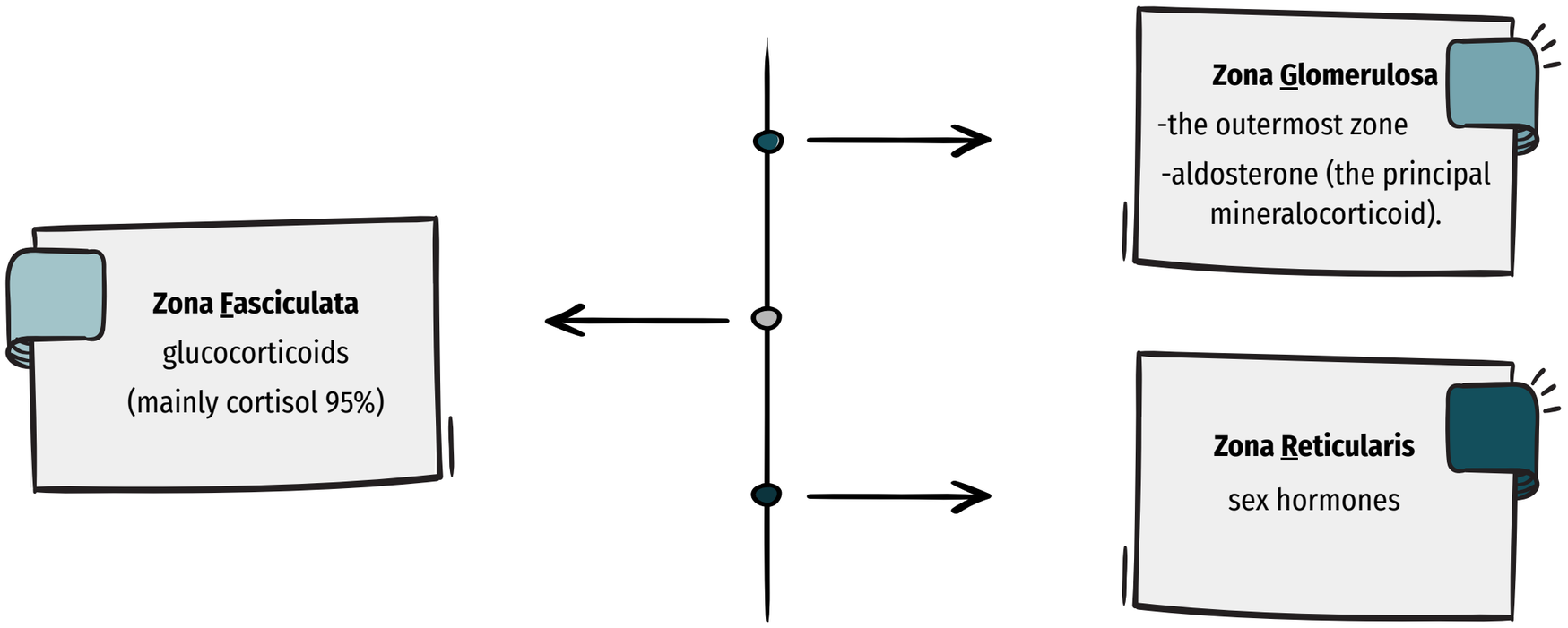


Histologically

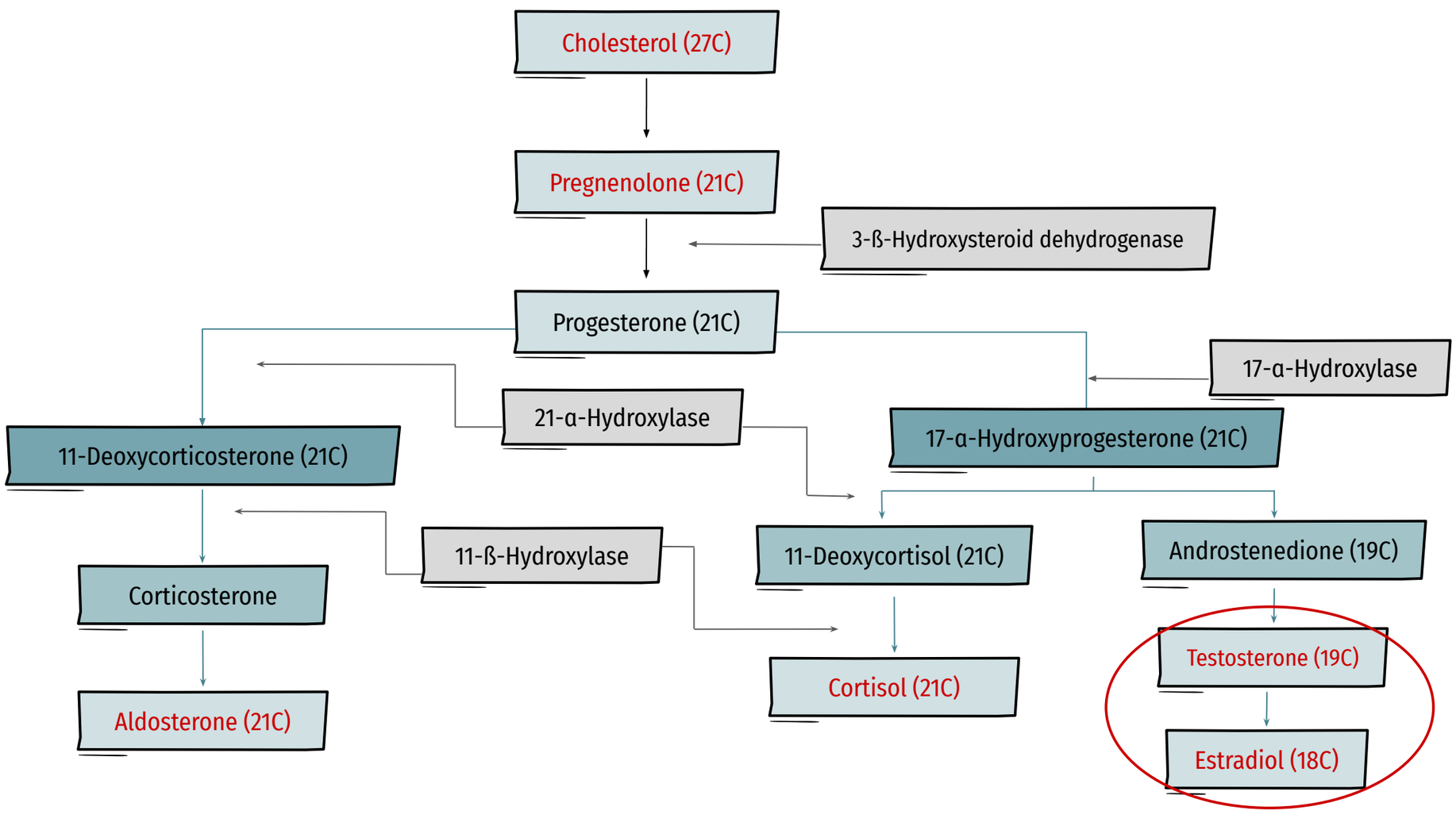
The adrenal gland consists of two distinct tissues of different embryological origin, the outer cortex and inner medulla



THE ADRENAL CORTEX



Steroid Hormone synthesis



Aldosterone Hormone

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

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.

When we reabsorbe Na+ we reabsorb H2O to reserve volume and prevent Hyppvolumia

By acting on the distal convoluted tubule of kidney, leads to:
➔ ↑↑ potassium excretion
➔ ↑↑ sodium and water reabsorption

The Renin-Angiotensin System

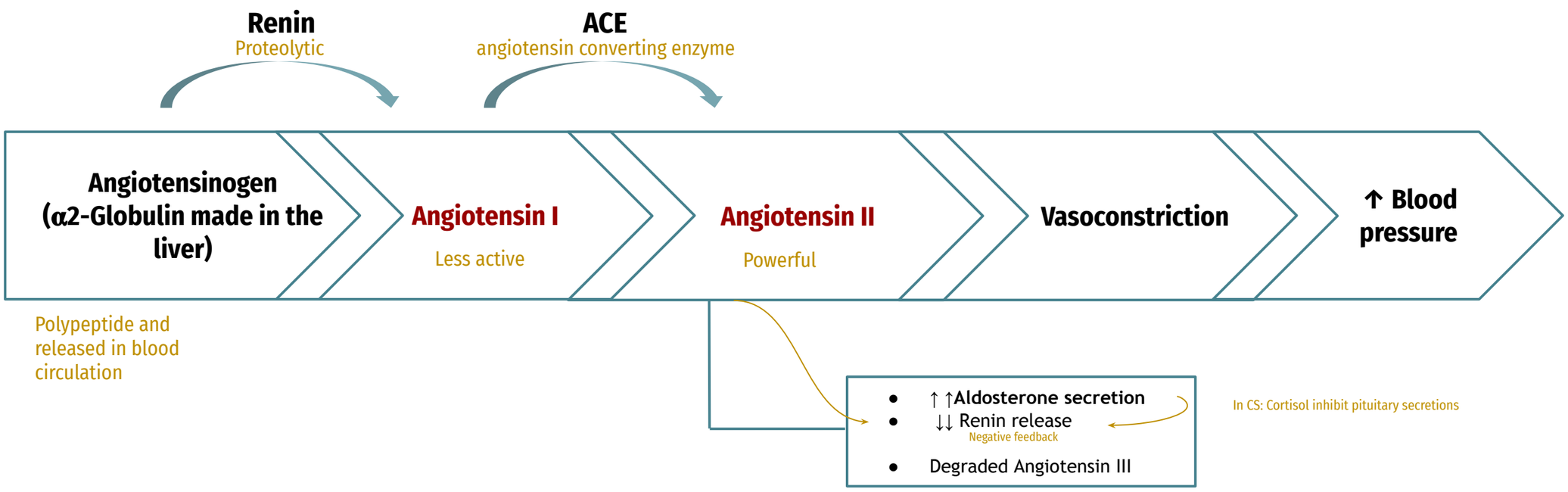
- **Renin-Angiotensin system** is the most important regulatory mechanism controlling **aldosterone secretion**
- Involved in blood pressure regulation

In CS: Hypothalmic-pituitary adrenal axis

	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+

Focus it is renin not rennin, you have to differentiate between them.

Aldosterone and Renin-Angiotensin system



In CS: Cortisol inhibit pituitary secretions

Adrenocortical Hypofunction (AC)

NO cortisol section to suppress ACTH , NO cells to secret Mineralocorticoids even with ACTH will not secret Aldosterone

Primary AC Hypofunction	**Destruction of adrenal gland, Addison's disease**	
Causes	• Autoimmune • Infection, e.g., tuberculosis • Infiltrative lesions, e.g., amyloidosis CS Hyper → Pituitary gland AD Hypo → Adrenal gland	
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	• 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 :** - Serum urea, Na+, K+ & glucose - 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). يجب أن نقيسها بشكل متتابع لأنها أحيانًا تكون Pulsatile	
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.

Secondary AC Hypofunction	**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).
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**

Adrenal gland hasn't worked for long time so it will not respond immediately (needs prolong stimulation)

Depot 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.

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

Investigations Summary from slides

	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.
- Confirmatory tests for Addison’s disease by short Synacthen test.

Extra **Summary**

Adrenal Gland	Adrenal cortex	• Zona glomerulosa (mainly release aldosterone) • Zona fasciculata (mainly release cortisol) • Zona reticularis (mainly release sex hormones)	
	Steroid hormone Synthesis	• Cholesterol (27C) is the precursor of Glucocorticoids, mineralocorticoids and sex hormones • The most important glucocorticoid is cortisol (21C) • The most important mineralocorticoid is aldosterone (21C)	
	Aldosterone hormone	• Is a major regulator of water and electrolyte balance, as well as blood pressure. • **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. • **By acting on the distal convoluted tubule of kidney, leads to:** ↑↑ potassium excretion & ↑↑ sodium and water reabsorption	
	Renin-Angiotensin system	• **Renin-Angiotensin system** is the most important regulatory mechanism controlling **aldosterone secretion** • Involved in blood pressure regulation	
Primary AC hypofunction (Addison's disease)	Causes	Autoimmune, Infection, e.g., tuberculosis and Infiltrative lesions, e.g., amyloidosis	
	Signs and symptoms	• 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	
	Investigations	• The patient should be hospitalized • **Basal measurement of :** - Serum urea, Na+, K+ & glucose - Serum cortisol and plasma ACTH • **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.
		2. Adrenal antibodies:	Detection of adrenal antibodies in serum of patients with autoimmune AD.
		3. Imaging (Ultrasound/CT)	Ultrasound or CT for adrenal glands for identifying the cause
Secondary AC hypofunction	Causes	Pituitary tumors, Vascular lesions, Head trauma, Hypothalamic diseases or Iatrogenic (steroid therapy,surgery or radiotherapy)	
	Signs and symptoms	In secondary adrenocortical insufficiency, skin darkening does not occur	
	Investigations	• Low serum cortisol with low plasma ACTH • 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).	
	Confirmatory test	**Depot synacthen test**	

MCQs

1- From which zone is cortisol secreted?			
A-Zona Glomerulosa	B-Zona Reticularis	C-Zona Fasiculata	D-All cortex
2- 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
3-After performing the depot Synacthen test, what is the expected result in a patient with addison's disease?			
A- Stepwise increase in serum cortisol	B- No rise in serum cortisol	C- Decrease in serum cortisol	D- All of them could occur
4-A 55 year old patient came to the ER complaining of hyperpigmentation, hypotension, and weight loss. What is the most likely diagnosis?			
A-Secondary AC hypofunction.	B- AC hyperfunction.	C-Primary AC hypofunction.	D-Hyperthyroidism
5- 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.
6-Which of the following describes 2ry AC insufficiency?			
A-High Serum cortisol & Normal Plasma ACTH.	B- Low serum cortisol & sky high Plasma ACTH.	C-Increased serum cortisol & Increased Urinary cortisol.	D-Low serum cortisol with low plasma ACTH.

Answers key

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

SAQs

1- Name the three zones of adrenal cortex and mention the hormones they secrete .

Answer
1- Zona Glomerulosa (mineralocorticoids)
2- Zona fasciculata (Glucocorticoids)
3- Zona reticularis (Sex hormones)

2- Name 3 tests that are used to confirm the diagnosis of Addison's disease?

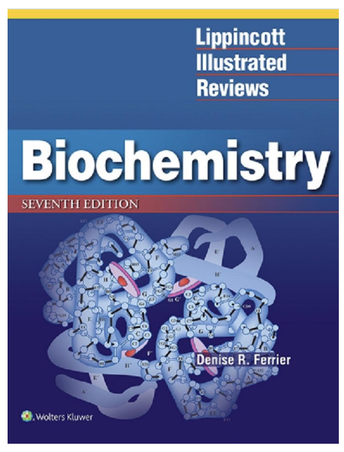
Answer
1. Short Synacthen (tetracosactrin) test (Short ACTH stimulation test)
2. Adrenal Antibodies
3. Imaging (CT, Ultrasound)

3- Mention 3 causes of Adrenocortical Hypofunction (AC)?

Answer
1. Autoimmune
2. Infection: TB
3. Infiltrative lesions: amyloidosis

Resources

Click on the book to download the resource



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Special thanks to Fahad AlAjmi for designing our team's logo.