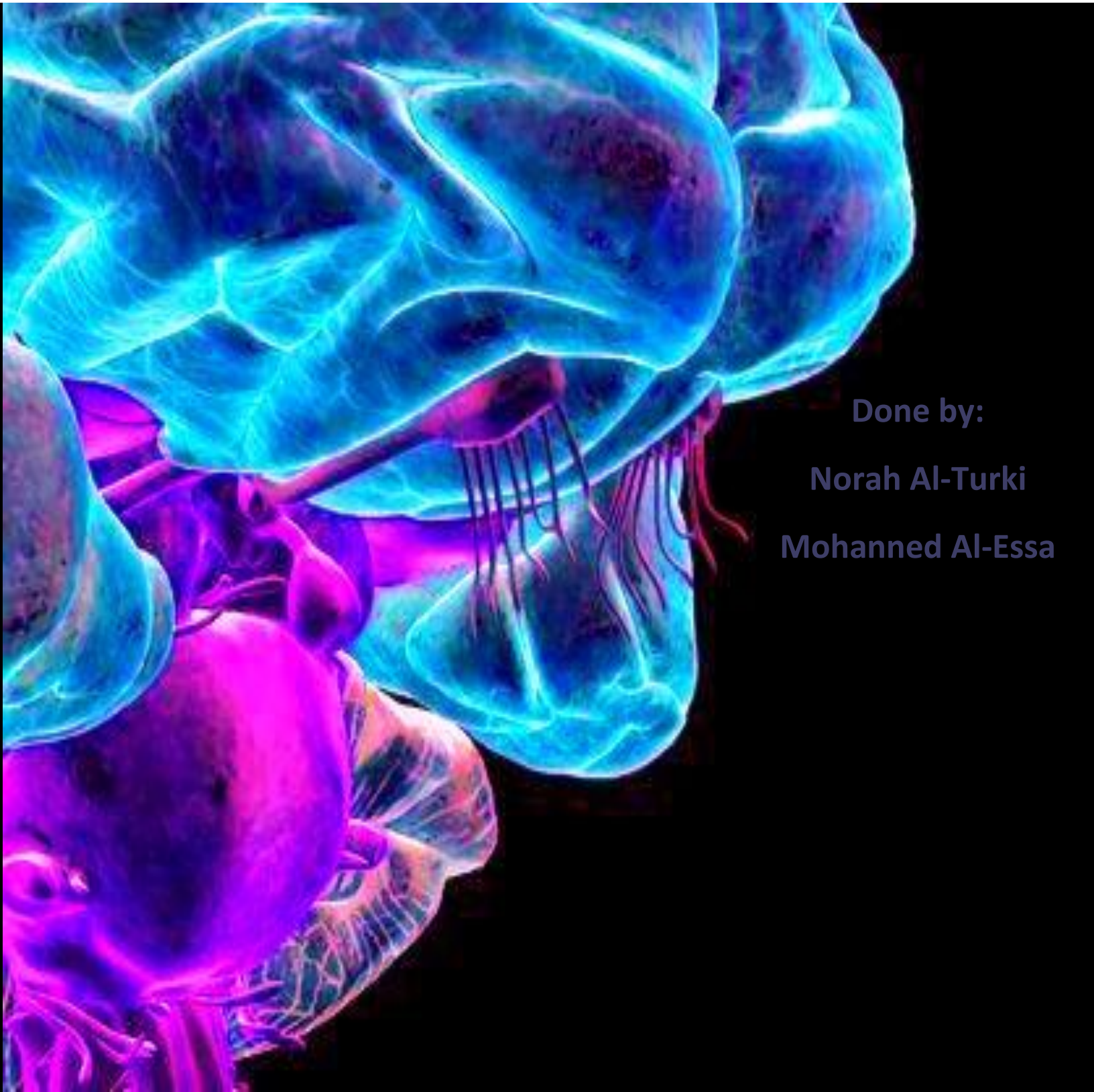
Biochemistry of Addison's Disease



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As we already know:

Anatomically:

- The adrenal gland is situated on the anteriosuperior aspect of the kidney and receives its blood supply from the adrenal arteries.

Histologically:

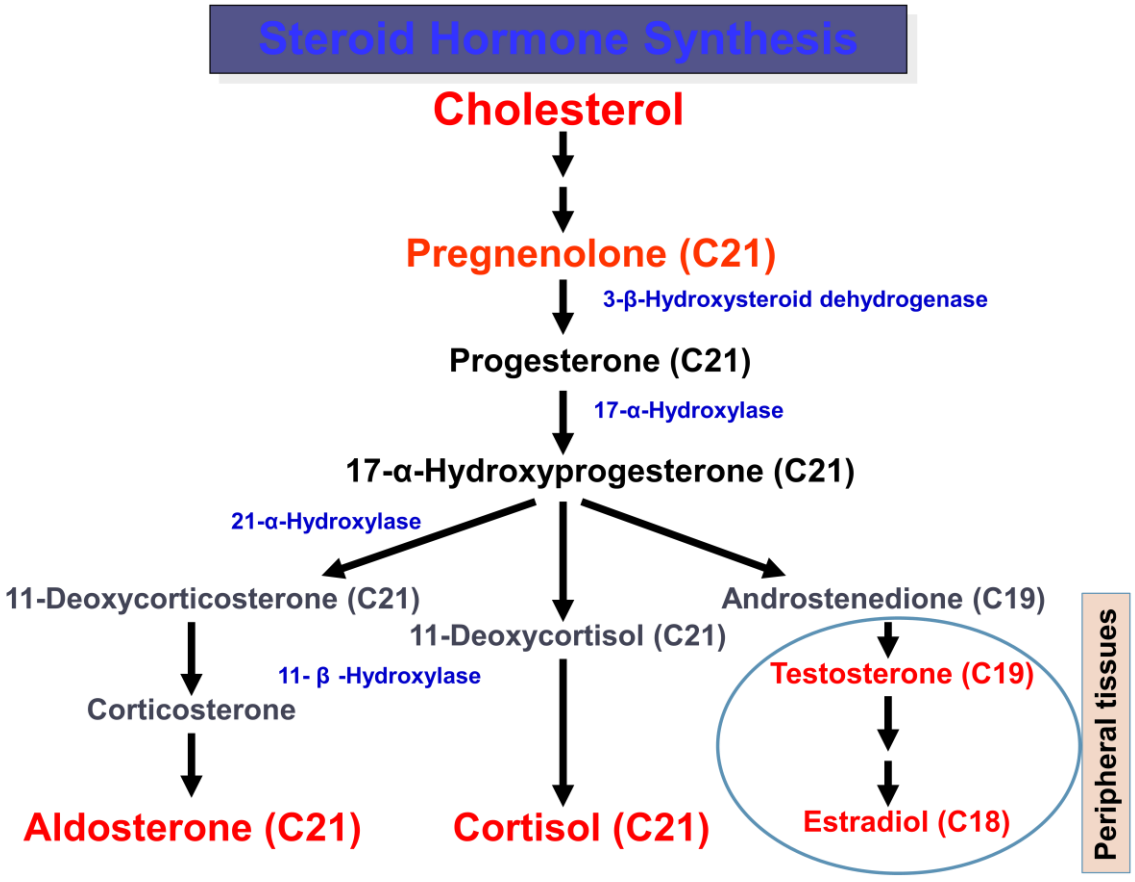
- The adrenal gland consists of two distinct tissues of different embryological origin, the outer cortex and inner medulla.

The adrenal cortex comprises three zones based on cell type and function:

- Zona glomerulosa: The outermost zone → aldosterone (the principal mineralocorticoid).

The deeper layers of the cortex:

- Zona fasciculate: → glucocorticoids – mainly cortisol (95%)
- Zona reticularis: → Sex hormones



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.
- Aldosterone is a major regulator of water and electrolyte balance, as well as blood pressure.
- Aldosterone, 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 for aldosterone** secretion

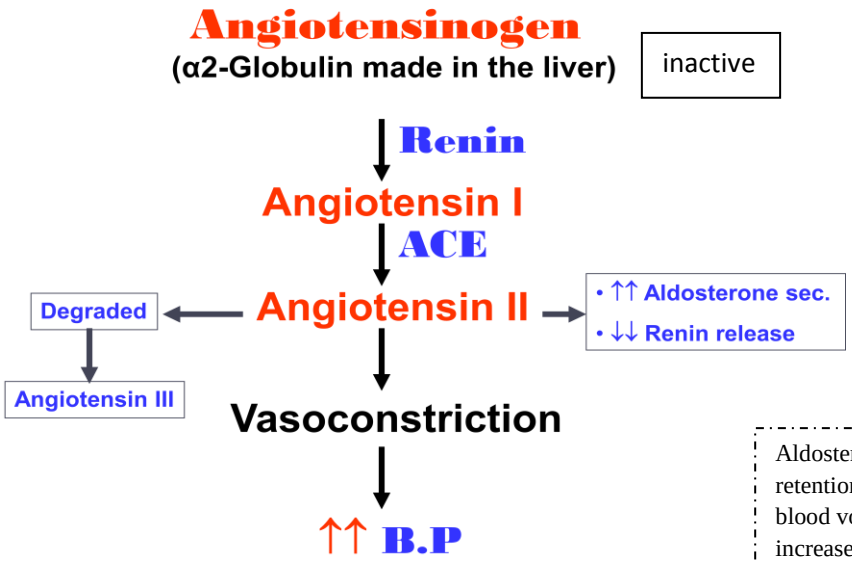
Renin-Angiotensin system → regulates aldosterone. (Aldosterone accounts for 1% of Adrenal gland secretion in comparison to Cortisol)
Hypothalamo-pituitary adrenal axis → regulates cortisol.

The renin - angiotensin system:

- It is the most important system controlling aldosterone secretion.
- It is involved in B.P. regulation.

Renin:

- a proteolytic (catalyzes protein) 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 :
  - a fall in circulating blood volume. (as in hemolysis)
  - a fall in renal perfusion pressure.
  - loss of Na^+.



Aldosterone will increase water retention, leads to increase blood volume which will cause increase in blood pressure

Causes of Adrenocortical Hypofunction: (aldosterone is low)

A. Primary destruction of adrenal gland: (Increased ACTH >> Leads to pigmentation)

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

B. Secondary to pituitary disease: (adrenal gland is intact)

- Pituitary tumors (↓ACTH → ↓aldosterone)
- Vascular lesions
- Trauma
- Hypothalmic diseases
- Iatrogenic (steroid therapy, surgery or radiotherapy)

As a result of low ACTH, the adrenal gland will be atrophied, which will lead to inability of the adrenal cells to produce aldosterone. (Indirect effect of ACTH on aldosterone secretion)

Steroid Therapy (Long term): will cause suppression to ACTH secretion which will lead to Atrophy of adrenal gland.

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) → same as in Cushing
Deficiency of both glucocorticoids and mineralocorticoids (Mainly mineralcorticoids)
Hypoglycemia, **↓ Na^+, ↑ K^+** and raised urea
Life threatening and need urgent care. (Replacement therapy needed)

- The highlighted ones are IMPORTANT to differentiate between **Addison's disease** and **Cushing Syndrome.**
-In the exam, we will get a case and the investigations will show

Na^+ is below the reference range
K^+ is increased
Hypoglycemia
} Hypofunction → **Addison** "YOU SHOUD NOT GET THIS WRONG"

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.
In secondary adrenocortical insufficiency, skin darkening does not occur. (Because the ACTH is already low)

So, there is hyperpigmentation in: 1. Cushing 2. Primary Addison

In **A**ddison (primary) = problem in **A**drenal (hypofunction)
In Cushing = problem in Pituitary (hyperfunction) "mainly".

Investigation of Addison's disease (AD)

- The patient should be hospitalized
- Basal measurement of:
  Serum urea, (↓)Na^+, (↑)K^+ &(↓)glucose
  Serum cortisol and plasma ACTH
  (In primary; high ACTH and low cortisol < 'cause no negative feedback, Secondary; low ACTH and low cortisol)
- Definitive diagnosis and confirmatory tests should be done later after crisis.
- Normal serum cortisol and UFC does not exclude AD. *UFC: urinary free cortisol

The hospitalization of the patient is to stabilize the patient's condition (severe hypotension & electrolyte imbalance) . After stabilizing pts condition, investigations can be done

When normal values are shown it doesn't exclude Addison's because pt might sometimes show normal values and no crises will appear when pt is not under stress. To confirm Addison's when normal values are shown, patient is put under stress, patient of Addison's will go through crises.

- Simultaneous measurement of cortisol and ACTH improves the accuracy of diagnosis of primary adrenal failure:
  Low serum cortisol (<200nmol/L) and **high** plasma ACTH (>200 ng/L) → **Primary Addisons**

- Simultaneous measurement means that we measure the cortisol and ACTH every two hours for example.

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 primary Addisons.
- Abnormal results:
  - emotional stress
  - glucocorticoid therapy
  - estrogen contraceptives.

- Tetra = 4, Cosactrin = 20 → **Tetracosactrin** = 24 amino acids
- **Synacthen:** synthetic ACTH
- The ACTH stimulation test (also called the cosyntropin test, tetracosactide test or Synacthen test) is a medical test usually ordered and interpreted by endocrinologists to assess the functioning of the adrenal glands stress response by measuring the adrenal response to adrenocorticotropic hormone (ACTH)
- **S. cortisol:** Serum cortisol

2. Adrenal antibodies

- Detection of adrenal antibodies in serum of patients with autoimmune Addison's disease (also detection of TB)

3. Imaging (Ultrasound/CT)

Ultrasound or CT for adrenal glands for identifying the cause of primary adrenal failure (Tumor or non-functioning adenoma)

Investigation of Secondary AC Insufficiency

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

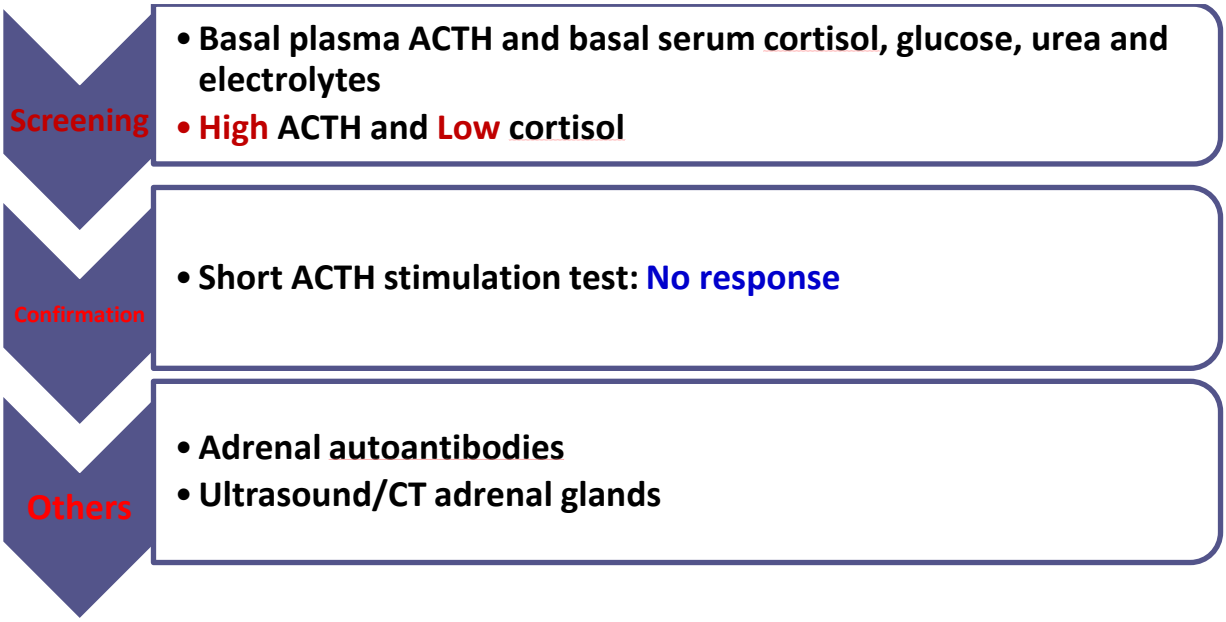
- Addison's disease: No rise of S. cortisol >600 nmol/L at 5 h after 3rd injection.
- Secondary AC: Stepwise increase in the S. cortisol after successive injections (gradual increase)
- Limitations:

  Hypothyroidism: Thyroid deficiency must be corrected before testing of adrenocortical functions

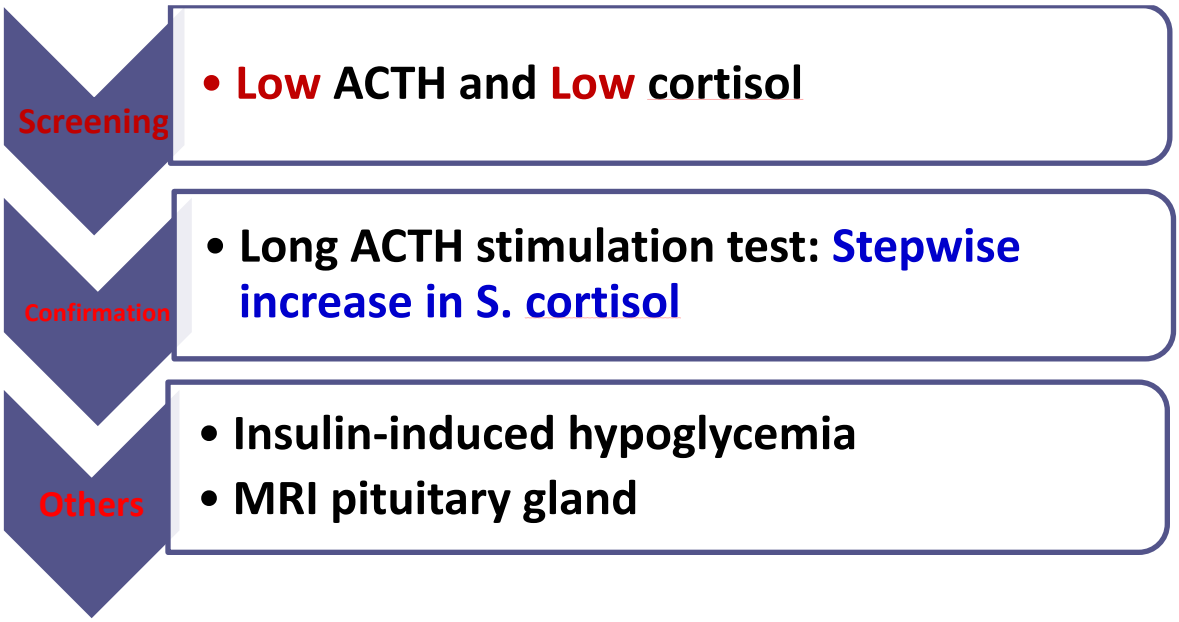
  Prolonged steroid therapy

- **Insulin-induced hypoglycemia:**
  Adrenal failure secondary to pituitary causes (Test Hypothalamic-pituitary-adrenal axis)
- **MRI for pituitary gland**

Investigation for Addison's disease



Investigation for Secondary AC Insufficiency



Summary:

- Aldosteron's main function is to conserve Na^+ by Na+ reabsorption & K^+ or H^+ secretion.
- Aldosterone is a major regulator of water and electrolyte balance, as well as blood pressure.
- Renin-Angiotensin system is the **most important regulatory mechanism for aldosterone** secretion
- Renin is a proteolytic (catalyzes protein) enzyme produced by the **juxtaglomerular cells** of the afferent renal arteriole.
- Hypotension especially on standing (postural), **Hypoglycemia**, **↓ Na^+, ↑ K^+** and raised urea & Hyperpigmentation (Primary Addison's) are very important symptoms of Addison's Disease.
- Hypotension, Hypoglycemia, Hyponetremia, & Hyperkalemia are important to differentiate between Addison's & Cushing's.
- Hyperpigmentation occus in Primary Addison's because ACTH & MSH share the POMC.
- Basal measurement of plasma cortisol & ACTH for investigating Addison's will show:
  - In primary; high ACTH and low cortisol < 'cause no negative feedback
  - Secondary; low ACTH and low cortisol
- Confirmatory tests (primary AD):
  - Short tetracosactrin (Synacthen) test (Short ACTH stimulation test) [Failure of S. cortisol to respond to stimulation, confirm primary Addisons]
  - Adrenal antibodies
  - Imaging (Ultrasound/CT)
- Investigation of Secondary AC Insufficiency:
  - Low serum cortisol with low plasma ACTH **(Gold standard)**
  - **Depot Synacthen test (confirmatory test):**
    - ✓ 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 (gradual increase)
  - Insulin-induced hypoglycemia
  - MRI for pituitary gland