Adrenal insufficiency

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Outlines

- **Introduction :struction and function of adrenal cortex**
- **Adrenal insufficiency**

❑Definition

❑Causes

❑Clinical features

❑Investigation and diagnosis

❑Treatment

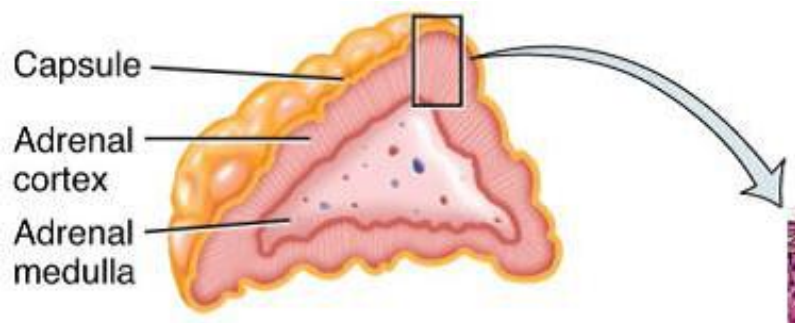
- **Adrenal crisis**

Adrenal gland

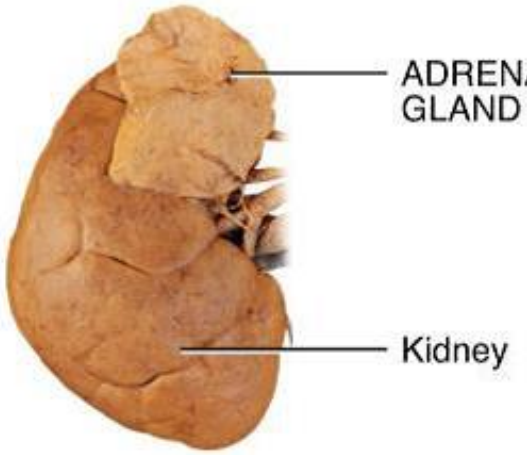
Anatomy

- Normal adrenal glands weigh 4–5g. cortex represents 90% of normal gland and surrounds the medulla.
- Arterial blood supply arises from renal arteries, aorta, and inferior phrenic artery. Venous drainage into the inferior vena cava on right and into left renal vein on left

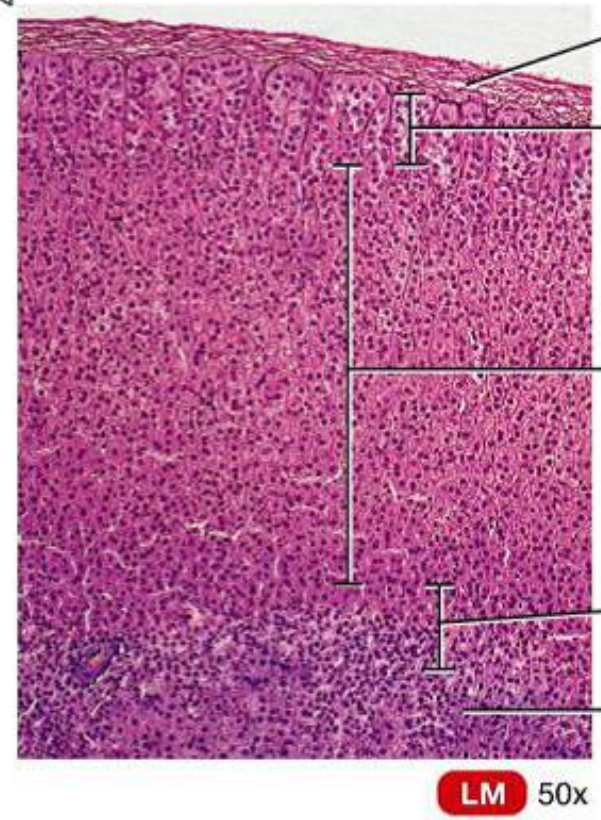
Adrenal gland



(b) Section through left adrenal gland



(c) Anterior view of adrenal gland and kidney



Capsule

Adrenal cortex:

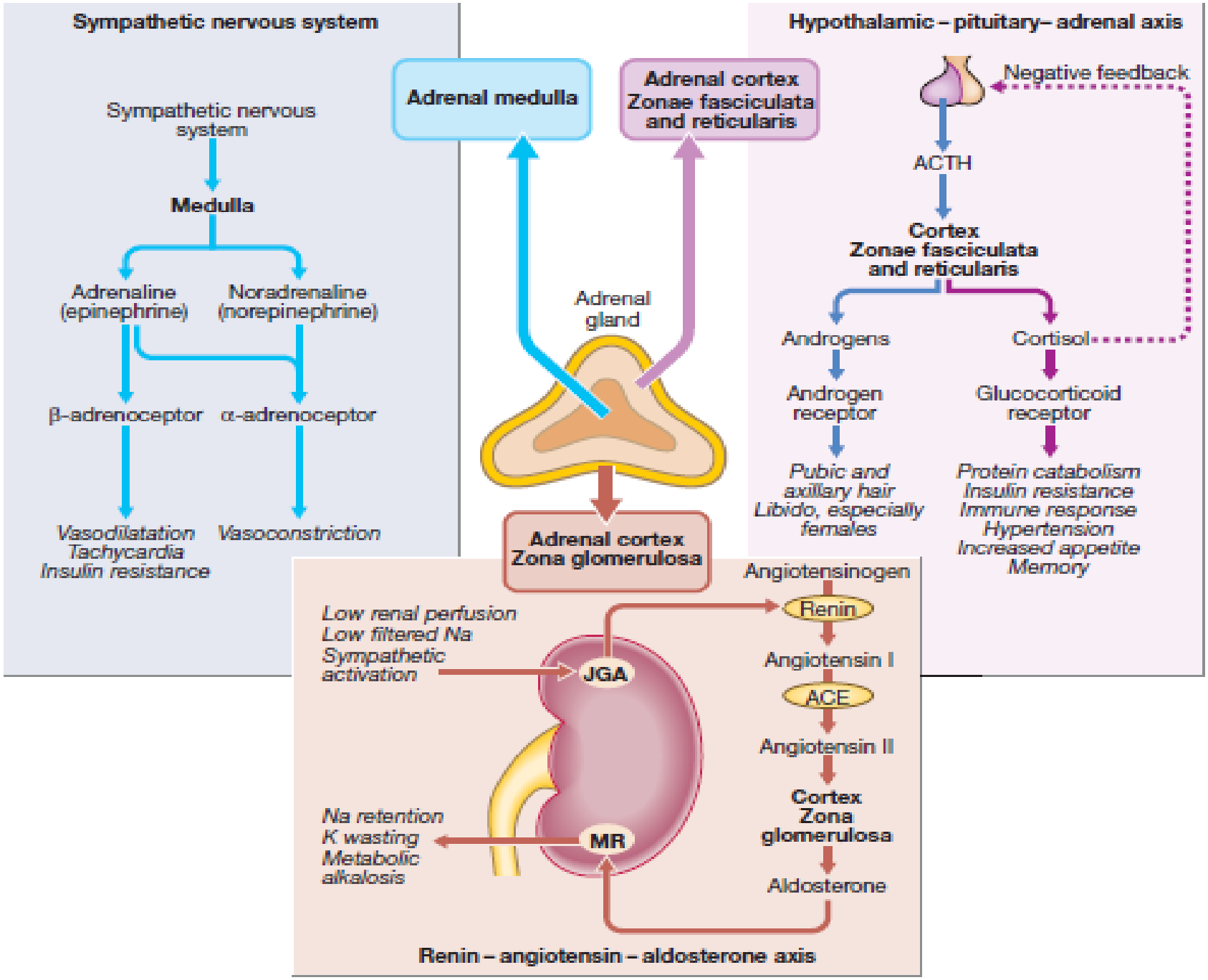
Zona glomerulosa secretes mineralocorticoids, mainly aldosterone

Zona fasciculata secretes glucocorticoids, mainly cortisol

Zona reticularis secretes androgens

Adrenal medulla chromaffin cells secrete epinephrine and norepinephrine (NE)

(d) Subdivisions of adrenal gland


Sympathetic nervous system
Sympathetic nervous system
Medulla
Adrenaline (epinephrine)
Noradrenaline (norepinephrine)
β-adrenoceptor
α-adrenoceptor
Vasodilatation
Tachycardia
Insulin resistance
Vasoconstriction
Adrenal medulla
Adrenal cortex
Zonae fasciculata and reticularis
Adrenal gland
Adrenal cortex
Zona glomerulosa
Hypothalamic – pituitary– adrenal axis
Negative feedback
ACTH
Cortex
Zonae fasciculata and reticularis
Androgens
Cortisol
Androgen receptor
Glucocorticoid receptor
Pubic and axillary hair
Libido, especially females
Protein catabolism
Insulin resistance
Immune response
Hypertension
Increased appetite
Memory
Angiotensinogen
Renin
Angiotensin I
ACE
Angiotensin II
Cortex
Zona glomerulosa
Aldosterone
Low renal perfusion
Low filtered Na
Sympathetic activation
JGA
Na retention
K wasting
Metabolic alkalosis
MR
Renin – angiotensin – aldosterone axis

Glucocorticoids

- **Cortisol**

➢ Controlled by **HPA** axis

➢ **H**ypothalamus →CRH and arginine vasopressin in circadian rhythm (max in early am)

➢ Anterior **P**ituitary →ACTH

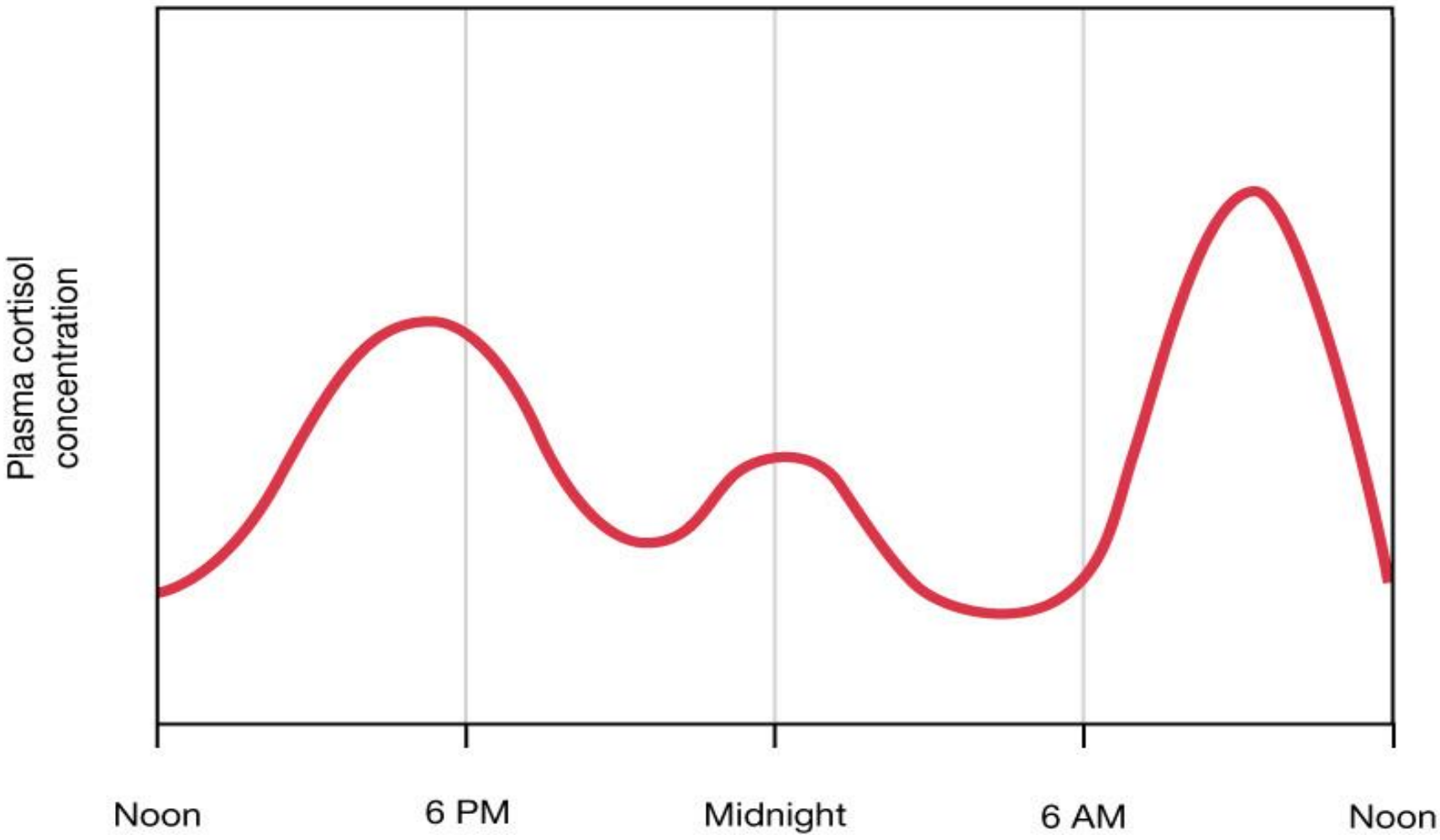
➢ **A**drenal cortex → cortisol

➢ Peak at 8 am; declines throughout day

➢ 25mg produced daily (non-stressed)

➢ Negatively feeds back to control hypothalamus

Circadian rhythm of cortisol secretion



Glucocorticoids action

- Metabolic homeostasis

- Regulate blood glucose level :increase gluconeogenesis, Increase glycogen synthesis,increase insulin resistant
- increase protein degradation, The released amino acids are mobilized from skeletal muscle to liver, for gluconeogenesis.
- Mobilization of stored fat ,oxidation of fatty acid and the production of ketone bodies

- Calcium homeostasis

- Stimulate osteoclasts, inhibit osteoblasts
- Reduce intestinal calcium absorption, stimulate parathyroid hormone release, increase urinary calcium excretion

Glucocorticoids action

- Cardiovascular effect

➢ Increase cardiac contractility and output

➢ Increase vascular tone by increase Catecholamine and b-adrenergic receptor synthesis

- Anti-inflammatory Effects

➢ Inhibit production of prostaglandins and leukotrines

➢ Decrease the inflammation reaction by decreasing permeability of capillary membranes, reducing swilling

➢ reduce effects of histamine

Mineralocorticoids

- Aldosteron is primarily involved with fluid and electrolyte balance.
- Aldosteron secretion causes Na+ reabsorption in distal renal tubule in exchange for K+ and H+
- net effects are, fluid retention, decrease in plasma potassium and metabolic alkalosis
- Aldosteron secretion is stimulated by: Reninangiotensinsystem, Hyperkalemia, Hypovolemia, and Hypotension
- aldosterone 100–150 micrograms/day

Adrenal androgens

- Most gonadocorticoids secreted are androgens mainly dehydroepiandrosterone (DHEA)
- Secreted in response to ACTH
- Androgens contribute to:

✓ The onset of puberty

✓ The appearance of secondary sex characteristics

✓ Sex drive in females

Adrenal insufficiency

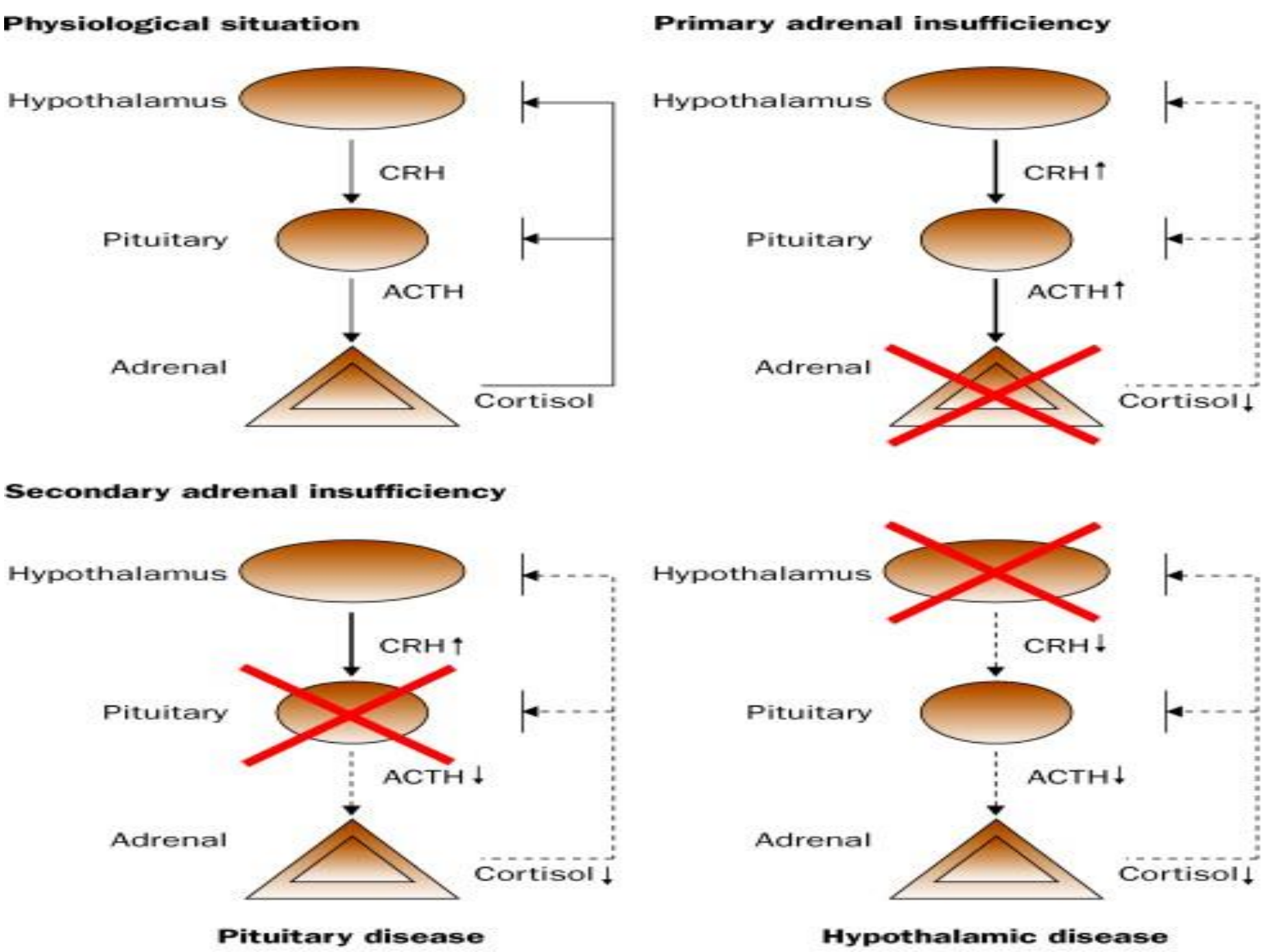
- Adrenal insufficiency results from inadequate secretion of cortisol and/or aldosterone
- It is potentially fatal and variable in its presentation.
- A high index of suspicion is required in patients with unexplained fatigue, hyponatraemia or hypotension.

Adrenal Insufficiency

- **Primary** : failure of adrenal glands
- **Secondary** :failure of HPA axis

– Usually due to chronic exogenous glucocorticoid administration

– Pituitary or hypothalamus dysfunction


Physiological situation
Hypothalamus
CRH
Pituitary
ACTH
Adrenal
Cortisol
Primary adrenal insufficiency
Hypothalamus
CRH↑
Pituitary
ACTH↑
Adrenal
Cortisol↓
Secondary adrenal insufficiency
Hypothalamus
CRH↑
Pituitary
ACTH↓
Adrenal
Cortisol↓
Pituitary disease
Hypothalamus
CRH↓
Pituitary
ACTH↓
Adrenal
Cortisol↓
Hypothalamic disease

Primary Adrenal Insufficiency (Addison's disease)

- **Loss of all three types of adrenal steroids**
- **90% of glands must be destroyed to manifest Clinically**
- **Ch. By ↑ACTH**

Common causes

- **Autoimmune:Sporadic/ Polyglandular syndromes)**
- **Tuberculosis**
- **HIV**
- **Metastatic carcinoma**
- **Bilateral adrenalectomy**
- **Corticosteroid synthesis reduction**

✓ Congenital adrenal hyperplasia

✓ Drugs: metyrapone, ketoconazole

Rare causes

- **Lymphoma**
- **Intra-adrenal haemorrhage**

(Waterhouse–Friderichsen syndrome following meningococcal sepsis)

- **Amyloidosis**
- **Haemochromatosis**

Secondary Adrenal Insufficiency

- HPA axis failure
  - deficiency of glucocorticoids and adrenal androgens
  - mineralcorticoids are unaffected
  - Ch. By low ACTH

- **Commonest cause is chronic exogenous glucocorticoid**
  - suppresses CRH release
  - both time- and dose-related
  - reversible
  - recovery may take up to a year

Secondary Adrenal Insufficiency

- **Less common causes**

- Pituitary tumors
- Mass lesions affecting the hypothalamic-pituitary region: Craniopharyngioma, meningioma, metastases
- Pituitary irradiation
- Autoimmune hypophysitis
- Pituitary apoplexy/hemorrhage
- Pituitary infiltration (TB, actinomycosis, sarcoidosis, histiocytosis X, Wegener's granulomatosis)

Epidemiology

- Permanent adrenal insufficiency is found in 5 in 10,000 population.
- The most frequent cause is hypothalamic–pituitary damage (60%) .
- Remaining 40% due to primary adrenal failure

- Secondary adrenal insufficiency due to suppression of HPA axis by exogenously administered, supraphysiological glucocorticoid is much more common (50–200 in 10,000 population).

Clinical features

Due to glucocorticoid insufficiency

Seen in both primary and secondary adrenal insufficiency

- Weight loss
- Malaise
- Weakness
- Anorexia
- Nausea
- Vomiting
- diarrhoea

- Postural hypotension
- Hypoglycaemia (increased peripheral utilization of glucose and increased insulin sensitivity)
- Hyponatraemia (SAIDH)
- Hypercalcaemia(cause is not well understood, may be present in a small percentage of patients).

Clinical features

- **Due to mineralocorticoid insufficiency**

Seen mainly in primary adrenal insufficiency

Hyperkalaemia,hyponatremia ,hypotension

- **Due to Adrenal androgen insufficiency**

Seen in primary adrenal insufficiency

Decreased body hair and loss of libido,especially in females

Clinical features

Due to ACTH excess

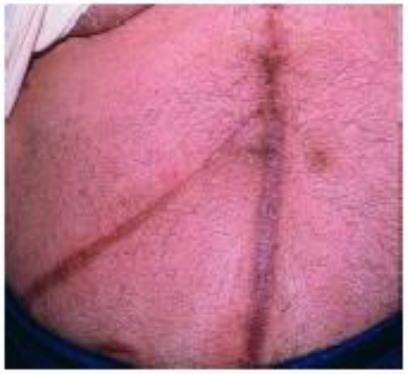
Seen only in primary adrenal insufficiency

Pigmentation:Sun-exposed areas,Pressure areas, e.g. elbows, knees,Palmar creases ,Knuckles ,Mucous membranes ,and Recent scars

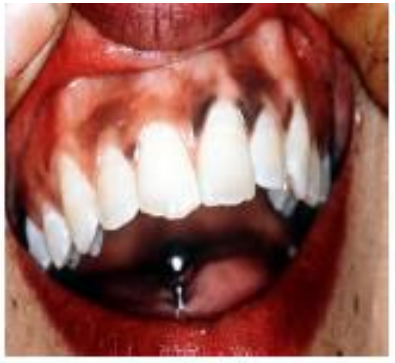
Due to deficiency of ACTH

Seen in secondary adrenal insufficiency

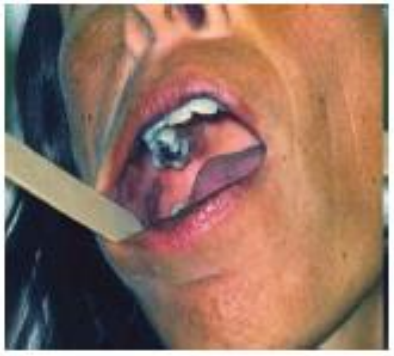
Pallor out of proportion to anemia

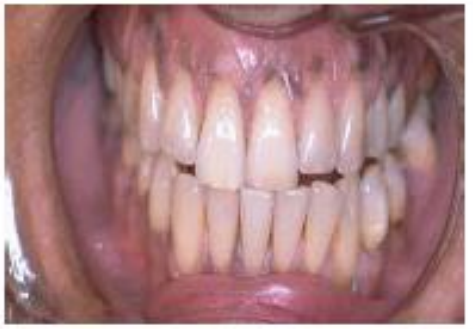


Pigmentation of scars

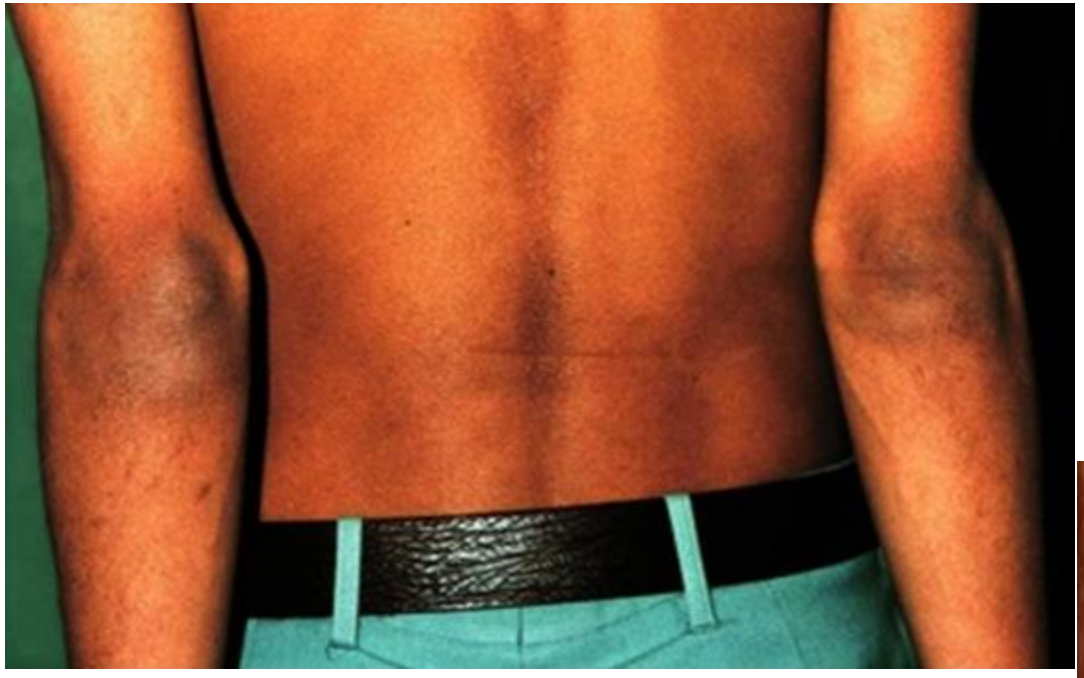


Hyperpigmented gingival

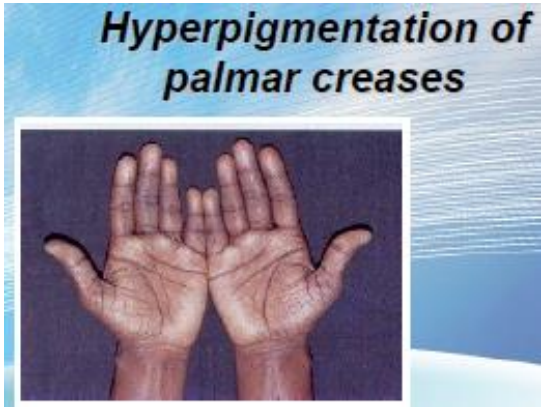


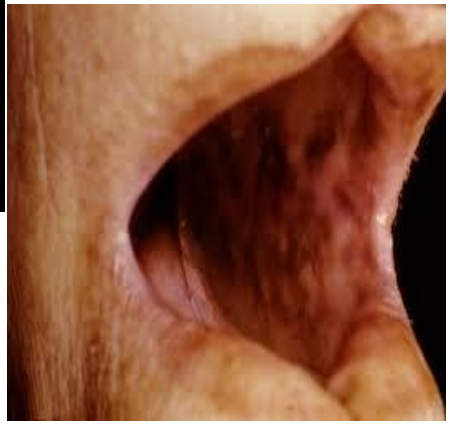


Pigmentations of the maxillary anterior gingiva



Pigmentation of elbows





Buccal pigmentation

Diagnosis of adrenal insufficiency

- A morning cortisol level of <3 mg/dL(83 nmol/L) is diagnostic
- A level of >18 mg/dL(500 nmol/l) should rule out Adrenal Insufficiency

- Normal cortisol dose not rule out the diagnosis and **short ACTH stimulation test** (Synacthen or cosyntropin test)is required to confirm the diagnosis

ACTH stimulation test

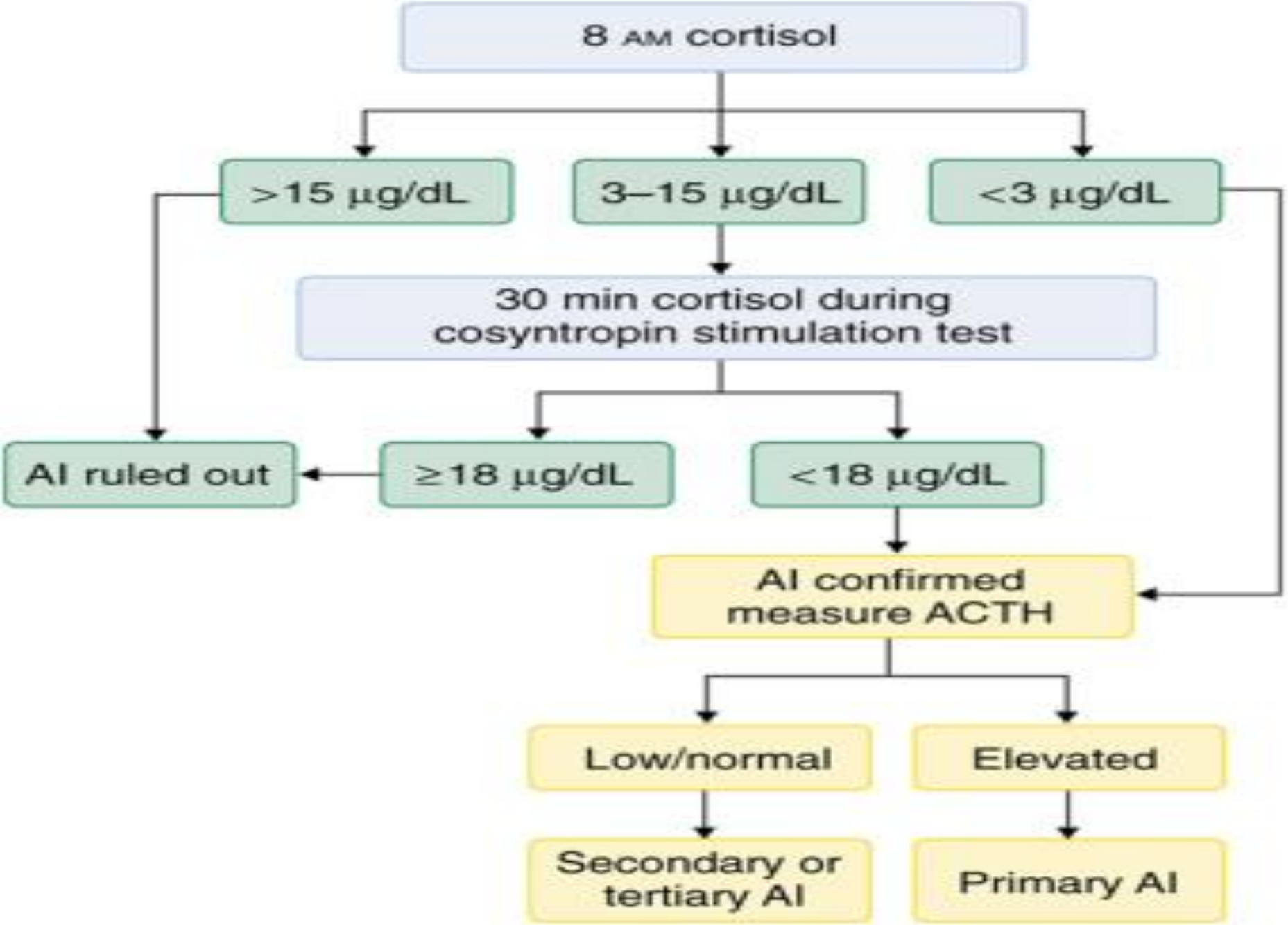
Method:

- 250 µg short acting ACTH (Synacthen) by IM injection
- Blood samples at 0 and 30 mins for plasma cortisol

Result:

- Normal subjects: plasma cortisol > 500 nmol/L (approximately 18 µg/dL) at 30 mins
- Patients with primary insufficiency will fail to respond to repeated administrations, however patients with secondary insufficiency may show an increased response to repeated testing/stimulation

- Primary and secondary adrenal insufficiency can be distinguished by measurement of ACTH (which is low in secondary adrenal insufficiency and high in Addison's disease.


8 AM cortisol
>15 µg/dL
3–15 µg/dL
<3 µg/dL
30 min cortisol during cosyntropin stimulation test
AI ruled out
≥18 µg/dL
<18 µg/dL
AI confirmed measure ACTH
Low/normal
Elevated
Secondary or tertiary AI
Primary AI

Other Investigation

CBC

Normocytic,normochromal anemia

Granulocytopenia,Eosinophilia,Lymphocytosis

Blood glucose-

Low or lower limit, specially during Addisonian crisis.

Electrolytes

Hyponatraemia.

Hyperkalaemia.

ABG

metabolic acidosis

Investigation to find out underlying causes

- **If primary adrenal insufficiency**
  - Screen for autoantibodies associated with autoimmune adrenalitis(Antibodies to 21-hydroxylase)
  - Adrenal imaging (ultrasound, MRI, CT)to detect: lesion, mass, infection, or hemorrhage of the adrenal gland
  - If an infectious etiology is suspected: screen for tuberculosis (chest x-ray) and HIV serology
- **If secondary adrenal insufficiency**
  - Head MRI: to detect pituitary destruction or compression (e.g., trauma, lesions, hemorrhage, tumors)
  - Test for other pituitary hormone deficiencies (e.g., TSH, LH,FSH, prolactin, GH)

Management

Patients with adrenocortical insufficiency always need glucocorticoid replacement therapy and usually, but not always, mineralocorticoid therapy.

There is some evidence that adrenal androgen replacement may also be beneficial in women

Glucocorticoid replacement

Adrenal replacement therapy consists of oral hydrocortisone (cortisol) 15–20 mg daily in divided doses, typically 10 mg on waking and 5 mg at around 1500 hrs.

These are physiological replacement doses that should not cause Cushingoid side-effects

Mineralocorticoid replacement

- Fludrocortisone is administered at the usual dose of 0.05–0.15 mg daily
- It is indicated for virtually every patient with primary adrenal insufficiency but is not needed in secondary adrenal insufficiency

Androgen replacement

- Androgen replacement with DHEAS (50 mg/day) is occasionally given to women with primary adrenal insufficiency who have symptoms of reduced libido and fatigue

Adrenal crisis

Definition

It is a medical emergency due to acute adrenocortical insufficiency

Precipitating Events

- Omission of medication
- Precipitating illness
  - Severe infection
  - Myocardial infarction
  - CVA
  - Surgery without adrenal support
  - Severe trauma
- Withdrawal of steroid therapy in a patient on long term steroid therapy (adrenal atrophy)

Clinical Presentation

- Nausea and vomiting
- Hyperpyrexia
- Abdominal pain
- Dehydration
- Hypotension and shock

Management of adrenal crisis

Correct volume depletion

- IV saline as required to normalise blood pressure and pulse
- **Fludrocortisone is not required during the acute phase of treatment**

Replace glucocorticoids

- IV hydrocortisone 100 mg stat, and 100 mg 4 times daily for first 12–24 hrs, Taper slowly over the next 72 h
- When oral feeds is tolerated change to oral replacement therapy

Correct other metabolic abnormalities

- Acute hypoglycaemia: IV 10% glucose

Identify and treat underlying cause

- Consider acute precipitant, such as infection

Advice to patients on glucocorticoid replacement therapy

Intercurrent stress

- Febrile illness: double dose of hydrocortisone

Vomiting

- Patients must have parenteral hydrocortisone if unable to take it by mouth

Surgery

- Minor operation: I V hydrocortisone 100 mg before surgery
- Major operation: IV hydrocortisone 100 mg 4 times daily for 24 hrs, then 50 mg 4 times daily until ready to take tablets

Bracelet and emergency pack

- Patients should carry bracelet engraved with the diagnosis
- Patients should be given a hydrocortisone emergency pack and trained in the self-administration of hydrocortisone(100 mg IM)

THANKS