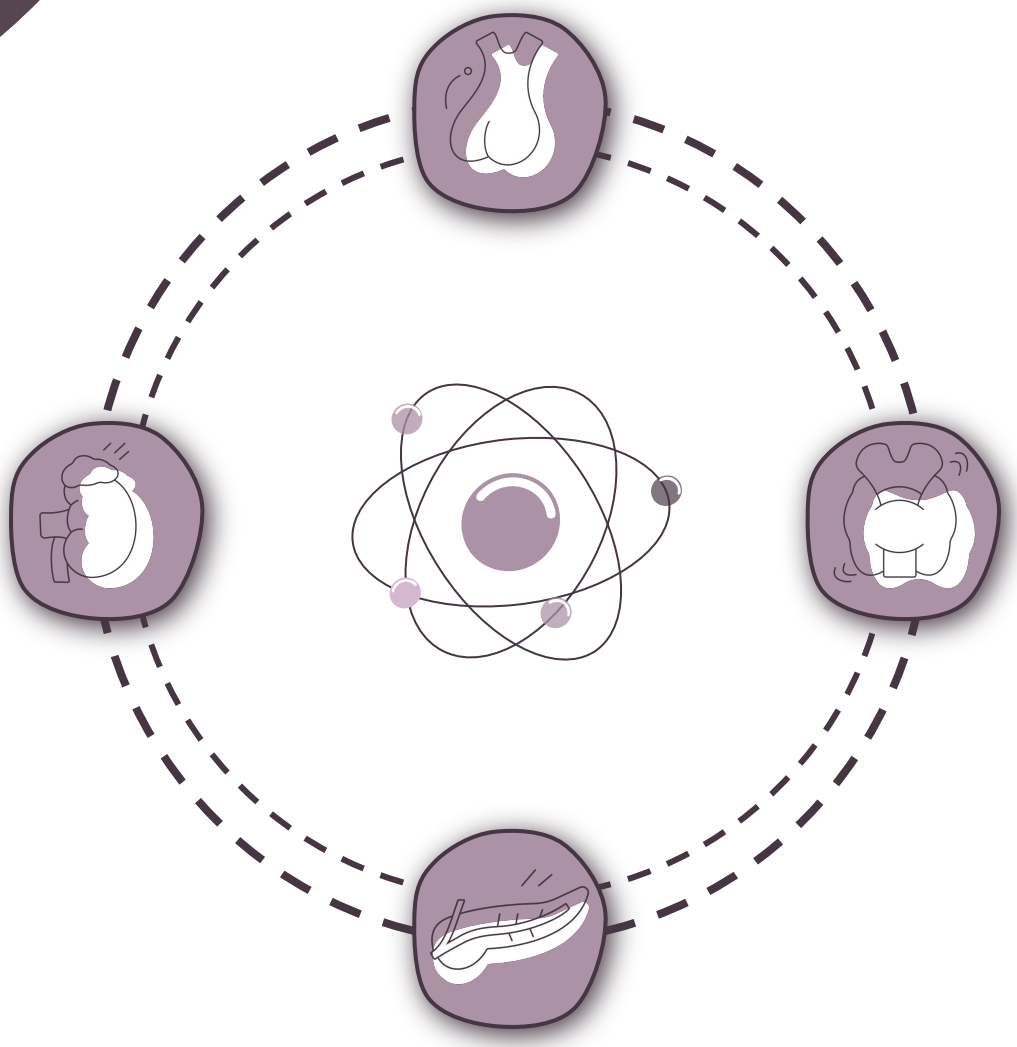

L4: Cushing syndrome

Presented by:
Dr. Ahmed & Dr. Rana

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Objectives

1. **To identify physiological and biochemical characteristics of cortisol.**
2. **To understand the diagnostic algorithm for cushing's syndrome.**
3. **To understand the interpretation of laboratory and radiological investigations for diagnosis of cushing's syndrome.**
4. **To identify different causes of Cushing's syndrome.**

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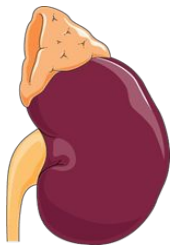
1

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, the outer cortex and inner medulla.

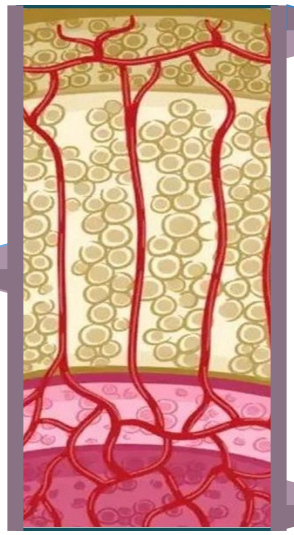
THE ADRENAL CORTEX

comprises three zones based on cell type and function

Zona Glomerulosa

-the outermost zone

-aldosterone (the principal mineralocorticoid).



Zona Fasciculata

glucocorticoids

(mainly cortisol 95%)

Zona Reticularis

sex hormones

Hypothalamic Pituitary-Adrenal (HPA) Axis

The hypothalamus secrete corticotropin releasing hormone (CRH)

The CRH stimulate the anterior pituitary gland to secrete ACTH

ACTH acts on the zona fasciculate cells

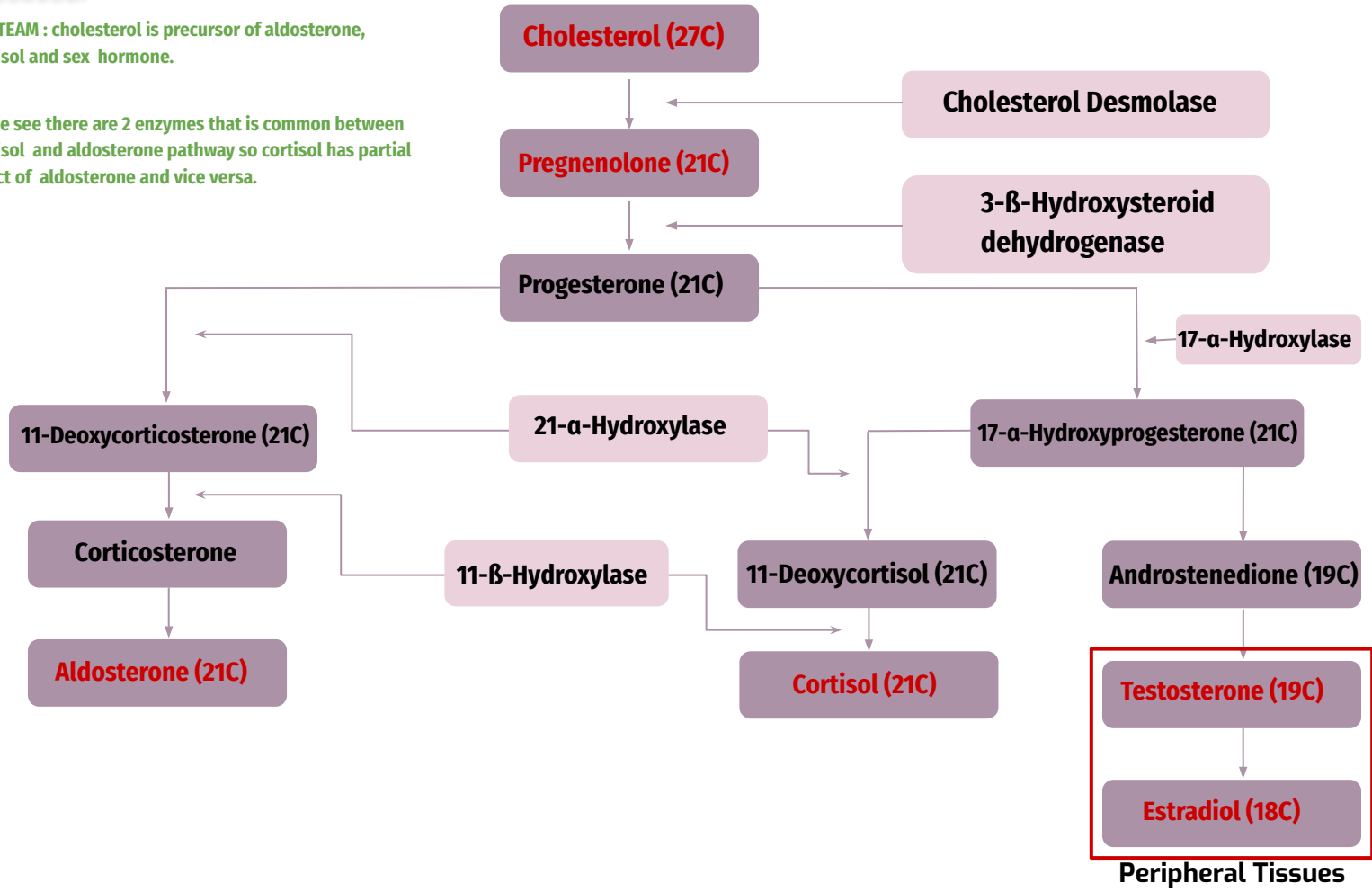
Release of glucocorticoids (cortisol)

2

Steroid Hormone Synthesis

439 TEAM : cholesterol is precursor of aldosterone, cortisol and sex hormone.

As we see there are 2 enzymes that is common between cortisol and aldosterone pathway so cortisol has partial effect of aldosterone and vice versa.

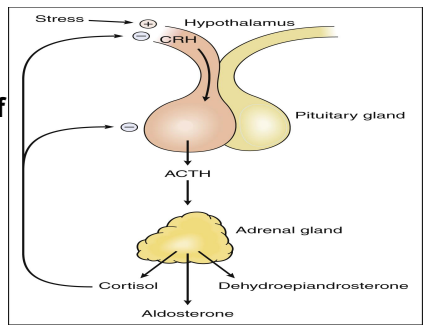


Regulation of ACTH and Cortisol Secretion

1

Negative feedback control

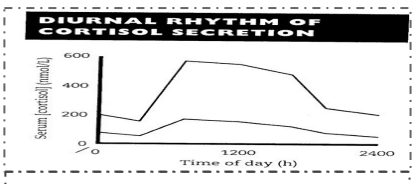
-ACTH release from the anterior pituitary is stimulated by hypothalamic secretion of corticotrophin releasing hormone (CRH).
-CRH → ↑ ACTH ↑(Cortisol)
- ↑(Cortisol) or synthetic steroid suppress CRH & ACTH secretion



2

Stress

E.g. major surgery, emotional stress and acute illness Stress → ↑↑CRH & ACTH →↑↑Cortisol



The diurnal rhythm of cortisol secretion; the area between the curves represents values that lie within the reference range.

3

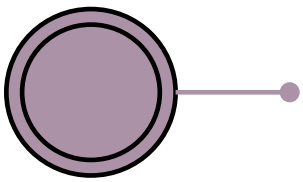
The diurnal rhythm of serum cortisol

-Highest Cortisol level in the morning (8-9 AM).

-Lowest Cortisol level in the late afternoon and evening (8-9 PM)

3

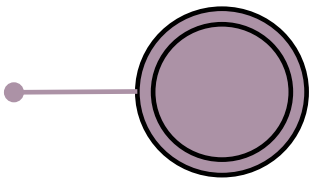
Plasma Cortisol Binding Globulin (CBG)

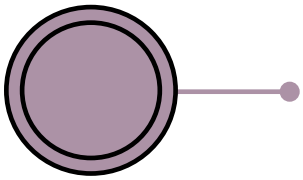


In the circulation, glucocorticoids are mainly protein-bound (about 90%), chiefly to cortisol-binding globulin CBG (transcortin).

- ↑↑ In pregnancy and with estrogen treatment (e.g. oral contraceptives)

-↓↓ In hypoproteinemic states (e.g. nephrotic syndrome),





The biologically active fraction of cortisol in plasma is the free (unbound) component.

Glucocorticoid Functions

Glucocorticoids have widespread metabolic effects on carbohydrate, fat and protein metabolism

Upon binding to its target, CORTISOL enhances metabolism in several ways:

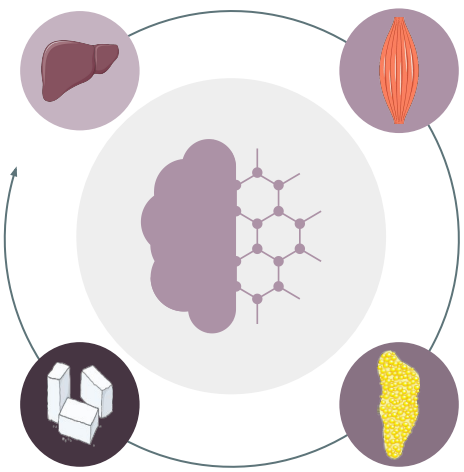
LIVER

Cortisol is an insulin antagonist and has a weak mineralocorticoid action:

1- ↑↑ Gluconeogenesis → production of glucose from newly-released amino acids and lipids

2- ↑↑ Amino acid uptake and degradation

3- ↑↑ Ketogenesis



MUSCLE

Cortisol → ↑↑ proteolysis and amino acid release.

Amino acids will be reuptaken by liver

Cortisol → ↑↑ Lipolysis through breakdown of fat

(producing fatty acid + TAG + ketone bodies)

Adipose tissue

By inhibiting uptake into muscle and fat cells

(leading to hyperglycemia)

Conserving glucose

4

Cortisol and ACTH Measurements

Serum (cortisol) and plasma(ACTH)

- Serum measurement is preferred for cortisol and Plasma for ACTH.
- Sample must be collected (without venous stasis) between 8a.m and 9a.m. and between 10p.m. and 12a.m. because of the diurnal rhythm.
- Temporary ↑↑ in these hormones may be observed as a response to emotional stress

Urinary cortisol excretion

- Cortisol is removed from plasma by the liver → metabolically inactive compound → excreted in urine mainly as conjugated metabolite (e.g. glucuronide).
- A small amount of cortisol is excreted unchanged in the urine (UFC).
- In normal individual:
  - Urinary free cortisol (UFC) is < 250 nmol/24h.
  - -Cortisol / Creatinine ratio in an early morning specimen of urine is < 25 µmol cortisol / mol creatinine.

Causes of Elevated Serum Cortisol

Increased cortisol secretion

- Cushing's syndrome
- Excessive Exercise
- Stress, Anxiety, Depression
- Obesity
- Alcohol abuse
- Chronic renal failure.

VS

Increased CBG

- Congenital
- Estrogen therapy
- Pregnancy

Causes of Adrenocortical Hyperfunction (Cushing's Syndrome)

ACTH-dependent

1-↑ Pituitary ACTH >90% - 70% (Cushing's disease)

2-Ectopic ACTH by neoplasm <10% (not from hypothalamic pituitary-adrenal axis e.g. lung cancer)

ACTH-independent

1- Adrenal Tumor <20%(adenoma or carcinoma)

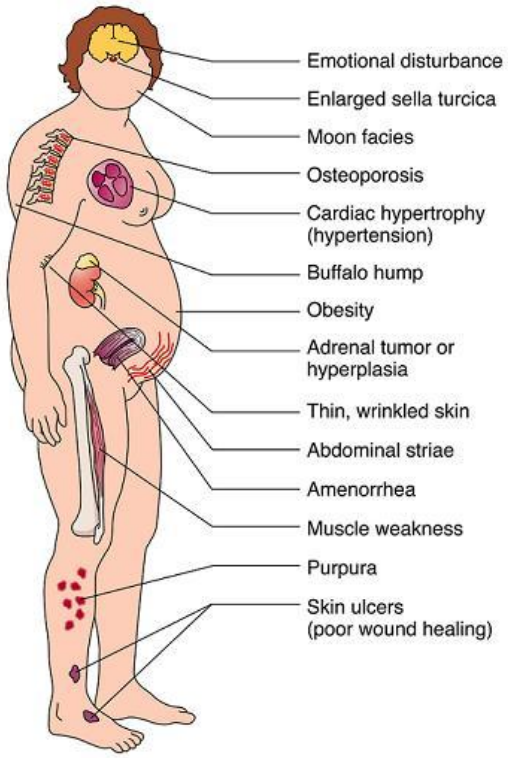
2- Glucocorticoid therapy

5

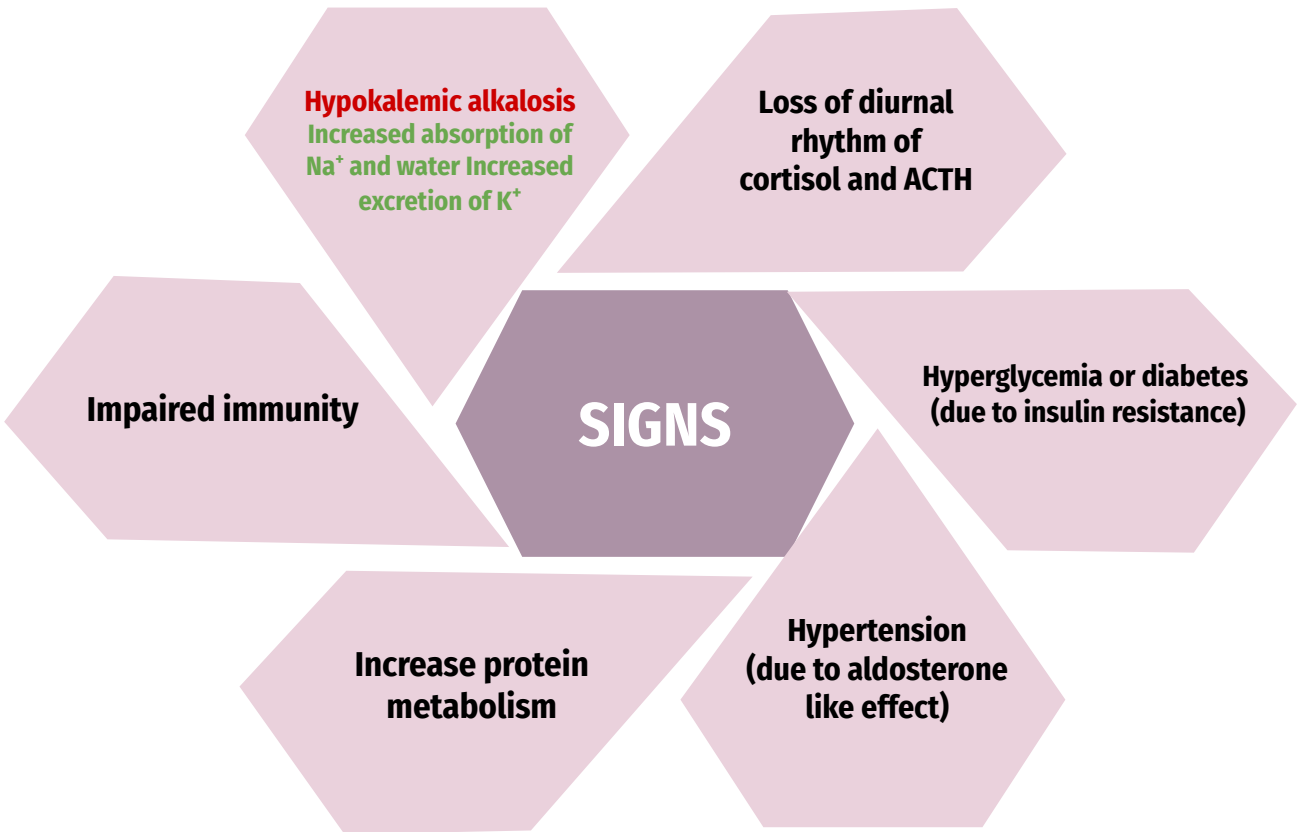
Symptoms of Cushing's Syndrome

Symptoms

1. Weight gain :trunk and face with sparing of the limbs. (central obesity)
2. Buffalo's hump
3. Moon face
4. Excessive sweating
5. Atrophy of the skin and mucous membranes
6. Proximal muscle weakness (hips-shoulders)
7. Hirsuitism
8. The excess cortisol may also affect other endocrine system → Libido, amenorrhoea and infertility.
9. Patients frequently suffers various psychological disturbances ranging from euphoria to frank psychosis
10. Purple striae on the trunk and legs.

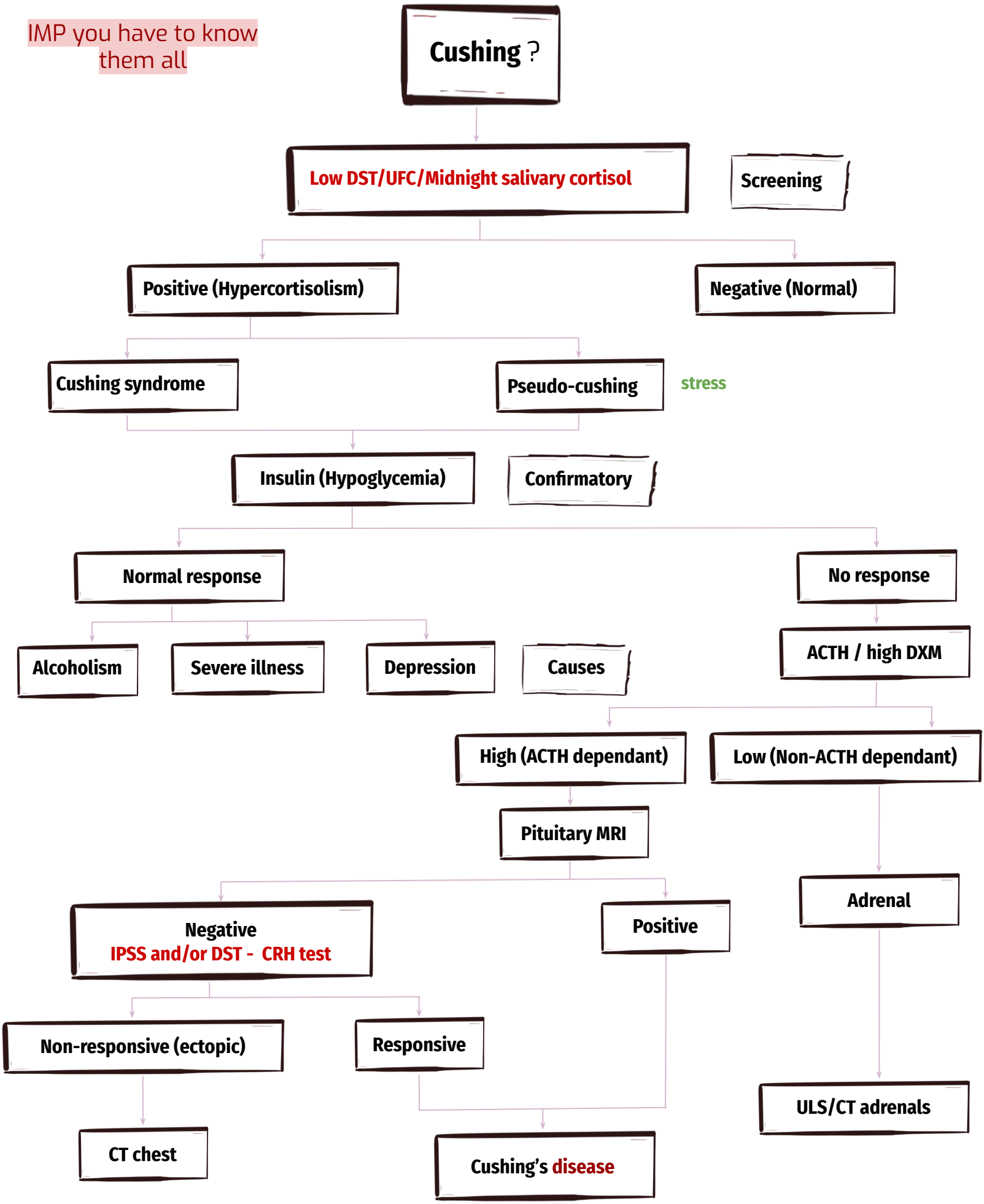


Signs of Cushing's Syndrome



6 Investigations of suspected Adrenocortical hyperfunction

IMP you have to know them all



1- Screening tests (outpatient)

To assess the clinical diagnosis of adrenocortical hyperfunction.

Effective screening tests need to be sensitive but do not have to be highly specific.

	Low-dose dexamethasone (DXM) suppression test (DST) (Overnight suppression test)	24-hour urinary free cortisol	Midnight salivary cortisol
Procedure	• 1 mg dexamethasone (DXM) administered at 11 PM - 12 AM the night before attending the clinic. • Serum cortisol is measured at 8-9 AM	• 24 hours urinary collection from the patient.	• Sample from patient's saliva at Midnight.
Results	• Dexamethasone → ↓ CRH → ↓ ACTH → ↓ cortisol • Cortisol < 50 nmol/L (suppression) → exclude hypercortisolemia (Cushing Syndrome)	• Cortisol < 250 nmol/day → exclude Cushing Syndrome	• Cortisol < 100 ng/dL → exclude Cushing Syndrome
Info	Precautions: Drugs that induce hepatic microsomal enzymes (Phenobarbitone & phenytoin) → ↑ DXM metabolism and ↓ DXM blood level to achieve CRH suppression (false diagnosis of Cushing).	Disadvantage: incomplete collection of urine → a false-negative result (patient may add some water to his urine to increase it). * An alternative is to determine the urinary cortisol : creatinine ratio on an early morning specimen	

Interpretation of tests (Female slides only)

- **The screening tests serve to** distinguish simple non-endocrine obesity from obesity due to Cushing's syndrome.
- **Confirmatory tests (in-patient basis)** are required to rule out pseudo-Cushing's syndrome
- **Psudo-cushing's Syndrome**
  - Depressed or extremely anxious patients
  - Severe intercurrent illness
  - Alcoholism

2- Confirmatory tests (Inpatient)

- to confirm or exclude the provisional diagnosis.
- Positive results of at least two screening tests would confirm the clinical diagnosis.
- Further investigations are required.

(Female slide)	Insulin induced hypoglycemia		
Procedure	• Insulin I.V. (0.15 U/kg) to lower blood glucose to 2.2 mmol/L or less . • Samples for simultaneous measurement of serum glucose and cortisol levels are taken basally (before insulin injection) and at 30, 45, 60 and 90 min after I.V. insulin injection. • Failure to achieve a glucose level of 2.2 mmol/L invalidates the test and should be repeated with increment in step of 0.05U/kg.		
Interpretation	• Normally: Basal serum cortisol: at least 145 nmol/L • – At 60 - 90 minutes: the level > 425 nmol/L. Patients with Cushing's syndrome: • Whatever the cause, do not respond normally to insulin-induced hypoglycemia. • High basal serum cortisol than normal . • At 60 - 90 minutes: no increase in S. cortisol, despite the production of an adequate degree of hypoglycemia.		
Info	• Hypoglycemia→↑CRH→↑ ACTH→↑cortisol • Pseudo-Cushing patients show abnormal diurnal rhythm of S. cortisol, but, with Insulin-induced hypoglycemia → ↑ CRH, ACTH and cortisol blood levels • True Cushing patients: No response to hypoglycemia.		
Used to	• To test the integrity of the hypothalamic pituitary-adrenal (HPA) axis • To distinguish true Cushing's syndrome from pseudo-Cushing's syndrome	**Contraindicated in**	Epilepsy or heart disease

3- Tests to determine the cause

To ascertain:

- **The site of the pathological lesion (adrenal cortex, pituitary or elsewhere?)**
- **The nature of the pathological lesion.**

To differentiate ACTH-dependant from ACTH-independent: Plasma ACTH (Diurnal rhythm)

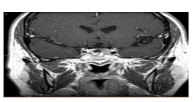
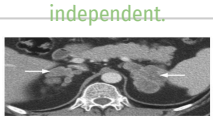
To distinguish between ACTH-dependent causes (Pituitary Vs Lung) → **High-dose DST**, **CRH stimulation test**, **Inferior petrosal sinus sampling**

Radiological tests: MRI of pituitary and ultrasound or CT of adrenals

1	**Plasma ACTH (Diurnal rhythm)**
Procedure	• It should be measured on Blood specimens at 8-9 AM and 8-9 PM
Results	• Undetectable : Functional adrenal tumor → confirmed by an abdominal CT scan to detect an adrenal mass • ↑↑ ACTH : Cushing's disease (pituitary-dependent) • ↑↑↑↑ ACTH : Ectopic (non-endocrine) origin of ACTH Sky high result because in cancer the number of cells is high (depend on stage) so the increase of ACTH is very high.

2	**High-dose dexamethasone suppression test (DST)**
Procedure	• 2mg DXM six-hourly for 48 hours to suppress cortisol secretion. • Basal (pre-DXM) serum cortisol or 24-hour urine free cortisol is compared with the results at the end of the 48-hour period. Basal means before serum cort. has suppressed
Results	• Suppression is defined as fall to less than 50% of basal value. • About 90% of patients with Cushing's disease show suppression of cortisol output (so insensitive test). • In contrast, only 10% of patients with ectopic ACTH production (or with adrenal tumors) show suppression.
Info	• It is used to distinguish Cushing's disease from ectopic ACTH secretion.

3	**CRH stimulation test** (Female slides only)
Procedure	Measures the ACTH and cortisol levels basally and 60 minutes after injection of 100 µg CRH.
Results	Ectopic ACTH & adrenal tumors: • No response • False-positive responses are unusual **Cushing's disease:** • ACTH & cortisol above basal at 60 min. • 10% of patients fail to respond. • High-dose dexamethasone suppression test + the CRH test → 100 % specificity and sensitivity.

4	**Radiological Investigations** (Female slides only)
Procedure	• CT scanning of the adrenal glands / Lungs • MRI of the pituitary gland • We do it on the lung in case of non-responsive to high dose of DST. • We do it to adrenal gland in case of ACTH independent.
Results	 Coronal contrast-enhanced MRI of the sella turcica in a patient with recurrent Cushing's disease  Contrast-enhanced CT scan shows massive hyperplasia of both adrenal glands

4-Other blood tests

Commonly performed for patients suspected to have Cushing's syndrome, are :

1	2	3	4	5
Full blood count	Blood glucose	Blood electrolytes and pH	Renal function tests	Liver function tests

Case study

58 years old man was admitted with weight loss and respiratory distress. He had increased pigmentation and BP was 140/80.

Lab tests	Patient results	Normal Value
Urea	8.6	2.5-7 mmol/L
Sodium	144	135-145 mmol/L
Potassium	2.0	3.5-4.5 mmol/L
Cortisol	1650	150-550 nmol/L
Post overnight DXM	1530 \ 1350	<50 nmol/L

Further investigation revealed the following

Qid: 4 times a day

DXM suppression test	Basal	After 48 h 0.5 mg qid	After 48 h 2.0 mg qid
Serum cortisol	1350	1420	1100 (No suppression)

	8 AM	22 PM	Reference range
Plasma ACTH (ng/L)	220	180	7-51

CRH showed flat response for cortisol and ACTH

Likely diagnosis: Ectopic tumor in lung

Female slides summary

Adrenal Hyperfunction			
Test	Cushing's disease	Adrenal tumor	Ectopic ACTH secreting tumor
S. cortisol	↑	↑	↑
Dexamethasone Low dose test	Not suppressed	Not suppressed	Not suppressed
Urinary cortisol	↑	↑	↑
Diurnal rhythm	Lost	Lost	Lost
Insulin-induced hypoglycemia	No response	No response	No response
Plasma(ACTH)	Normal or ↑	Not detectable	↑↑↑
Dexamethasone High dose test	suppressed	Not suppressed	Not suppressed
CRH test	↑	No response	No response

Take Home Messages

1. -Initial screening for Cushing by 24 h urine free cortisol, low-dose dexamethasonesuppression test or midnight Salivary Cortisol.

2. -Confirmatory tests for Cushing by getting positive results of at least two of the screening tests.

3. -Tests to determine the cause of Cushing: Plasma ACTH, high-dose dexamethasone suppression test, Inferior Petrosal Sinus Sampling and radiological investigations.

4. -ACTH-dependent Cushing: due to pituitary causes (Cushing's disease) and due to ectopic production of ACTH.

5. -ACTH-independent Cushing: due to adrenal adenoma or carcinoma and due to steroid therapy (iatrogenic).

Test Yourself!

MCQs

Answers: 1-B 2-C 3-D 4- C

Q1: How many carbon atoms in cortisol?
A. 27
B. 21
C. 19
D. 18

Q2: What is the normal range of UFC?
A. >50 nmol\24h
B. <50 nmol\24h
C. <250 nmol\24h
D. >250 nmol\24h

Q3:A 44 year-old patient's urinary free cortisol is 312 nmol/L. The endocrinologist doubts that the patient has pseudo-cushing because he is depressed and drinks alcohols. What is the best test to confirm the diagnosis?

A. Liver function test
B. High DXM
C. Adrenal CT
D. Insulin-induced hypoglycemia

Q4: Which of the following is not a symptom of cushing's syndrome?
A. Weight gain
B. Hirsutism
C. Increase muscle bulk
D. Purple stiae

SAQs

Q1: Mention 3 causes of pseudo-cushing?
-Alcoholism, depression, severe illness

Q2: Mention 3 signs of cushing's syndrome?
-Hypertension, hyperglycemia, hypokalemic alkalosis , impaired immunity , loss of diurnal rhythm ,increase protein metabolism.

Meet The Team!

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