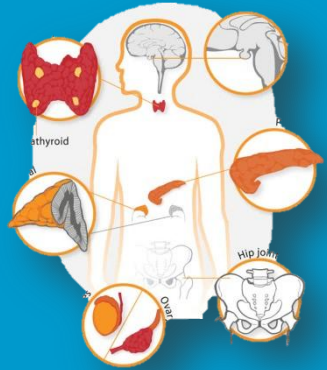


[lecture 6]

Cushing Syndrome



Endocrine system



The Objectives

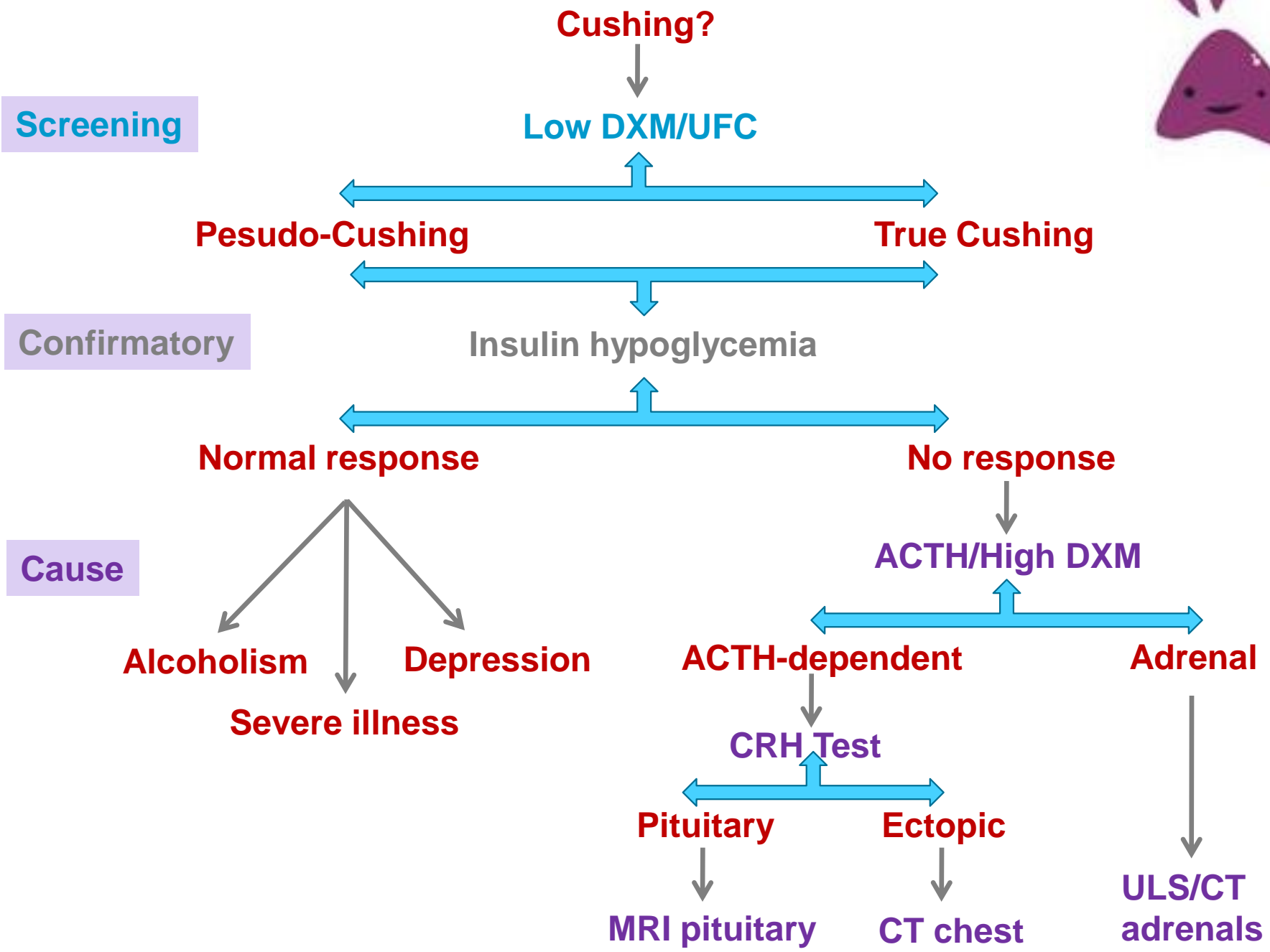
- To identify different causes of Cushing's syndrome
- To understand the diagnostic algorithm for Cushing's syndrome
- To understand the interpretation of laboratory and radiological tests of Cushing's syndrome

Red =
Important

Blue =
explain

Green =
addition
notes

Mind Map

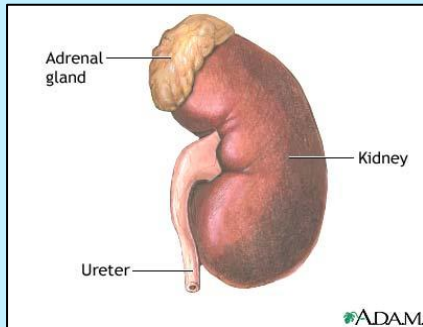


background

1

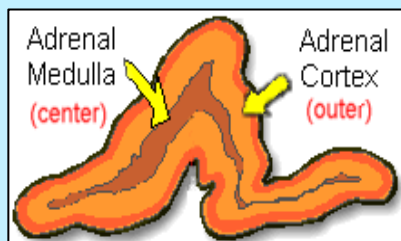
Anatomy:

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



Histology:

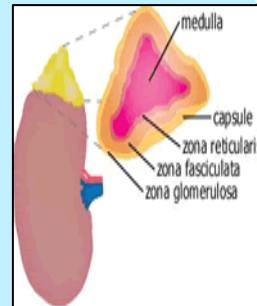
The adrenal gland consists of two distinct tissues of different embryological origin, the outer cortex and inner medulla.



2

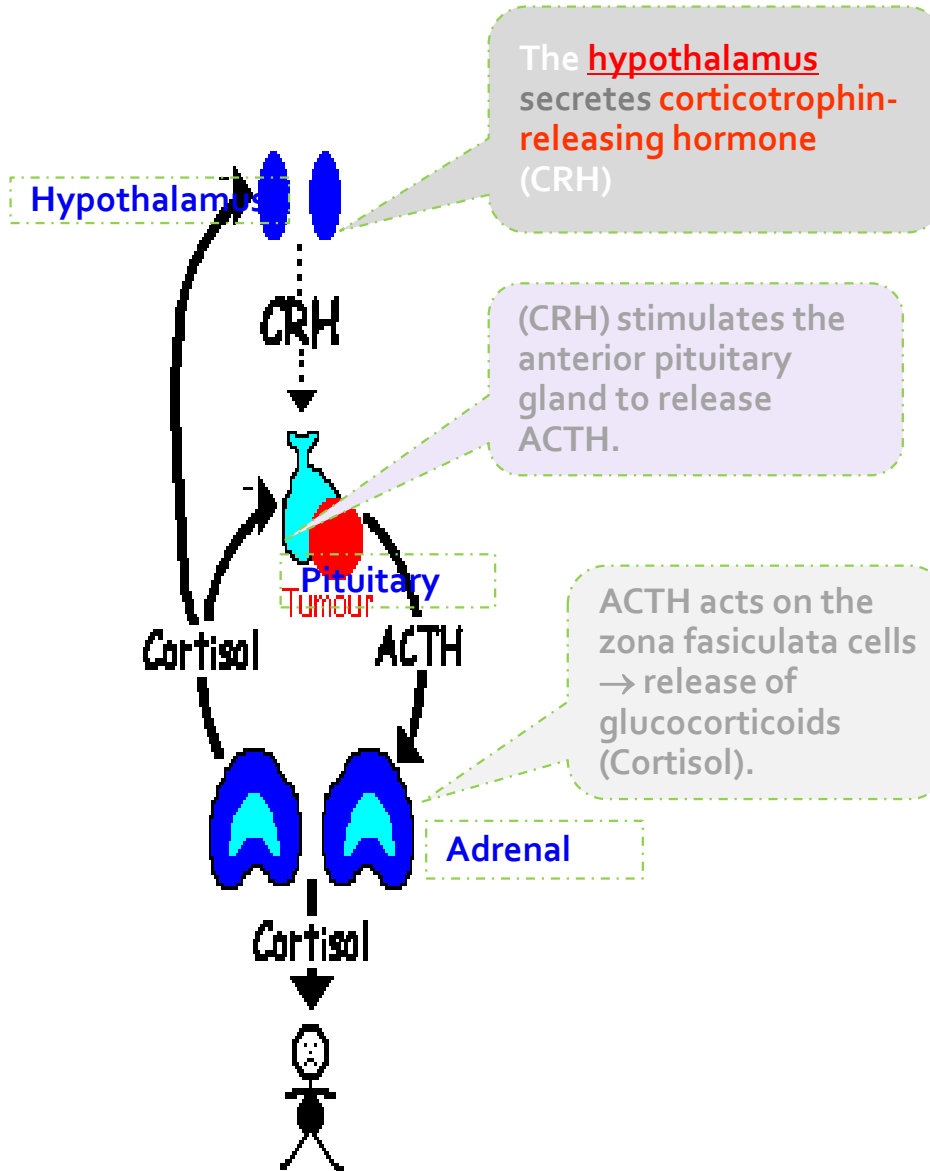
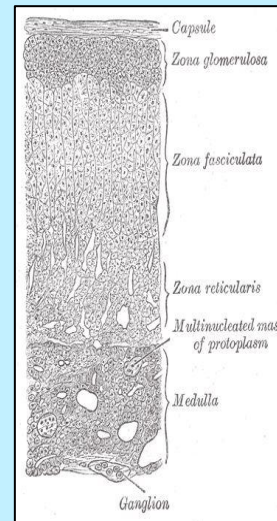
The adrenal cortex comprises three zones based on cell type and function:

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



The deeper layers of the cortex:

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



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) Stress → ↑↑ CRH & ACTH → ↑↑ Cortisol

3) The diurnal rhythm of plasma cortisol:

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

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

Cortisol and ACTH measurements

1- Serum [cortisol] and plasma [ACTH]:

•Serum measurement is preferred for cortisol and Plasma for ACTH.

•must be collected (without venous stasis * which affect the amount) between 8 a.m. and 9 a.m. and between 10 p.m. and 12 p.m. because of the diurnal rhythm.

•Temporary ↑↑ in these hormones may be observed as a response to emotional stress.

Plasma [CBG]: In the circulation, glucocorticoids are mainly protein-bound (about 90%), chiefly to cortisol-binding globulin (CBG or transcortin)
 -CBG↑↑ in pregnancy and with estrogen treatment (e.g. oral contraceptives). that lead the cortisol LEVEL to go up .
 -CBG↓↓ in hypoproteinemic states (e.g. nephrotic syndrome).. that lead the cortisol LEVEL to go down.
 Whenever we do a test IN THE BLOOD we measure the TOTAL cortisol.

Urinary cortisol excretion:

•Cortisol is removed from plasma by the liver → metabolically inactive compounds → excreted in urine mainly as conjugated metabolites (e.g. glucuronides).

•A small amount of cortisol is excreted unchanged in the urine (UFC).

In normal individuals:

-Urinary free cortisol (UFC) is < 250 nmol/24 h. reflects how much free cortisol present in the blood while when you measure it in the BLOOD you measure the TOTAL..

-you are not sure that the 24 h is exactly 24 h so you have to do the Cortisol / Creatinine ratio: in an early morning specimen of urine is < 25 μmol cortisol / mol creatinine.

* is a condition of slow blood flow in the veins

Causes of elevated serum cortisol concentrations:

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

1. Increased cortisol secretion:

- Congenital
- Estrogen therapy
- Pregnancy

2. Increased cortisol binding globulin (CBG):

CAUSES OF ADRENOCORTICAL HYPERFUNCTION: CUSHING'S SYNDROME

•ACTH - dependent :

1. ↑ Pituitary ACTH 70% (Cushing's disease).
2. Ectopic ACTH by neoplasms 10%.
3. ACTH therapy.

•ACTH - independent :

1. Adrenal tumor 20% (adenoma or carcinoma).
2. Glucocorticoid therapy.

Glucocorticoid functions

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

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

- In the liver, Cortisol is an insulin antagonist and has a weak mineralocorticoid action →

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

↑↑ Amino acid uptake and degradation

↑↑ Ketogenesis.

- In the adipose tissue: Cortisol → ↑↑ Lipolysis through breakdown of fat.

- In the muscles: Cortisol → ↑↑ proteolysis and amino acid release.

- Conserving glucose: by inhibiting uptake into muscle and fat cells.

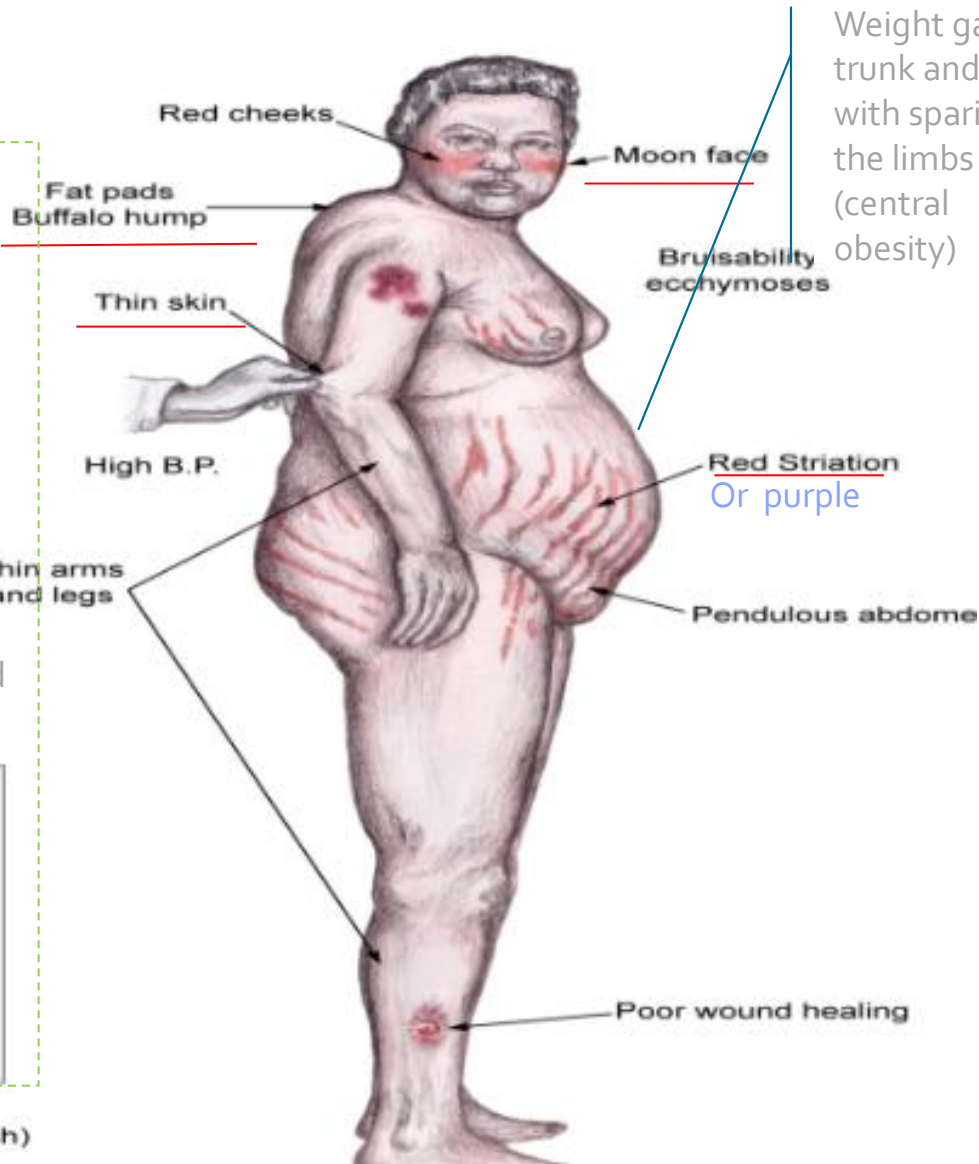


Cushing's Syndrome

Other symptoms

- Excessive sweating
- Atrophy of the skin and mucous membranes
- Proximal muscle weakness (hips, shoulders)
- Hirsutism
- The excess cortisol may also affect other endocrine systems → ↓ libido, amenorrhoea and infertility
- Patients frequently suffer various psychological disturbances ranging from euphoria to frank psychosis.

ish)



Weight gain:
trunk and face
with sparing of
the limbs
(central
obesity)

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- Loss of diurnal rhythm of cortisol and ACTH.
- Hypertension (due to the aldosterone - like effects)
- Hyperglycemia or diabetes due to insulin resistance.
- Hypokalemic alkalosis
- ↑ protein metabolism.
- Impaired immunity.

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Investigations of suspected adrenocortical hyperfunction

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Investigation	Significance	Types	Interpretation
A. Screening tests (out-patient):	to assess the clinical diagnosis of adrenocortical hyperfunction.	<p>Effective screening tests need to be sensitive but do not have to be highly specific.</p> <p>It includes:</p> <ol style="list-style-type: none"> Low-dose dexamethasone suppression test: (Overnight suppression test) Dexamethasone → ↓ CRH → ↓ ACTH → ↓ cortisol 24-hour urinary free cortisol 	Serve to: distinguish simple non-endocrine obesity from obesity due to Cushing's syndrome.
B. Confirmatory tests (in-patient):	to confirm or exclude the provisional diagnosis	Insulin-induced hypoglycemia	Required to rule out pseudo-Cushing's syndrome (Depressed or extremely, anxious patients, Severe intercurrent illness, Alcoholism).
C. Tests to determine the cause	to ascertain: a- The site of the pathological lesion (adrenal cortex, pituitary or elsewhere?) b- The nature of the pathological lesion.	<ol style="list-style-type: none"> Plasma ACTH (Diurnal rhythm) High-dose dexamethasone suppression test CRH stimulation test Radiological tests: MRI of pituitary & ultrasound or CT of adrenals 	

A-Screening Tests

Screening Tests	Procedure	Results	Other
<p><u>Low-dose dexamethasone (DXM) suppression test:</u> (outpatient procedure)</p>	<p>-One mg DXM administered at 11-12 PM the night before attending the clinic.</p> <p>-Serum cortisol is measured at 8-9 AM.</p>	<p>Cortisol < 50 nmol/L (suppression)→ exclude Cushing's disease</p>	<p>Precautions: Drugs that induce hepatic microsomal enzymes (Phenobarbitone & phenytoin) lead to→ ↑ DXM metabolism & ↓ DXM blood level to achieve CRH suppression (false diagnosis of Cushing)</p>
<p>24-hour urinary free cortisol (UFC):</p>		<p>Cortisol < 250 nmol/day → exclude Cushing's disease.</p>	<p>Disadvantage: Incomplete collection of urine (e.g. collection of urine for only 22 hours) → a false-negative result</p> <p>An alternative to this test: The urinary cortisol : creatinine ratio on an early morning specimen</p>

Cushing **syndrome** refers to the manifestations of excessive cortisol, while Cushing **disease** refers to hypercortisolism due to ACTH hypersecretion by a benign **pituitary** adenoma.

Insulin-induced hypoglycemia

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



C. Tests used to determine the cause of Cushing's syndrome:

	Procedure	Results	Other
1- Plasma ACTH (Diurnal rhythm)	Plasma [ACTH] should be measured on blood specimens collected at 8-9 a.m. and 8-9 p.m.	Plasma ACTH level could be one of the following: 1-Undetectable ACTH: indicates functional adrenal tumor → confirmed by an abdominal CT scan to detect an adrenal mass. 2-High ACTH: Cushing's disease (pituitary-dependent). 3-Very high ACTH: Ectopic (non-endocrine) origin of ACTH	
2- High-dose dexamethasone suppression test	<ul style="list-style-type: none"> • 2 mg dexamethasone every six hours for 48 hours to suppress cortisol secretion. • Basal (pre-dexamethasone) serum cortisol or 24-hour urine free cortisol is compared with the results at the end of the 48-hour period. 	Suppression is defined as a fall to less than 50 % of basal value. -About 90 % of patients with Cushing's disease show suppression of cortisol output. -In contrast, only 10% of patients with ectopic ACTH production (or with adrenal tumors) show suppression. (in other words: patients with ectopic ACTH production will show no response or no suppression).	It is used to distinguish Cushing's disease from ectopic ACTH secretion.
3- CRH stimulation test	Measures the ACTH and cortisol levels basally and 60 minutes after injection of 100 µg CRH.	-Cushing's disease: ↑↑ ACTH & cortisol above basal at 60 min. 10% of patients fail to respond. -Ectopic ACTH & adrenal tumors: No response False-positive responses are unusual	<u>In Cushing's disease:</u> High-dose dexamethasone suppression test + the CRH test → 100 % specificity & sensitivity.
4-Radiological tests: MRI of pituitary & ultrasound or CT of adrenals	Ultrasound or CT scanning of the adrenal glands MRI of the pituitary gland		

Other blood tests commonly performed for patients suspected to have Cushing's syndrome are:

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- Full blood count
- Blood glucose
- Blood electrolytes & pH
- Renal function tests
- Liver function tests

Summary of Biochemical Tests for Adrenal Hyperfunction

Test	Cushing's disease	Adrenal tumor	Ectopic ACTH secreting tumor
Serum 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

summary

- Highest Cortisol level is in the morning (8 - 9 AM) & the lowest Cortisol level is in the late afternoon & evening (8 - 9 PM).
- Serum measurement is preferred for cortisol and Plasma for ACTH.
- Glucocorticoids have widespread metabolic effects on carbohydrate, fat & protein metabolism.
- Disorders of the adrenals are uncommon.
- Sensitive screening tests (low-dose dexamethasone suppression test & 24-hour urinary free cortisol) for adrenocortical functions are important.
- Additional confirmatory tests (insulin-induced hypoglycemia) are required to establish the diagnosis and rule out pseudo-Cushing.
- Other biochemical tests (Full blood count, Blood glucose, Blood electrolytes & pH, Renal function tests, Liver function tests) and radiological investigation (Pituitary MRI & Adrenal US or CT) are required to determine the cause of Cushing's syndrome.

Test your knowledge ...!



1- B

2- A

3- D

4- C

1: There will be an increase in cortisol binding globulins in which of the following:

- A- Exercise.
- B- Pregnancy.
- C- Obesity.
- D- Alcoholism.

2: Which of the following causes of Cushing syndrome is ACTH-independent:

- A- Adrenal tumor.
- B- Pituitary adenoma.
- C- Small cell carcinoma of the lung.
- D- ACTH therapy.

3: Which of the following is a confirmatory test for Cushing syndrome?

- A- Urinary cortisol: creatinine ratio.
- B- 24-hour urinary free cortisol.
- C- Low-dose dexamethasone.
- D- Insulin-induced hypoglycemia.

4: Which of the following tests give 100% sensitivity & specificity for the diagnosis of Cushing disease?

- A- CRH+ low-dose DXM.
- B- Plasma ACTH + CRH.
- C- High-dose DXM + CRH.
- D- UFC + Plasma ACTH.

Test your knowledge ..!

5: 58 years old man was admitted with weight loss and respiratory distress. He had increased pigmentation and BP was 140/80.

Lab tests

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 DMX	1530	(<50nmol/L)

Further investigation revealed the following

	Basal	After 48 h	After 48 h	comment
DXM suppression test	_____	0.5 mg qid	2.0 mg qid	(qid means 4 times a day)
Serum cortisol	1350	1420	1100	(No suppression)

Plasma ACTH (ng/L): at 8 am : 220, at 22.00 pm: 180 (Ref. range: 7-51).

CRH showed flat response for cortisol & ACTH, in this patient Cushing syndrome is caused by?

- A- Adrenal tumor.
- B- Ectopic ACTH secreting tumor.
- C- Cushing's disease.

6: A 54-year-old woman presents to the physician with diabetes mellitus, osteoporosis, & hypertension. She has noted a recent weight gain & abdominal striae. Laboratory studies show a decreased ACTH level. A single mass is noted adjacent to the right kidney on abdominal CT scan. Neither low- nor high-dose dexamethasone suppresses the patient's cortisol production. Which of the following is the most likely explanation for these findings?

- A- Adrenal adenoma
- B- Bilateral adrenal hyperplasia
- C- Ectopic ACTH secretion
- D- Exogenous corticosteroid administration
- E- Pituitary adenoma



If you find any mistake, please contact us =>
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THANK YOU

