

Revised & Approved



Cushing Syndrome

Editing File

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Objectives



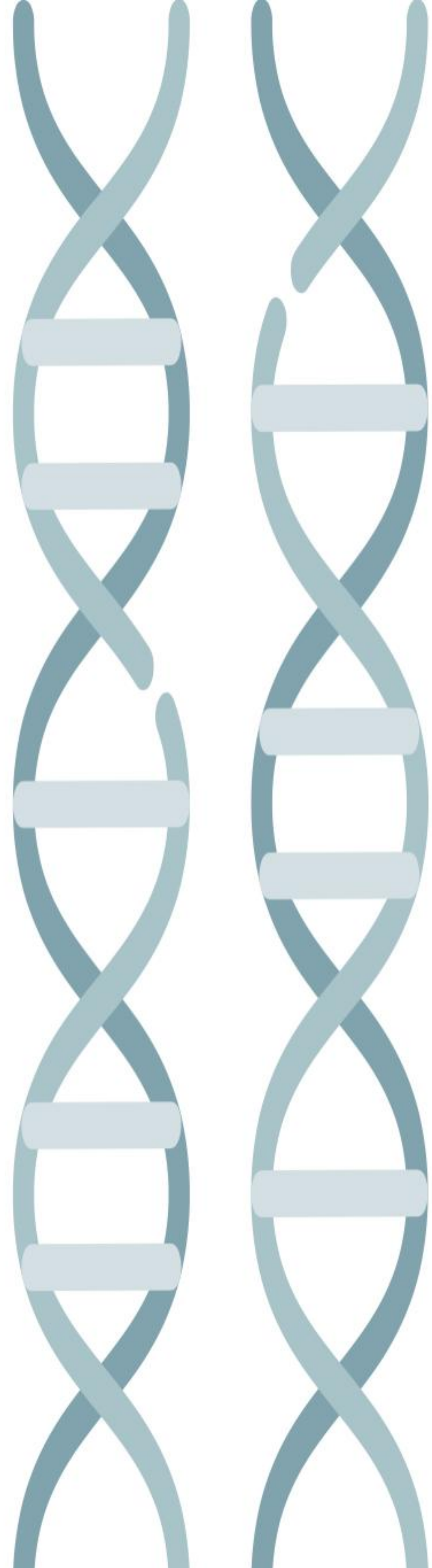
To identify physiological and biochemical characteristics of Cortisol.



To understand the diagnostic algorithm for Cushing's Syndrome .



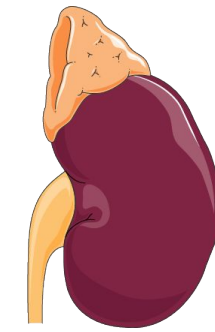
To understand the interpretation of laboratory and radiological investigations for diagnosis of Cushing's Syndrome.



Adrenal Gland

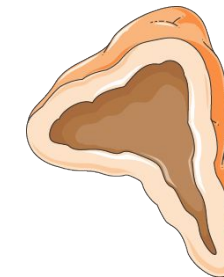
Anatomically:

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



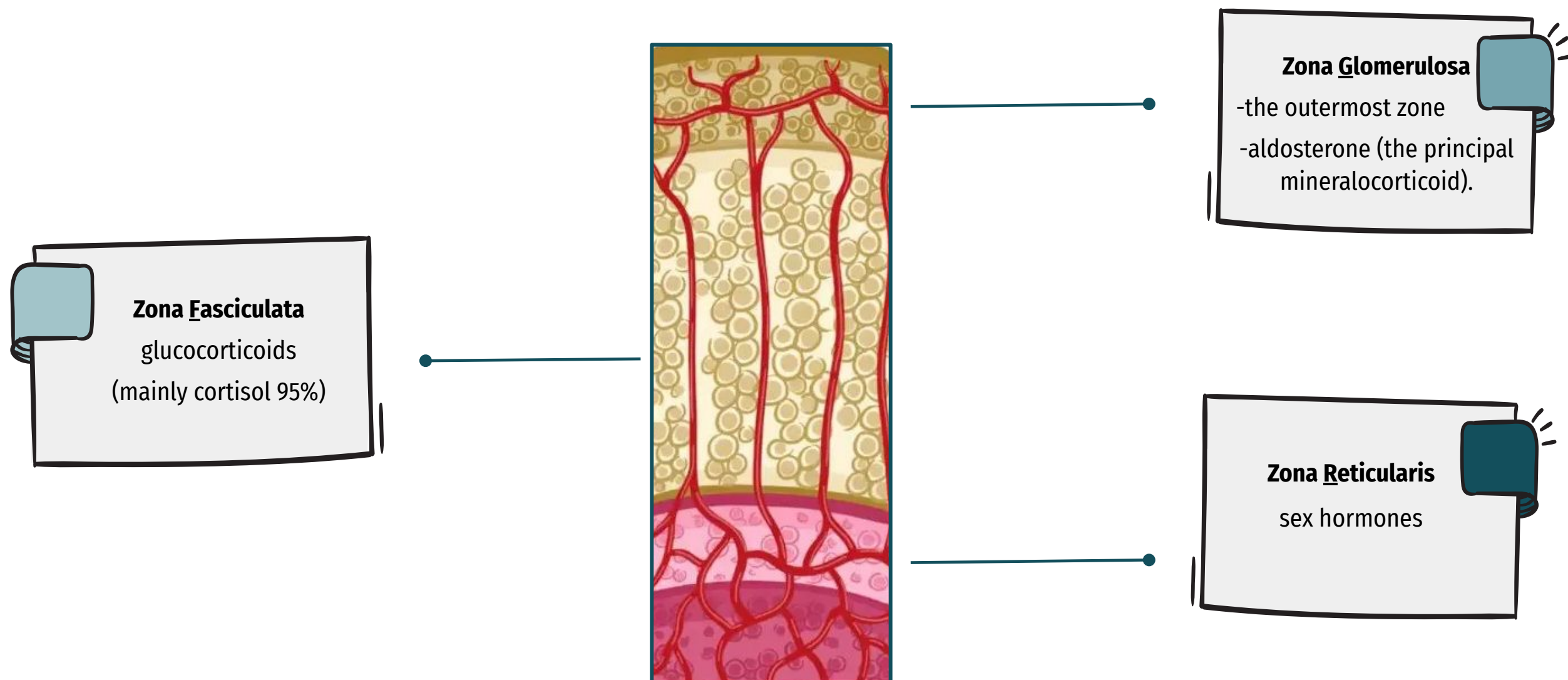
Histologically:

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



Hypothalamic Pituitary-Adrenal (HPA) Axis

The hypothalamus secretes corticotropin releasing hormone (CRH).

The CRH stimulates the anterior pituitary gland to secrete ACTH.

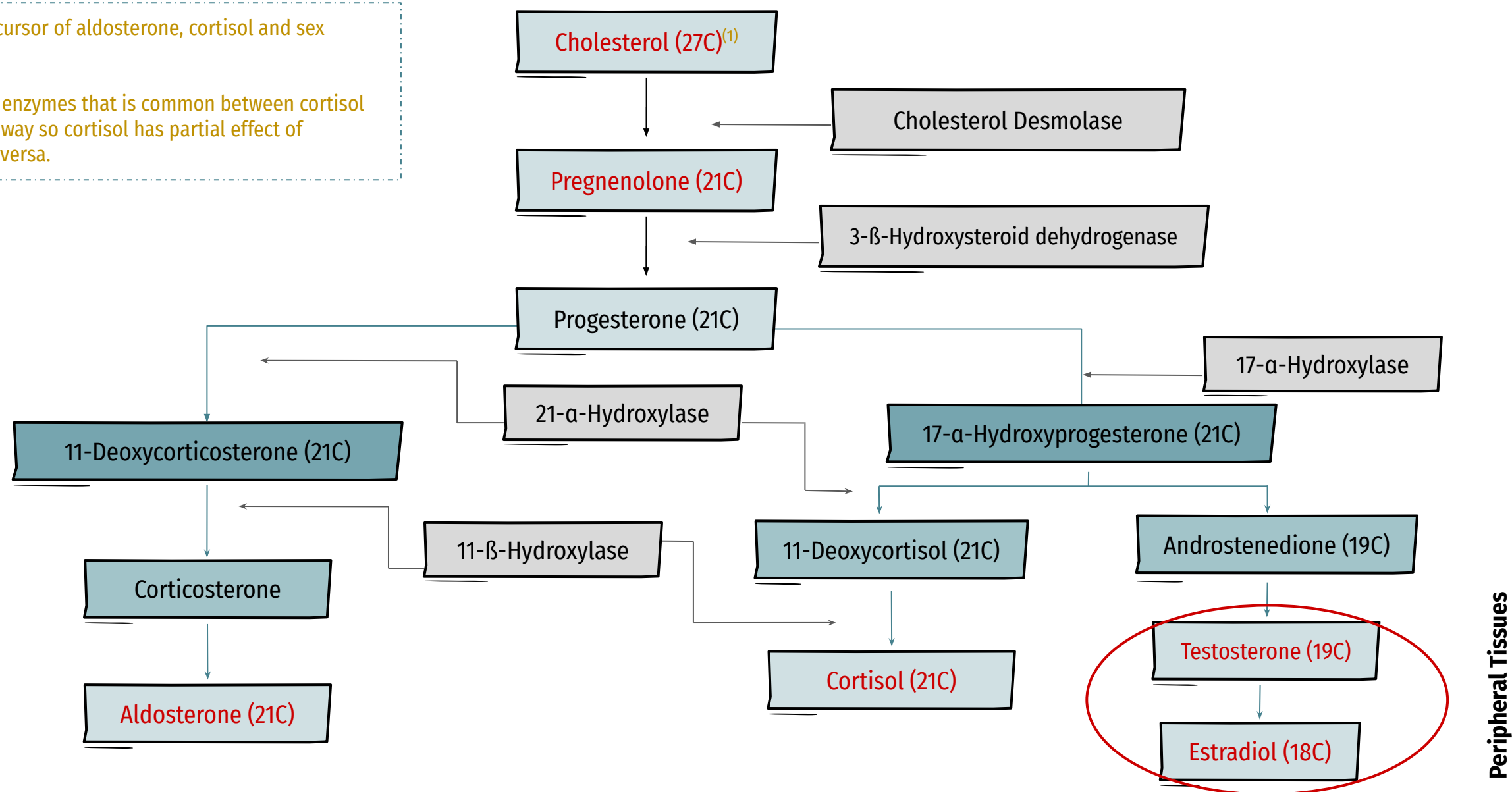
ACTH acts on the zona fasciculata cells.

Release of glucocorticoids (Cortisol).

Steroid Hormone Synthesis

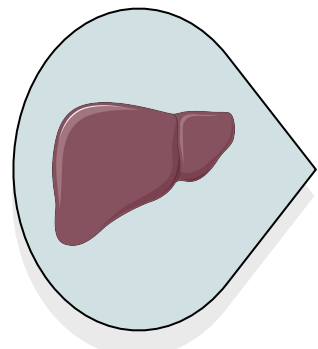
(1): cholesterol is precursor of aldosterone, cortisol and sex hormone.

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.



Glucocorticoid Functions

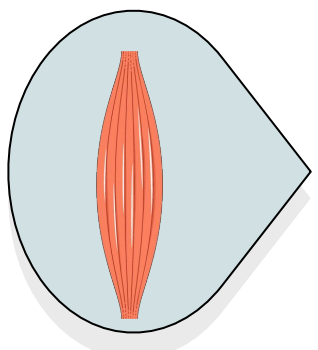
- Glucocorticoids have widespread metabolic effects on carbohydrate, fat and protein metabolism
 - Upon binding to its target, CORTISOL enhances metabolism in several ways:



In Liver

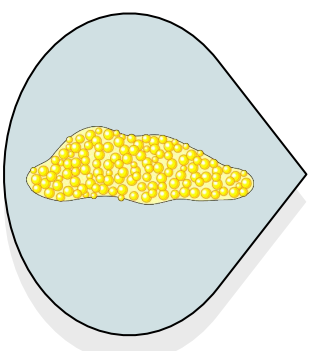
Cortisol is an insulin antagonist and has a weak mineralocorticoid action:

- 1- $\uparrow\uparrow$ Gluconeogenesis \rightarrow production of glucose from newly-released amino acids and lipids.
- 2- $\uparrow\uparrow$ Amino acid uptake and degradation (**Smaller muscles**)
- 3- $\uparrow\uparrow$ Ketogenesis (**from lipid breakdown**)



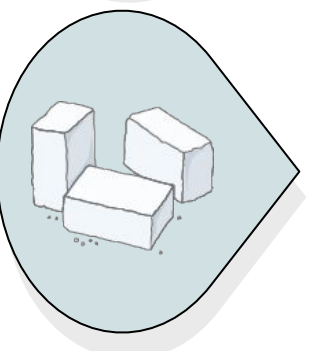
In Muscles

Cortisol \rightarrow $\uparrow\uparrow$ proteolysis and amino acid release.



In Adipose Tissue

Cortisol \rightarrow $\uparrow\uparrow$ Lipolysis through breakdown of **fat** (**producing fatty acid + TAG + ketone bodies**)



Conserving Glucose

By inhibiting uptake into **muscle** and **fat cells** (**leading to hyperglycemia**)

اللي عنده cushing syndrome يصير عنده trunk obesity و upper limb و lower limb وتصير رجوله مثل اعواد الكبريت، لأن proteolysis فما فيه عضلات. وما فيه بصيرون thin ، وذلك بسبب break down of lipid فيصير عنده trunk obesity.

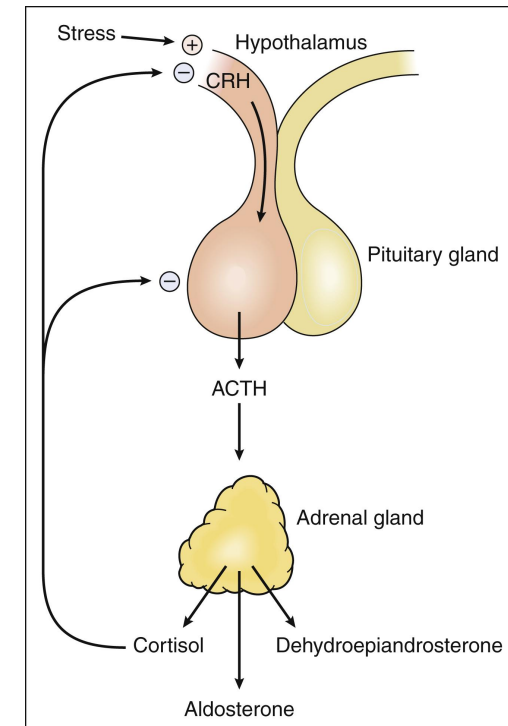
Regulation of ACTH and Cortisol Secretion

01

Negative feedback control

- ACTH release from the anterior pituitary is stimulated by hypothalamic secretion of corticotropin releasing hormone (CRH).
- CRH → ↑ ACTH → ↑ [Cortisol]
- ↑ [Cortisol] or synthetic steroid⁽²⁾ suppress CRH & ACTH secretion

(2). وقت ناخذ
حيات cortisol خارجي او
cortisone



02

Stress

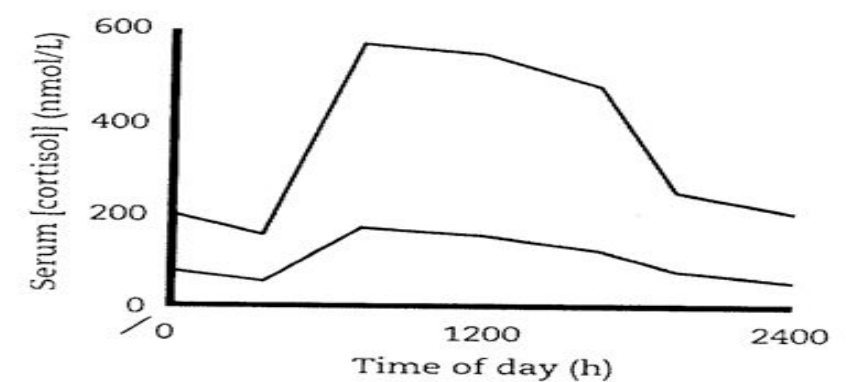
- (e.g. major surgery, emotional stress) Stress → ↑↑ CRH & ACTH → ↑↑ Cortisol
- It returns back to normal level when the stress is gone so it is temporary

03

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). نصف الموجود بالصباح
- The benefit of this is to know the appropriate time for taking the sample)

DIURNAL RHYTHM OF CORTISOL SECRETION

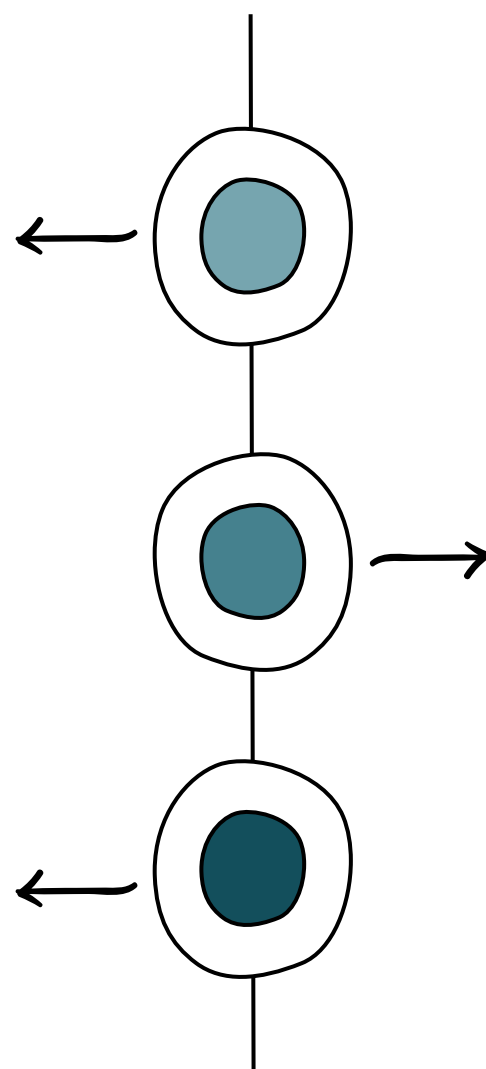


The diurnal rhythm of cortisol secretion; the area between the curves represents values that lie within the reference range.

يستخدموه لتشخيص Cushing syndrome.

Plasma Cortisol Binding Globulin (CBG)

- In the circulation, glucocorticoids are mainly protein-bound (about 90%), chiefly to cortisol-binding globulin CBG (transcortin). Because it is hydrophobic and needs a carrier.



- ↑↑ In pregnancy and with estrogen treatment (e.g. oral contraceptives)
- ↓↓ In hypoproteinemic states (e.g. nephrotic syndrome), because CBG is a protein and one of the proteins that will decrease.

- The biologically active fraction of cortisol in plasma is the free (unbound) component. But in the lab we usually measure CBG.

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).⁽³⁾
- 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.

(3): to be excreted in the urine, it has to be converted from hydrophobic to hydrophilic, so should conjugate with another metabolites.

Causes of Elevated Serum Cortisol

Increased cortisol secretion

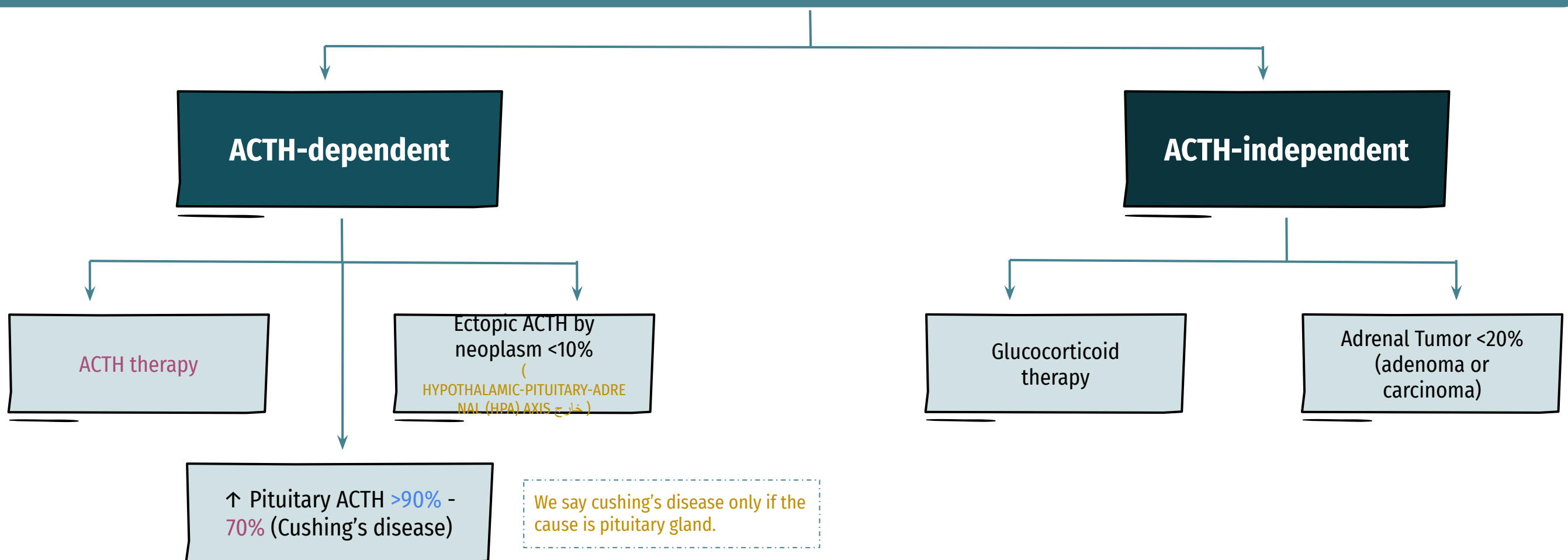
- Cushing's syndrome
- Excessive Exercise
- Stress, Anxiety, Depression
- Obesity
- Alcohol abuse
- Chronic renal failure

VS

Increased CBG

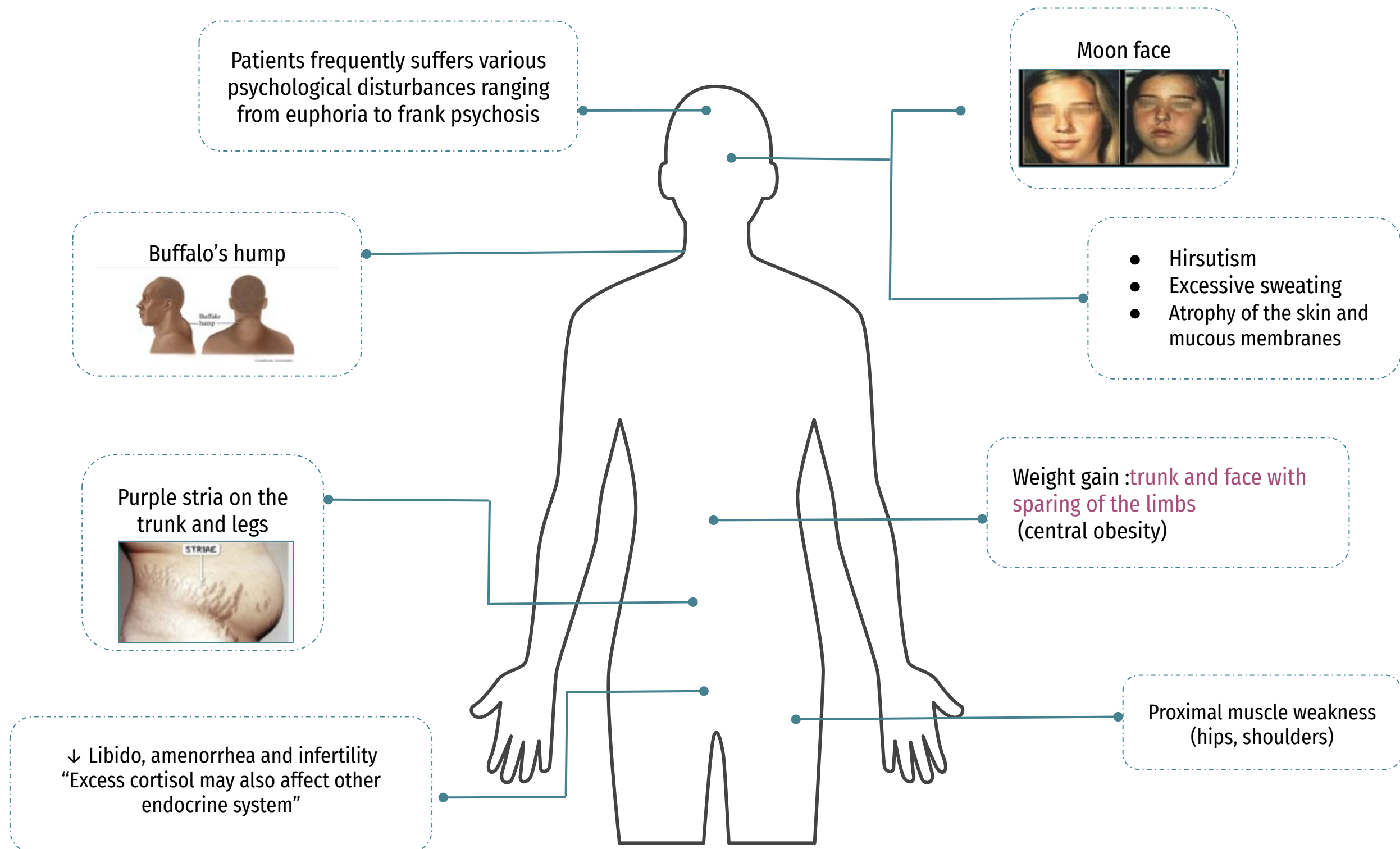
- Congenital
- Estrogen therapy
- Pregnancy

Causes of Adrenocortical Hyperfunction (Cushing's Syndrome)

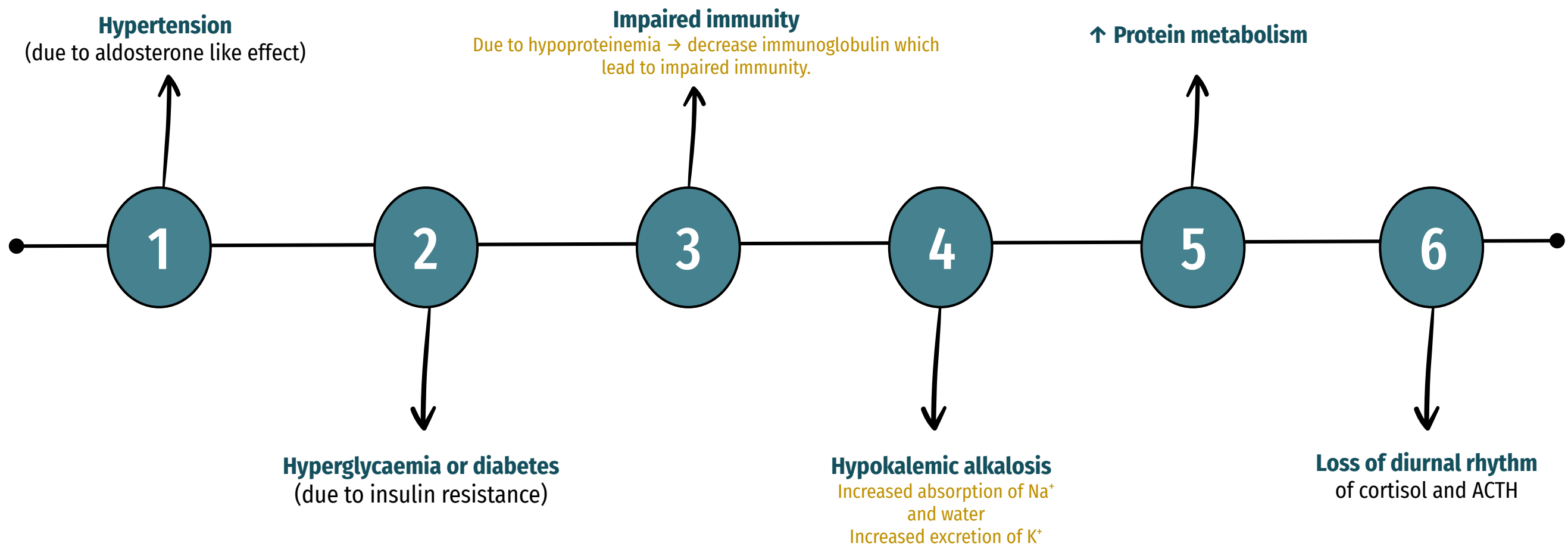


Signs and Symptoms of Cushing's Syndrome

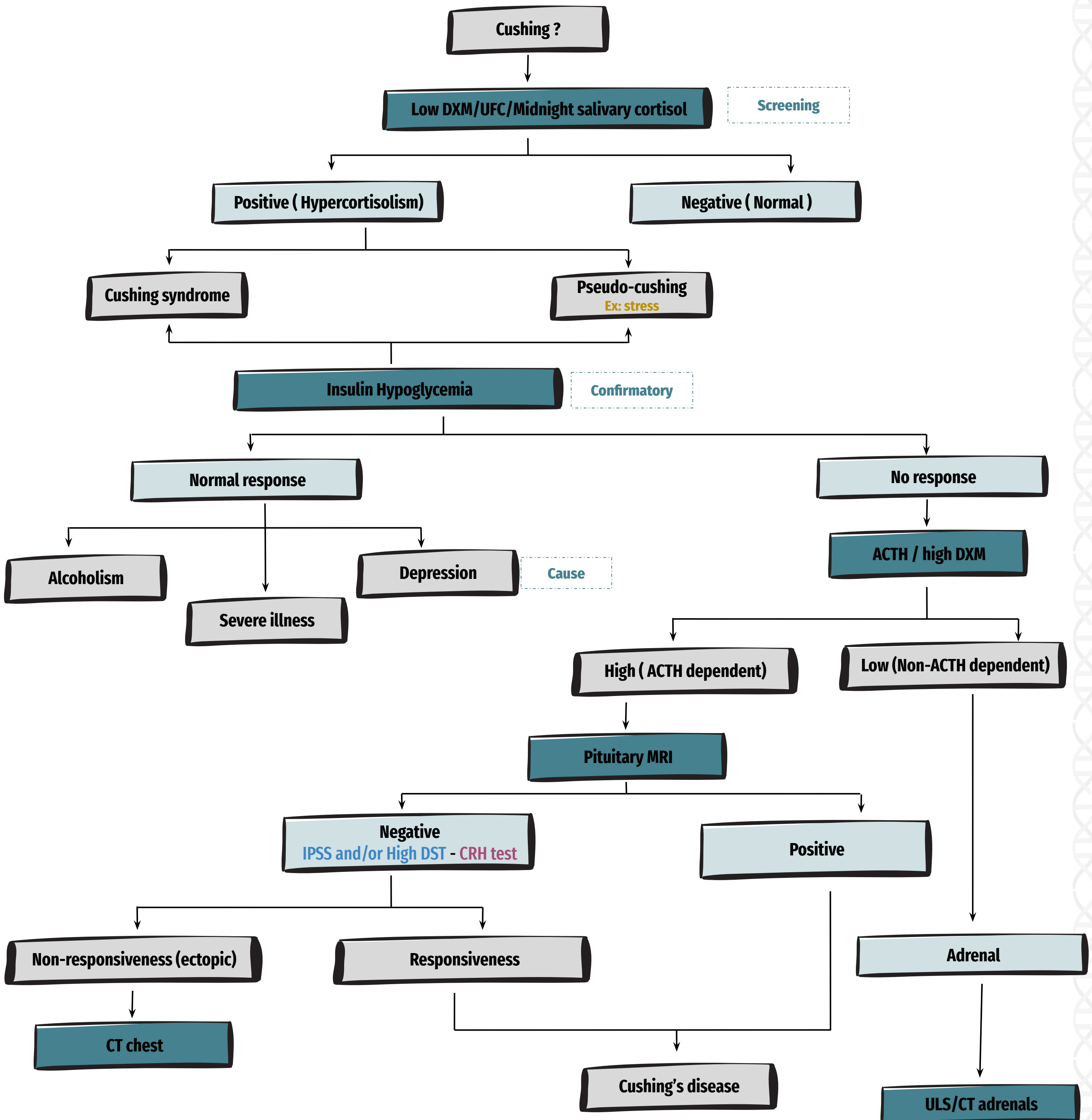
Symptoms



Signs



Investigations of Suspected Adrenocortical Hyperfunction



I. 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.

- We have to know: 1) In case of hyperfunction: we use suppressing test

2) In case of hypofunction: we use stimulating test (as Addison)

	Low-dose dexamethasone (DXM) suppression test (Overnight suppression test)	24-hour urinary free cortisol	Midnight salivary cortisol *
Procedure	<ul style="list-style-type: none"> 1 mg dexamethasone⁽⁵⁾ (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.
Result	<p>- Dexamethasone → ↓ CRH → ↓ ACTH → ↓ cortisol</p> <p>- Cortisol < 50 nmol/L (suppression) → exclude hypercortisolemia (Cushing Syndrome)</p>	Cortisol < 250 nmol/day → exclude Cushing Syndrome	Cortisol < 100 ng/dL → exclude Cushing Syndrome.
Info	<p>Precautions: enzyme inducers drugs (Phenobarbitone & phenytoin)⁽⁶⁾ → ↑ DXM metabolism and ↓ DXM blood level to achieve CRH suppression (false diagnosis of Cushing)</p>	<p>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</p>	-

Interpretation of screening tests : *

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

Pseudo-Cushing's syndrome :

- Depressed or extremely anxious patients
- Severe intercurrent illness
- Alcoholism

II. Confirmatory tests (Inpatient) : (7)

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

Insulin induced hypoglycemia *

Procedure	<ul style="list-style-type: none"> 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	<p>Normally: Basal serum cortisol: at least 145 nmol/L – At 60 - 90 minutes: the level > 425 nmol/L</p> <p>Patients with Cushing's syndrome:</p> <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> To test the integrity of the hypothalamic pituitary-adrenal (HPA) axis To distinguish true Cushing's syndrome from pseudo-Cushing's syndrome
Contraindicated in :	<ul style="list-style-type: none"> Epilepsy or heart disease

(5): هو عبارة عن cortisol ، لو أخذناها بالليل:

1. المفروض تعمل suppression لل hypothalamus ، بعدين يصير ACTH suppression ، فيصير عندي low cortisol = طبيعي وما عنده Cushing syndrome.

2. لكن لو صار عالي وما عمل suppression ، فمعناها فيه شيء مو طبيعي (tumor - adrenal cortex - pituitary).

(6): لو كانوا مرضى الصرع يأخذون هذه الأدوية، لازم يوقفونها لأنه يصير لها catabolism.

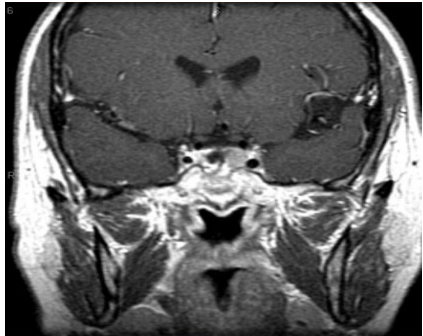
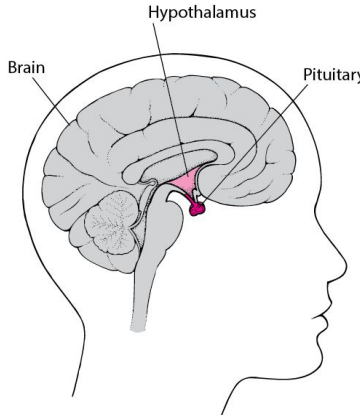
(7): لو صار عنده cortisol عالي في الصباح على الرغم من إنه أخذ DXM ، وكمان عنده 24h urinary free cortisol عالي وش نسوي؟ CONFIRMATORY TESTS

To distinguish between pseudo and true Cushing.

III. Tests to determine the cause :

to ascertain: A) The site of the pathologic lesion(adrenal cortex, pituitary or elsewhere?) B) The nature of the pathologic lesion .

1. **To differentiate ACTH-dependent from ACTH-independent** : Plasma ACTH (Diurnal rhythm)
2. **To distinguish between ACTH-dependent causes (Pituitary Vs Lung)** : **a)** High-dose DST **b)** Inferior Petrosal Sinus Sampling **c)** CRH stimulation test.
3. **Radiological tests** : MRI of pituitary and ultrasound or CT of adrenals.

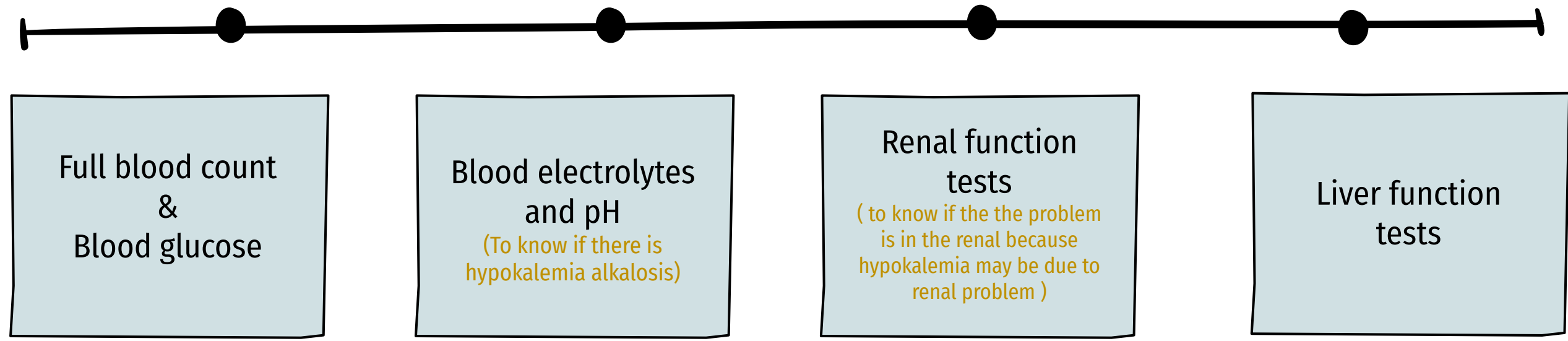
1	Plasma ACTH (Diurnal rhythm)
Procedure	It should be measured on Blood specimens at 8-9a.m and 8-9 p.m
Result	<ul style="list-style-type: none"> • Undetectable : Functional adrenal tumor → confirmed by an abdominal CT scan to detect an adrenal mass • ↑↑ ACTH : Cushing's disease (pituitary-dependent) • ↑↑↑↑ 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	<ul style="list-style-type: none"> • 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.
Result	<ul style="list-style-type: none"> • 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).⁽⁸⁾ • In contrast, only 10% of patients with ectopic ACTH production (or with adrenal tumors) show suppression.⁽⁹⁾
Info	It is used to distinguish Cushing's disease from ectopic ACTH secretion.
3	CRH stimulation test
Procedure	Measures the ACTH and cortisol levels basally and 60 minutes after injection of 100 µg CRH.
Result	<p>Ectopic ACTH & adrenal tumors :</p> <ul style="list-style-type: none"> • No response • False-positive responses are unusual <p>Cushing'S disease :</p> <ul style="list-style-type: none"> • 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
Procedure	<ul style="list-style-type: none"> • Ultrasound or CT scanning of the adrenal glands • 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.
Result	<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p>Coronal contrast-enhanced MRI of the sella turcica in a patient with recurrent Cushing's disease</p> </div> <div style="text-align: center;">  </div> </div>

(8): If I give one shot of DST (small Amount) will not inhibit Pituitary at all (because it already stimulated). But if I give him dose each 6 hours until 24 ⇒ Pituitary start to be suppressed ⇒ cortisol start to decrease (But not from small does ⇒ it need continuous does for 2 days).

(9): But If it was ectopic (not related to HYPOTHALAMIC-PITUITARY-ADRENAL AXIS) ⇒ even If I give DST ⇒ will not have any effect on the negative feedback ⇒ Because I have another source of ACTH out of this axis ⇒ so, I will not have any suppression.

IV. Other blood tests :

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



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	<50 nmol/L

Urea increase in cushing is due to protein catabolism

Further investigation revealed the following:

- CRH showed flat response for cortisol and ACTH

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

Because fall is not less than 50% of basal value.

	8am	22 pm	Ref. range
Plasma ACTH (ng/L)	220	180	7-51

Large increase in plasma ACTH so it may be due to lung cancer (ectopic) know we do radiological test.

Females 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 ⁽¹⁰⁾	No response	No response	No response
Plasma(ACTH)	Normal or ↑	Not detectable ⁽¹¹⁾	↑ ↑ ↑ ⁽¹²⁾
Dexamethasone High dose test	suppressed	Not suppressed ⁽¹³⁾	Not suppressed ⁽¹³⁾
CRH test	↑	No response	No response

(10): all of them no response ? All of them are Cushing syndrome.

(11): since it has a lot of cortisol and will leads to suppression of Pituitary.

(12): in Adenoma e.x. lung cancer will be very high because It's not controlled or regulated.

(13). since we have a already tumor in the adrenal, so already we have high Amount of cortisol and even If we give another high Amount of cortisol will not suppress pituitary.

Take Home Messages



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



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



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



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



ACTH-independent Cushing: due to adrenal adenoma or carcinoma and due to steroid therapy (iatrogenic **يعني نأخذه من برا**).*



Disorders of the adrenals are uncommon.*



Sensitive screening tests for adrenocortical functions are important.*



Additional confirmatory tests are required to establish the diagnosis and rule out pseudo-Cushing.*



Other biochemical tests and radiological investigation are required to determine the cause of Cushing's syndrome.*



Extra Summary

Adrenal Gland	Adrenal cortex	<ul style="list-style-type: none"> • Zona glomerulosa (mainly release aldosterone) • Zona fasciculata (mainly release cortisol) • Zona reticularis (mainly release sex hormones) 	
	Steroid hormone Synthesis	<ul style="list-style-type: none"> • 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) 	
	Glucocorticoids function	<p>In the liver :</p> <ul style="list-style-type: none"> • Increases amino acids uptake into liver and utilize them for gluconeogenesis • Increases ketogenesis <p>In muscles :</p> <ul style="list-style-type: none"> • Increases proteolysis and amino acids release <p>In adipose tissue :</p> <ul style="list-style-type: none"> • Increases lipolysis <p>Conserving glucose by :</p> <ul style="list-style-type: none"> • Inhibiting glucose uptake into peripheral tissues 	
	Regulation of ACTH and cortisol secretion	<ul style="list-style-type: none"> • Negative feedback • Stress • The diurnal rhythm of serum cortisol 	
	Cortisol transport	<p>90% is protein-bound to Cortisol Binding Globulin (CBG) which :</p> <ul style="list-style-type: none"> • ↑↑ In pregnancy and with estrogen treatment • ↓↓ In hypoproteinemic states <p>The biologically active cortisol is free in the serum</p>	
	Cortisol and ACTH measurements	<ul style="list-style-type: none"> • Plasma (ACTH) and serum (cortisol) • Urinary cortisol excretion (normal UFC is < 250 nmol/24h) 	
	Cushing's Syndrome	Symptoms	<ul style="list-style-type: none"> • Weight gain (truncal obesity). Red striae and proximal muscle weakness • Hirsutism, moon-face and excessive sweating • Buffalo hump
Signs		<ul style="list-style-type: none"> • Hypertension and hyperglycemia/diabetes • Immune suppression and increased protein metabolism • Hypokalemic alkalosis and loss of diurnal rhythm 	
Investigations		1) Screening tests	<ul style="list-style-type: none"> • DXM suppression test (Cortisol < 50 nmol/L) • 24-hour urinary free cortisol • Midnight salivary cortisol
		2) Confirmatory tests	<ul style="list-style-type: none"> • Insulin induced hypoglycemia
		3) Tests to determine the cause	<ul style="list-style-type: none"> • Plasma ACTH (diurnal rhythm) • High dose DST • CRH stimulation test • Radiological investigation
Other blood tests	Full blood count & blood glucose, renal function test, liver function test and blood electrolytes and PH		



MCQs

1-How many carbon atoms in cortisol?

A-27

B-21

C-19

D-18

2- Which of the following causes of Cushing's syndrome does the phrase "Cushing's disease" specifically refer to?

A-Adrenal adenoma

B-Pituitary Adenoma

C-Iatrogenic

D-Ectopic ACTH production

3-what is the normal range of urinary free cortisol (UFC) ?

A->50 nmol /24h

B- < 50 nmol /24h

C- >250 nmol/24h

D-< 250 nmol/24h

4-29 year old female patient, came to the clinic with a history of increased facial hair over the past year. Her husband mentioned that she is having mood swings and her face seems to have become round. They also mentioned that they are not very financially capable. Which of the following tests would you order to confirm your diagnosis of Cushing's Syndrome ?

A-Insulin Induced Hypoglycemia

B- CRH Suppression

C- CBC + MRI + CT + Blood Glucose + LFT + Ultrasound

D-Low Dose Dexamethasone

5- If the patient didn't collect his urine completely in 24- hours urinary free cortisol test , the result will be ?

A- false-negative result

B-false- positive result

C- true-negative result

D-true-negative result

6-Which of the following is not a symptom of Cushing's syndrome?

A-Weight gain

B-Hirsutism

C-Increased proximal muscles bulk

D-Purple striae on the trunk and legs

Answers key

1-B

2- B

3- D

4- A

5- A

6-C



SAQs

1- Mention 3 causes of Pseudo-Cushing.

Alcoholism, Severe illness, Depression

2- Mention 3 functions of cortisol.

- Increase gluconeogenesis in the liver.
- Increase amino acid uptake and degradation in the liver.
- Increase ketogenesis in the liver.
- Increase proteolysis and amino acids release in the muscles.
- Increase lipolysis through breakdown of fat in adipose tissue.
- Conserve glucose by inhibiting its uptake into muscle and fat cells.

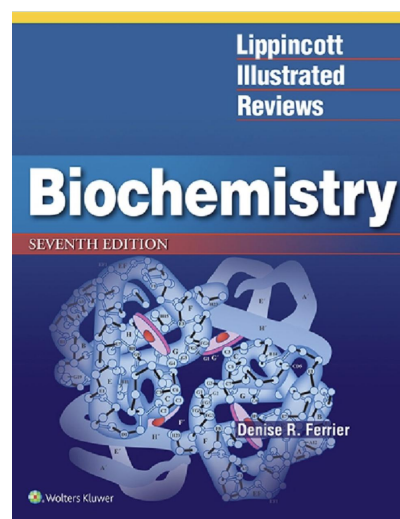
3- Mention 3 signs of Cushing syndrome

Hypokalemic alkalosis, hyperglycemia or diabetes due to insulin resistance, hypertension, impaired immunity, loss of diurnal rhythm of cortisol and ACTH, increase protein metabolism.

Resources

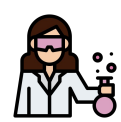


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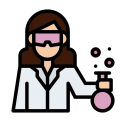




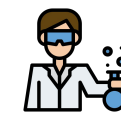
Leaders



Sadeem Alzayed

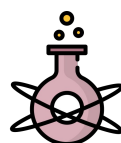


Ghada Alabdi

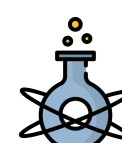


Osama Alharbi

Members



Banan Alqady
Budoor Almubarak
Dana Naibulharam
Farah Alsayed
Ghaida Alassiry
Mais Alajmi
Mayasem Alhazmi
Noura Alkathiri
Rania Almutiri
Renad Alhomaiddi
Shatha Aldossari
Shayma Alghanoum
Yara Alasmari
Yasmine Alqarni



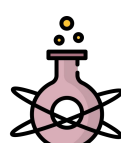
Abdulmohsen Alqadeeb
Abdulrhman Alsuhaibany
Albara Aldawoud
Mohammed Alturki
Mubarak Alanazi
Osama Mobeirek

Organizers

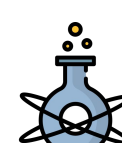
Arwa Alqahtani
Banan Alqady
Ghada Alothman

Mona alomiriny
Norah aldakhil
Reem Alamri

Notetakers



Lama Alahmadi
Raghad Albarrak
Reem Alqahtani



Mohammed Benhji
Mohammed Beyari
Nawaf Alshahrani

Revisers

Noura Alshathri

Rania Almutiri



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