

Motto Vision; The Dream/Tomorrow



- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine





Endocrinology Module <u>2nd</u> Year MBBS (CBL) <u>Addison's Disease</u>

Department of Biochemistry Rawalpindi Medical University Rawalpindi

Presenter: Dr Nayab Ramzan Deptt of Biochemistry RMU Date: 07-02-25

LEARNING OBJECTIVES

At the end of this session student should be able to:

- 1. Describe the Synthesis of Cortisol and Aldosterone
- 2. Discuss the Role of Cortisol and Aldosterone in the body
- 3. Explain the Mechanism of Action of Aldosterone and Cortisol
- 4. Describe the Related Disorders
- 5. Integrate Anatomical, Physiological and Clinical aspects
- 6. Correlate and build core knowledge on the basis of latest Research, Family Medicine, Artificial Intelligence & Bioethics.



Professor Umar Model of Integrated Lecture



Anatomical Aspects

ADRENAL GLANDS :

OR Suprarenal glands

- Paired organ each weight about 4 grams, pyramidal in shape, located on the top of the kidneys, one on each side at the level of the T12
- It enclosed by fibro elastic connective tissue capsule.





Structure of the adrenal gland

Adrenal Cortex

Adrenal Cortex

Region	Types	Hormones	
Zona Glomerulosa	Mineralo corticoids	1. Aldosterone (mainly)	
Zona Fasciculata	Glucocorticoids	 Cortisol (mainly) Corticosterone Androgens (small amount) Estrogens (small amount) 	
Zona Reticularis	Gonado corticoids	 <u>Androgens:</u> DHEA "dehydroepiandrosterone" (mainly) Androstenedione Estrogen (small amount) <u>Glucocorticoids</u> small amounts 	

Physiological Aspects

Hormones	Functions			
Adrenal cortex				
Aldosterone	The cells appear normal			
Cortisol	Reacts to body stress (flight or fright response), management and utilisation of macronutrients			
Androgens	Male sex hormone that helps in the development of the reproductive organs and male sexual features such as cracking of the voice, facial hair and body hair growth			
Adrenal Medulla				
Adrenaline	Supports the body's reaction to stress by increasing heart rate, blood pressure and blood sugar levels			
Noradrenaline	Constriction of blood vessels along with increased heart rate, blood pressure and blood sugar levels			

Core Knowledge Synthesis of Cortisol and Aldosterone



Regulation Of Cortisol Secretion

Regulation of Cortisol secretion

The secretion of cortisol by zona fasciculata is regulated exclusively by the hypothalamicpituitary axis Cortisol secreted by the adrenal cortex suppresses secretion of CRH and ACTH.



Role Of Cortisol In The Body



Mechanism of Action Cortisol

- Most of the known effects of the glucocorticoids are mediated by widely distributed glucocorticoid receptors.
- These proteins are members of the superfamily of nuclear receptors, which includes steroid, sterol (vitamin D), thyroid, retinoic acid, and many other receptors with unknown or nonexistent ligands (orphan receptors). All these receptors interact with the promoters of—and regulate the transcription of target genes.
- In the absence of the hormonal ligand, glucocorticoid receptors are primarily cytoplasmic, in oligomeric complexes with heat-shock proteins (hsp). The most important of these are two molecules of hsp90.
- Free hormone from the plasma and interstitial fluid enters the cell and binds to the receptor, inducing **conformational changes** that allow it to dissociate from the heat shock proteins.
- The ligand-bound receptor complex then is actively transported into the nucleus, where it interacts with DNA and nuclear proteins. As a homodimer, it binds to glucocorticoid receptor elements (GREs) in the promoters of responsive genes. The GRE is composed of two palindromic sequences that bind to the hormone receptor dimer.



Core Knowledge Regulation of Aldosterone



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Core Knowledge Role Of Aldosterone In The Body



Core Knowledge Role of Aldosterone in the body



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Mechanism of Action of Aldosterone

 Binding of Aldosterone with receptors initiates
 DNA Transcription, initiating transcription of specific proteins resulting an increase in the number of sodium channels Na-K-ATPase molecules.



Role of Adrenal Hormones In Stress





<u>Pregnenolone</u> is the major precursor of Corticosterone and Aldosterone.

17- hydroxypregnenolone is the major precursor of cortisol. The <u>Enzymes and Cofactors</u> for the reactions progressing down each column are shown on left side & top. When a particular enzyme is deficient, hormone production is blocked at the points indicated by the shaded bars.18 Core Knowledge

Clinical Scenario - Case

Clinical Scenario (Addison's Disease)

• A 25 year old female accountant came to OPD of BBH with complaint of progressive weakness and fatigue. She complained that at times she felt dizzy and had fainted on one occasion. She felt nausea off & on and anorexia with few episodes of vomiting. There was also off & on diarrhea. She had noticed gradual loss of weight for last few months. She complains of irritability of mood.

- Examination showed low pulse rate and low B.P. Lab investigations showed markedly low cortisol level, raised serum potassium and low sodium.
- Provisional diagnosis of Addison's Disease was made.

Adrenal Insufficiency (AI)

Types Of Adrenal Insufficiency:

There are three major types of Adrenal Insufficiency:

Primary Adrenal Insufficiency: It is due to impairment of the adrenal glands (Addison's Disease)

Secondary Adrenal Insufficiency: It is caused by impairment of the pituitary gland i.e reduced ACTH.

Tertiary Adrenal Insufficiency: It is due to hypothalamic disease and decrease in corticotropin releasing factor (CRF)

		Biochemistry		
•	Primary Adrenal Insufficiency (PAI)			
	Diseases of the adrenal gland	↓ cortisol		
		↑ACTH		
		+/-↓ Aldosterone, ↑renin		
\cap	Secondary Adrenal Insufficiency			
0	Interference with corticotropin (ACTH) secretion by the pituitary	↓ cortisol		
		↓ACTH		
	The ACTH deficiency may be isolated or occur in conjunction with other pituitary hormone deficiencies	↔Aldosterone and renin		
	Tertiary Adrenal Insufficiency			
D	Interference with corticotropin- releasing hormone (CRH) secretion by the hypothalamus	↓cortisol ↓ACTH ↔Aldosterone and renin		

Vertical Integration





Vertical Integration

Mnemonic



Vertical Integration

Diagnostic Approach



Pharmacological Integration

Table 3. Medications for the Treatment of Addison Disease

Medication	Dosage	Comments	Monitoring
Glucocorticoids			
Prednisone	3 to 5 mg once daily	Use stress doses for illness, surgical procedures, and hospitalization	Symptoms of adrenal insufficiency; low to normal plasma adrenocorticotropic hormone levels indicate over-replacement
Hydrocortisone	15 to 25 mg divided into two or three doses per day	Use stress doses for illness, surgical procedures, and hospitalization	
Dexamethasone	0.5 mg once daily	Use intramuscular dose for emergencies and when unable to tolerate oral intake	
Mineralocorticoid			
Fludrocortisone	0.05 to 0.2 mg once daily	Dosage may need to increase to 0.2 mg per day in the summer because of salt loss from perspiration	Blood pressure; serum sodium and potassium levels; plasma renin activity in the upper normal range
Androgen			
Dehydroepiandrosterone (DHEA)	25 to 50 mg once daily	Available as an over-the-counter supplement; can improve mood and quality of life in women	Libido, mood, and sense of well- being

Family Medicine

Family Medicine plays important role in following manner:

- Diagnosis
- Education
- Dietary Guidance
- Monitoring
- Refer to Specialists

Artificial Intelligence

Artificial Intelligence plays role in following aspects:

- Personalized Nutrition
- Diagnostic Tools
- Food Recommendations
- Drug Development

Bioethics

- Informed Consent
- Equal Access to healthcare
- Resource Allocation
- Confidentiality & Privacy

Suggested Research Article

Link: https://www.ncbi.nlm.nih.gov/ pmc/articles/PMC10243343/

- Journal Name: International Journal of General Medicine, Published online 2023 Jun 2.
- Title: Addison's Disease: Diagnosis and Management Strategies

Author Name:

Mara Carsote, Claudiu Nistor

Abstract: We aim to overview Addison's disease (AD) with regard to current diagnosis and management. This is a narrative review of full-length articles published in English between January 2022 and December 2022 (including online ahead of print versions) in PubMedindexed journals. We included original studies in living humans regardless of the level of statistical significance starting from the key search terms "Addison's disease" or "primary adrenal insufficiency" in title or abstract. We excluded articles with secondary adrenal insufficiency. Briefly, 199 and 355 papers, respectively were identified; we manually checked each of them, excluded the duplicates, and then selected 129 based on their clinical relevance in order to address our 1year analysis. We organized the data in different subsections covering all published aspects on the subject of AD. To our knowledge, this is the largest AD retrospective from 2022 on published data. A massive role of genetic diagnosis especially in pediatric cases is highlighted; the importance of both pediatric and adult awareness remains since unusual presentations continue to be described. COVID-19 infection is a strong player amid this third year of pandemic although we still not do have large cohorts in this particular matter as seen, for instance, in thyroid anomalies. In our opinion, the most important topic for research is immune checkpoint inhibitors, which cause a large panel of endocrine side effects, AD being one of them.

CBL --- Questions

- 1. What is the role of cortisol on carbohydrate metabolism?
- 2. What is anti-inflammatory effect of cortisol?
- 3. What is the effect of ACTH on serum cortisol level?
- 4. What are the effects of excess cortisol in the body?
- 5. What is the mechanism of action of cortisol?

Learning Resources

- Harper's illustrated Biochemistry32nd edition, chapter41, pages 485-488, 491-492
- Lippincott Illustrated Reviews BIOCHEMISTRY, Eighth Edition, chapter 18, pages 262 266.
- Google scholar
- Google images

How To Access Digital Library

- 1. Steps to Access HEC Digital Library
- 2. Go to the website of HEC National Digital Library.
- 3. On Home Page, click on the INSTITUTES.
- 4. A page will appear showing the universities from Public and Private Sector and other Institutes which have access to HEC National Digital Library HNDL.
- 5. Select your desired Institute.
- 6. A page will appear showing the resources of the institution
- 7. Journals and Researches will appear
- 8. You can find a Journal by clicking on JOURNALS AND DATABASE and enter a keyword to search for your desired journal.

