Adrenal GLAND DISORDERS

Raniah A. Al-Jaizani
Lecturer
Clinical Pharmacy Dept.
Adrenal gland

- Adrenal glands are paired small organs setting atop the upper poles of each kidney, which weighs 4 g.
- Each gland has:
  - Adrenal medulla (inner part)
  - Adrenal cortex (outer part)

Adrenal cortex

- Occupies 90% of the total adrenal gland.
- It’s consist of three zones (cell):

<table>
<thead>
<tr>
<th>Zona glomerulosa</th>
<th>Mineralocorticoids (aldosteron)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zona fasciculate</td>
<td>Glucocorticoids (cortisol)</td>
</tr>
<tr>
<td>Zona reticularis</td>
<td>Sex steroids (androgen, estrogen)</td>
</tr>
</tbody>
</table>
Adrenal medulla

- 10% of the total gland (central portion).
- Responsible for production of catecholamines which are:
  - Epinephrine
  - Nor epinephrine
- The regulation of these hormones by sympathetic nerves system.

Negative feedback inhibition of ACTH secretion by cortisol

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Episodic and Diurnal Rhythm of ACTH Secretion

- ACTH is secreted in episodic bursts throughout the day, after a diurnal (circadian) rhythm, with bursts most frequent in the early morning and least frequent in the evening.
- The peak level of cortisol in the plasma normally occurs between 6:00 and 8:00 AM (during sleep, just before awakening) and the nadir at around 12:00 AM.
- The diurnal rhythm is altered also by changes in patterns of sleep, light-dark exposure, or food intake; physical stress such as major illness, surgery, trauma, or starvation; psychologic stress, including severe anxiety, depression, and mania; CNS and pituitary disorders; liver disease and other conditions that affect cortisol metabolism; chronic renal failure; alcoholism; and antiserotonergic.

Fluctuations in plasma ACTH and glucocorticoids (11-OHCS) throughout the day. Note the greater ACTH and glucocorticoid rises in the morning before awakening.
Major factors control ACTH secretion & thus control of cortisol secretion

1. Modulating impact of stressors on the hypothalamus.
2. Inhibitory effect of increase free cortisol on ACTH release.
3. Sleep-wake cycle (cortislo peak @ 8:00 am & nadir @ ~ 10 pm).

Metabolic Effects of Glucocorticoids

• Glucocorticoids excess causes alteration in:
  1. Protein & CHO metabolism.
  2. Distribution of adipose tissue.
  3. Electrolytes.
  4. The Immune system.
  5. Gastric secretion.
  7. Erythropoisis.
### Metabolic Effects of Glucocorticoids

<table>
<thead>
<tr>
<th>Target Tissue</th>
<th>Effect</th>
<th>Mechanism</th>
</tr>
</thead>
</table>
| Muscle | Catabolic | Inhibit glucose uptake and metabolism  
Decrease protein synthesis  
Increase release of amino acids, lactate |
| Fat | Lipolytic | Stimulate lipolysis  
Redistribution of fat to face & trunk |
| Liver | Synthetic | Increase gluconeogenesis  
Increase glycogen synthesis, storage  
Increase blood glucose |
| Immune system | Suppression | Reduce number of circulating lymphocytes, monocytes, eosinophils, basophils  
Inhibit T lymphocyte production of interleukin-2  
Interfere with antigen processing, antibody production and clearance |
| | Anti-inflammatory | Decrease migration of neutrophils, monocytes, lymphocytes to sites of injury |
| Other | | Stimulate release of neutrophils from marrow  
Interfere with neutrophil migration out of vascular compartment |
### Metabolic Effects of Glucocorticoids

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<tr>
<th>Target Tissue</th>
<th>Effect</th>
<th>Mechanism</th>
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</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Increase cardiac output</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increase peripheral vascular tone</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>Increase glomerular filtration rate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aid in regulating water, electrolyte balance</td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>Osteoprosis</td>
<td>Loss of protein in matrix of bone</td>
</tr>
<tr>
<td>Brain</td>
<td>Emotional liability, euphoria, and insomnia</td>
<td></td>
</tr>
<tr>
<td>GI</td>
<td>HCL, pepsin</td>
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</tbody>
</table>

### Pharmacological effect of glucocorticoids

- Antiinflammatory effects.
- Suppress delayed hypersensitivity reactions.
Cushing’s syndrome

- Results from the combined metabolic effects of persistently elevated blood levels of glucocorticoids
- Can occur:
  - Excessive cortisol secretion caused by a disturbance in the hypothalamic-pituitary adrenal axis (spontaneous).
  - Long term Administration of pharmacologic doses of glucocorticoids (iatrogenic)
Cushing’s syndrome types

ACTH dependent
- Nontumours adrenocortical Hyperfunction
- Ectopic ACTH syndrome

ACTH independent
- Autonomous adrenocortical Hyperplasia
- Tumorous adrenocortical hyperfunction
  - Carcinoma
  - Adenoma

Ectopic ACTH: In this syndrome, ACTH or an ACTH-like peptide is elaborated by a tumor such as carcinoma of the lung. The adrenals are stimulated, circulating cortisol is increased, and pituitary ACTH secretion is inhibited.

Ectopic CRH: In this rare syndrome, CRH is elaborated by a tumor such as a bronchial carcinoid. The pituitary is stimulated, and there is elaboration of excess ACTH. The adrenals are stimulated, and circulating cortisol is increased.
Clinical features

Psychiatric effects
- "Insomnia, euphoria, depression, apathy" (in 50-80%)

Growth retardation
- (in child) (85%)

Abdominal Striae

Alteration in mental function
- "Insomnia, euphoria, depression, apathy" (50-80%)

Acne, oily skin, and hirsutism
- (in female) (50%)

Thinning of hair
- (in female) (60%)

Hair thinning
- (in female) (70%)

Increased appetite
- (in female) (70%)

Increased hunger
- (in female) (70%)

Diabetes mellitus
- (in female) (50%)

Cortisol in insulin antagonist

Abdominal Striae

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Diagnostic tests

1. 24-Hour Urinary Free Cortisol Level (free scanning).
2. Dexamethasone Suppression Test.
4. CRH Stimulation Test.
5. Metyrapone Test.
6. Radiologic Imaging.

24-Hour Urinary Free Cortisol Level

- Urinary free cortisol measurement is the most sensitive and specific test to screen for and confirm the presence of Cushing's syndrome.
- The patient's urine is collected over 24-hour period & tested for the amount of cortisol.
- The cortisol reference range is less than 80 to 120 µg per 24 hours (220–330 nmol/24 hours); free cortisol less than 10 µg per 24 hours (<28 nmol/24 hours) excludes Cushing's syndrome.
- Once Cushing's syndrome has been diagnosed, other tests are used to find the exact location of the abnormality that leads to excess cortisol production.
Dexamethasone Suppression Test

- The high-dose dexamethasone suppression test is useful for differentiating pituitary from ectopic ACTH secretion.
- Patients with Cushing's syndrome lack normal negative feedback cortisol regulation.
- Dexamethasone, used to test for negative feedback control.
- Patients with either ectopic ACTH or primary adrenocortical disease do not suppress ACTH or cortisol level.

Basal plasma ACTH concentration

- ↑ In pt with ACTH dependent Cushing’s syndrome
  (A plasma ACTH more than 20 pg per mL (>4.4 pmol/L) indicates ACTH-dependent Cushing's syndrome).
- ↓ In pt with ACTH independent Cushing’s syndrome.
  (A plasma ACTH less than 5 pg per mL (<1.1 pmol/L) indicates ACTH-independent Cushing's syndrome).
Corticotropin-Releasing Hormone Stimulation Test

- It helps to distinguish between pituitary adenomas & ectopic ACTH Syndrome or cortisol-secreting adrenal tumors.
- CRH stimulates ACTH secretion in patients with Cushing's disease but not ectopic ACTH-secreting tumors.

Metyrapone Test

- Metyrapone blocks the synthesis of 11-deoxycortisol to cortisol at the level of the adrenal enzyme ➔ decreased circulating cortisol.
- Plasma 11-deoxycortisol increases in response to increased pituitary ACTH secretion.
- Patients with Cushing's disease have a supranormal increase in plasma 11-deoxycortisol.
- Patients with ectopic ACTH-secreting tumors show little or no response.
Radiologic Imaging

- CT is used to determine the location and size of tumors and to differentiate between adrenal adenomas and carcinomas

Aldosteronism

- Aldosterone (the mineralocorticosteroid hormone of the adrenal cortex):
  - Is major regulator of extracellular fluid volume by causing Na & H2o retention and is controlled by renin-angiotensin-aldosteron mechanism.
  - It is also major determinant of K balance.
- Results from excessive production of aldosterone.
Type of aldosteronism

Primary aldosteronism (conn’s syndrome)
excessive aldosterone occurs as a result of tumor or hyperplasia of the adrenal cortex.

Secondary aldosteronism
Occurs in conditioning the activation of renin angiotension system (CHF, liver cirrhosis).

The clinical consequences of aldosteronism

- Excess aldosterone cause Na & H2O retention.
- Expansion of the ECF volume which lead to hypertension, hypernatremia, hypokalemia, metabolic alkalosis & edema.
Diagnosis

1. Inc. levels of aldosterone in plasma, urine.
   • In primary ald. renine level is low.
   • In secondary ald. renine level is high.
3. Abnormal electrolyte levels (↑ Na, ↓ K, metabolic alkalosis)
4. CT scan or MRI can help detect & localized an adrenal lesion in patient with pri. ald.

Syndromes of androgen excess

Androgen physiology:
• Various androgen are normally secreted by both men & women.
• The three major types of androgen are:
  1. Dehydroepiandrosterone (DHEA).
  2. Delta 4-androstenedione.
  3. Testosterone.
Syndromes of androgen excess

• Excess secretion of androgen in female cause virilization, acne, deeping of voice, baldness, oligomenorrhea or amenorrhea and hirsutism (excessive growth of body hair in the female in a characteristic masculine distribution over the face, nipples, and pubic area).

Differential Diagnosis of Androgen Excess

• Four major categories of conditions are associated with androgen excess:
  1. Adrenocortical.
  2. Ovarian.
  3. Simple or idiopathic hirsutism.
  4. Miscellaneous states.
Clinical and laboratory evaluation of hirsute women

• Determine whether the hirsutism is by itself or accompanied by manifestations of virilization.
• Determine whether the symptoms are those of androgen excess alone or are accompanied by symptoms of cortisol excess.
• Patient suspected of an adrenal or ovarian tumor should undergo pelvic examination, abdominal & pelvic CT scan & MRI.
• ↑ Level of total & free testosterone.
Pheochromocytoma:

- A rare cause of secondary hypertension, is an adrenal medullary tumor that releases excessive amounts of catecholamines.

- Clinical manifestations:
  - Mainly hypertension that may be paroxysmal (45% of cases) or sustained
  - With:
    1. Headaches on the top of the head.
    2. Palpitations.
    3. Pallor.
    4. Diaphoresis.
    5. Dysrhythmias.

Diagnosis

- Basal plasma Catecholamines: ↑
- 24-Hour Urinary catecholamines test : ↑
- Clonidine suppression test: fail to supress Catecholamines secretion.
- CT scan: help locate the tumor.
Addison's disease

- Deficiency of all three hormone groups produced by the adrenal gland (glucocorticoids, mineralcorticoids and androgens).
- Adrenocritical hormones secretion insufficient because:
  1. Insufficiency of the adrenal cortex (Primary adrenal insufficiency).
  2. Deficient secretion of ACTH (Secondary adrenal insufficiency).
     - More 80% of both glands are destroyed before signs & symptoms occur
Primary insufficiency

- Due to destruction of adrenal cortex by:
  1. Autoimmune diseases >50%.
  2. Tuberculosis, AIDS.
  3. Adrenal hemorrhage secondary to anticoagulant therapy

Secondary insufficiency

- Due to disease or drug that decrease ACTH:
  1. Panhypopituitarism.
  2. Sudden withdrawal of exogenous corticosteroid drugs.
Clinical Manifestations

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Weight loss</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Abdominal pain</td>
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<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Hypotension</td>
</tr>
<tr>
<td>Amenorrhea</td>
</tr>
<tr>
<td>Dec. libido</td>
</tr>
<tr>
<td>Dec. Axillary &amp; pubic hair</td>
</tr>
<tr>
<td>Hyperpigmentation (important characteristic of primary adrenocortical insufficiency)</td>
</tr>
<tr>
<td>Dehydration</td>
</tr>
<tr>
<td>Dec. cardiac output</td>
</tr>
<tr>
<td>Tachycardia</td>
</tr>
<tr>
<td>Metabolic acidosis,</td>
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<tr>
<td>Hyponatremia</td>
</tr>
<tr>
<td>Hyperkalemia</td>
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<tr>
<td>Depression</td>
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</table>

Laboratory tests can indicate primary adrenocortical insufficiency

1. ✇ Plasma cortisol level
2. ✇ Urinary excretion of the degradation products or metabolites of cortisol (urinary 17-hydroxycorticoid).
3. ↑ Plasma ACTH level.
4. Serum electrolyte levels are abnormal (⬇ Na, ↑ K).
5. ↑ Serum renin.
6. ✇ Serum aldosterone.
Laboratory tests of secondary adrenal insufficiency

1. ✅ Plasma ACTH level.
2. ✅ Level of cortisol & its urinary metabolites.
3. Aldosterone levels is normal.

Addisonian crisis

- Acute adrenal insufficiency.
- An episode of severe hypotension, vascular collapse, acute renal failure and hypothermia caused by a combined lack of cortisol and aldosterone. It may be precipitated by infection, trauma and dehydration in individuals with Addison’s disease and can be life-threatening.
Iatrogenic acute adrenocortical (secondary) failure

- Prolonged high dose therapeutic corticosteroids $\rightarrow$ abruptly stopped $\rightarrow$ acute adrenocortical failure with hypovolimic, hypotensive shock, hypoglycemia, and risk of sudden death.
- Corticosteroids drug dosage must be tapered before complete withdrawal to allow time for adrenocortical function to recover.

Questions ????