Adrenal gland disorders

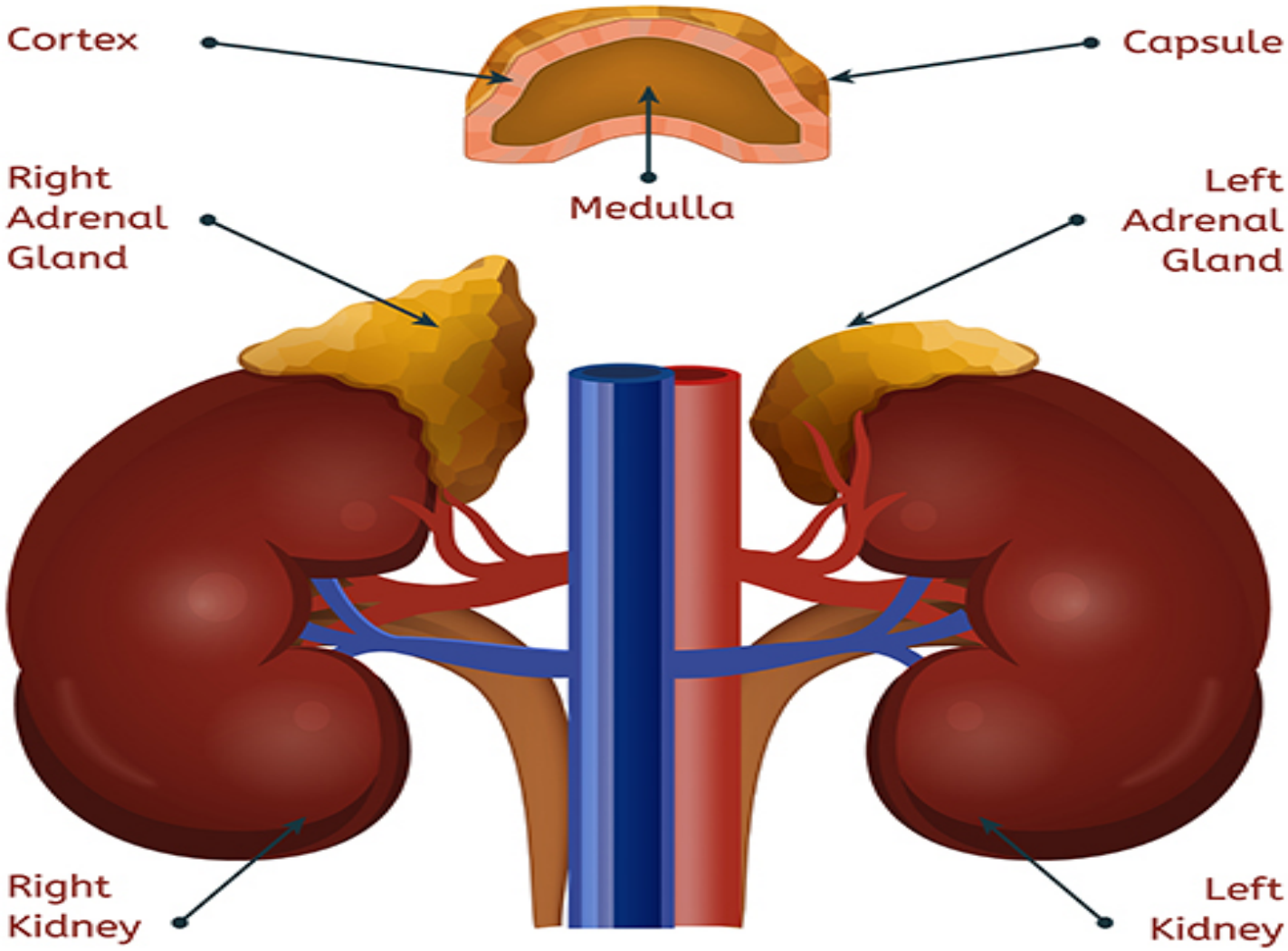
The adrenal glands are important in the synthesis and regulation of key hormones.

They play a crucial role in water and electrolyte homeostatsis, as well as regulation of blood pressure, carbohydrate and fat metabolism, physiologic response to stress, and sexual development and differentiation.

The adrenal medulla secretes the catecholamines epinephrine (also called adrenaline) and norepineprhine (also called noradrenaline), which are involved in regulation of the sympathetic nervous system.

The adrenal cortex consists of three histologically distinct zones: **zona glomerulosa**, **zona fasciculata**, and an innermost layer called the **zona reticularis**.

KIDNEYS & ADRENAL GLANDS



The zona glomerulosa is responsible for the production of the mineralocorticoids **aldosterone,** deoxycorticosterone, and 18-hydroxy-deoxycorticosterone.

The zona fasciculata produces the glucocorticoid hormone **cortisol.** The normal rate of cortisol production is approximately 8 to 15 mg/day.

Its production increases markedly during physiologic stress, such as during acute illness, surgery, or trauma.

Cortisol is converted in the liver to an inactive metabolite known as cortisone.

The zona reticularis produces the androgens **androstenedione,**

dehydroepiandrosterone (DHEA), and the sulfated form of **dehydroepiandrosterone** (DHEA-S).

- Androstenedione and DHEA are converted in the periphery, largely to testosterone and estrogen.

- Adrenal hormone production is controlled by the hypothalamus and pituitary gland.

- When sufficient or excessive cortisol levels are reached, a **negative feedback** is exerted on the secretion of CRH and ACTH, thereby decreasing overall cortisol production.

- The control of adrenal androgen synthesis also follows a similar negative feedback mechanism.

Adrenal insufficiency:

- ✓ Adrenal insufficiency generally refers to the inability of the adrenal glands to produce adequate amounts of ***cortisol*** for normal physiologic functioning or in times of stress.

- ✓ The condition is usually classified as **primary**, **secondary**, or **tertiary** depending on the etiology. Chronic adrenal insufficiency is rare.

- ✓ Primary adrenal insufficiency usually is diagnosed in the third to fifth decades of life, whereas secondary adrenal insufficiency is commonly detected during the sixth decade.

- ✓ Adrenal insufficiency is more prevalent in women than in men.

Pathophysiology:

- It occurs from destruction of the adrenal cortex, usually from an autoimmune process.

- Secondary adrenal insufficiency occurs as a result of a pituitary gland dysfunction whereby decreased production and secretion of ACTH leads to a decrease in cortisol synthesis.

- Tertiary adrenal insufficiency is a disorder of the hypothalamus that results in decreased production and release of CRH, which, in turn, decreases pituitary ACTH production and release.

- Acute adrenal insufficiency (i.e., adrenal crisis) results from the body's inability to increase endogenous cortisol sufficiently during periods of excessive physiologic stress.

- ✓ Medications that inhibit cortisol synthesis (e.g., ketoconazole) or accelerate cortisol metabolism (e.g., phenytoin, rifampin, phenobarbital) can also cause primary adrenal insufficiency.

- ✓ Secondary adrenal insufficiency most commonly results from exogenous corticosteroid use, leading to suppression of the hypothalamic-pituitary- adrenal axis and decreased release of ACTH, resulting in impaired androgen and cortisol production.

- ✓ Mirtazapine and progestins (e.g., medroxy- progesterone acetate, megestrol acetate) have also been reported to induce secondary adrenal insufficiency. Secondary disease typically presents with normal mineralocorticoid concentrations.

Clinical Presentation and Diagnosis of Adrenal Insufficiency:

- The cardinal symptoms and signs are weakness and fatigue requiring rest periods, gastrointestinal symptoms, weight loss, and hypotension.

- Weight loss, dehydration, hyponatremia, hyperkalemia, and elevated blood urea nitrogen are common in Addison's disease.

- Hyperpigmentation is common in Addison's disease and may involve exposed and nonexposed parts of the body. Hyperpigmentation is usually not seen in secondary adrenal insufficiency because of low amounts of melanocyte-stimulating hormone.

- The short cosyntropin-stimulation test can be used to assess patients with suspected hypocortisolism. An increase to a cortisol level ≥18 mcg/dL (500 mmol/L) rules out adrenal insufficiency.

- Patients with Addison's disease have an abnormal response to the short cosyntropin-stimulation test. Plasma ACTH levels are usually 400 to 2,000 pg/mL in primary insufficiency versus normal to low (0 to 50 pg/mL) in secondary insufficiency.

- A normal cosyntropin-stimulation test does not rule out secondary adrenal insufficiency.

- Other tests include the insulin hypoglycemia test, the metyrapone test, and the corticotrophin-releasing hormone stimulation test.

Laboratory Tests:

- Decreased basal and stress-induced cortisol levels.
- Decreased aldosterone level (in primary adrenal insufficiency only).
- Lack of increase in cortisol and aldosterone level after ACTH stimulation.

Other Diagnostic Tests:

- Computed tomography (CT) or magnetic resonance imaging (MRI).
- The presence of anti-adrenal antibodies.

Treatment and Outcome Evaluation:

DESIRED OUTCOME

- The goals of treatment for adrenal insufficiency are to limit morbidity and mortality, return the patient to a normal functional state, and prevent episodes of acute adrenal insufficiency.

Nonpharmacologic Therapy

- Patients must be informed of treatment complications, expected outcome, proper medication administration and adherence, and possible side effects.

- **Pharmacotherapy of Adrenal Insufficiency**

Corticosteroids:

- Hydrocortisone, cortisone, and prednisone are the glucocorticoids of choice, administered twice daily at the lowest effective dose while mimicking the normal diurnal rhythm of cortisol production.

- Recommended starting total daily doses are hydrocortisone 15 mg, cortisone acetate 20 mg, or prednisone 2.5 mg. Two-thirds of the dose is given in the morning, and one-third is given in the evening.

- The patient's symptoms can be monitored every 6 to 8 weeks to assess proper glucocorticoid replacement.

- Fludrocortisone acetate 0.05 to 0.2 mg orally once daily can be used to replace mineralocorticoid loss. If parenteral therapy is needed, 2 to 5 mg of deoxycorticosterone trimethylacetate in oil can be administered intramuscularly every 3 to 4 weeks.

- The major reason for adding the mineralocorti- coid is to minimize development of hyperkalemia.

- Because most adrenal crises occur because of glucocorticoid dose reductions or lack of stress-related dose adjustments, patients receiving corticosteroid- replacement therapy should add 5 to 10 mg hydrocortisone (or equivalent) to their normal daily regimen shortly before strenuous activities such as exercise.

- times of severe physical stress (e.g., febrile illnesses, after accidents), patients should be instructed to double their daily dose until recovery.

- Treatment of secondary adrenal insufficiency is identical to primary disease treatment with the exception that mineralocorticoid replacement is usually not necessary.

Pharmacotherapy of Acute Adrenal Insufficiency:

- ✓ Acute adrenal insufficiency (also known as adrenal crisis or Addisonian crisis) represents a true endocrine emergency.

- ✓ Stressful situations, surgery, infection, and trauma are potential events that increase adrenal requirements, especially in patients with some underlying adrenal or pituitary insufficiency.

- ✓ The most common cause of adrenal crisis is abrupt withdrawal of exogenous glucocorticoids in patients receiving chronic treatment that resulted in hypothalamic-pituitary-adrenal–axis suppression.

- Hydrocortisone given parenterally is the corticosteroid of choice because of its combined glucocorticoid and mineralocorticoid activity.

- The starting dose is 100 mg IV by rapid infusion, followed by a continuous infusion or intermit- tent bolus of 100 to 200 mg every 24 hours. IV administration is continued for 24 to 48 hours.

- If the patient is stable at that time, oral hydrocortisone can be started at a dose of 50 mg every 8 hours for another 48 hours.

- A hydrocortisone taper is then initiated until the dosage is 30 to 50 mg/day in divided doses.

- Fluid replacement often is required and can be accomplished with IV dextrose 5% in normal saline solution at a rate to support blood pressure.

- If hyperkalemia is present after the hydrocortisone maintenance phase, additional mineralocorticoid usually is required. Fludrocortisone acetate 0.1 mg orally once daily is the agent of choice.

- Patients with adrenal insufficiency should carry a card or wear a bracelet or necklace that contains information about their condition.

- They should also have easy access to injectable hydrocortisone or glucocorticoid suppositories in case of an emergency or during times of physical stress, such as febrile illness or injury.

- The end point of therapy for adrenal insufficiency is difficult to assess in most patients, but a reduction in excess pigmentation is a good clinical marker.

- Development of features of Cushing's syndrome indicates excessive replacement.

HYPERCORTISOLISM (CUSHING'S SYNDROME):

- Cushing's syndrome refers to the pathophysiologic changes associated with exposure to supraphysiologic cortisol concentrations (endogenous hypercortisolism) or pharmacologic doses of glucocorticoids (exogenous hypercortisolism).

- Patients receiving chronic supraphysiologic doses of glucocorticoids, such as those with rheumatologic disorders, are at high risk of developing Cushing's syndrome.

Pathophysiology:

- Cushing's syndrome can be classified as ACTH-dependent or ACTH-independent.

- ACTH-dependent Cushing's syndrome results from ACTH-secreting (or rarely, CRH-secreting) **adenomas.**

- ACTH-independent Cushing's syndrome is due either to excessive cortisol secretion by the adrenal glands (independent of ACTH stimulation) or to exogenous glucocorticoid administration.

- Patients with Cushing's syndrome owing to endogenous or exogenous glucocorticoid excess typically present with similar clinical manifestations.

The term ***Cushing's disease*** refers specifically to Cushing's syndrome from an ACTH secreting pituitary adenoma.

Circadian rhythm is lost in most patients with Cushing's syndrome. As such, detection of elevated *midnight cortisol concentrations* can be useful in the diagnosis of Cushing's syndrome.

Mortality in patients with Cushing's syndrome is mostly attributed to cardiovascular disease.

Hypertension, **hyperglycemia**, and **hyperlipidemia** are common findings and can be associated with cardiac hypertrophy, atherosclerosis, and hypercoagulability.

Osteopenia, osteoporosis, and increased fractures also have been reported.

- Pituitary adenomas account for about 80% of these cases. Ectopic ACTH-secreting tumors and nonneoplastic corticotropin hypersecretion are responsible for the remaining 20% of cases.

- Ectopic ACTH syndrome refers to excessive ACTH production resulting from an endocrine or nonendocrine tumor, usually of the pancreas, thyroid, or lung (e.g., small-cell lung cancer).

- ACTH-independent Cushing's syndrome is usually caused by adrenal adenomas and carcinomas.

Clinical Presentation and Diagnosis of Cushing's Syndrome:

- Weight gain and obesity.
- A rounded and puffy face.
- Dorsocervical ("buffalo hump") and supraclavicular fat accumulation.
- Hirsutism (75%).
- Thin skin.
- Facial plethora (70%).
- Skin striae.
- Acne (35%).
- Hyperglycemia.
- Hyperlipidemia (70%).
- Polyuria (30%).
- Hypertension (75 – 85%).
- Menstrual irregularities (amenoria) (70%).
- Erectile dysfunction (85%).
- Psychiatric changes (55%).
- Glucose intolerance is seen in 60% of patients.

Laboratory Tests:

1- 24-hour urinary free cortisol determination.

2- Overnight low-dose dexamethasone suppression test (DST).

3- Imaging studies may be used to distinguish between pituitary, ectopic, and adrenal tumors.

Other tests that can help determine the etiology include the high-dose dexamethasone suppression test, plasma ACTH test, metyrapone stimulation test, corticotropin-releasing hormone stimulation test or inferior petrosal sinus sampling.

Treatment:

- The goal of treatment in patients with Cushing's syndrome is reversal of hypercortisolism and management of the associated comorbidities, including the potential for long-term sequelae such as cardiac hypertrophy.

- Surgical resection is considered the treatment of choice for Cushing's syndrome from endogenous causes if the tumor can be localized and if there are no contraindications.

- The treatment of choice for Cushing's syndrome from exogenous causes is gradual discontinuation of the offending agent.

Nonpharmacologic Therapy:

1- Transsphenoidal pituitary microsurgery.

2- Pituitary irradiation or bilateral adrenalectomy.

3- Bilateral adrenalectomy.

4- Bilateral laparoscopic adrenalectomy.

5- Unilateral laparoscopic adrenalectomy.

Pharmacologic Therapy:

Pharmacotherapy generally is reserved for patients:

1- With ectopic ACTH-secreting tumor cannot be localized.

2- who are not surgical candidates.

3- who have failed surgery.

4- who have had a relapse after surgery.

5- in whom adjunctive therapy is required to achieve complete remission.

Pharmacological treatment of cushing syndrome includes the following classes:

1- Inhibitors of Adrenal Steroidogenesis (as **aminoglutethimide**, **Ketoconazole**, **Metyrapone**, **Etomidate**, **Adrenolytic Agent Mitotane.**

These agents are used primarily in preparation for surgery, as adjunctive treatment after unsuccessful surgery or radiotherapy, or for refractory patients who are not surgical candidates. They should not be used after successful surgery.

2- Central Neuromodulators of ACTH Release as Bromocriptine, Cyproheptadine, Octreotide, Ritanserin, Sodium valproate.

3- Peripheral Glucocorticoid Antagonist as *Mifepristone*.

- Metyrapone inhibits 11-hydroxylase activity, resulting in inhibition of cortisol synthesis.

- Initially, patients can demonstrate an increase in plasma ACTH concentrations because of a sudden drop in cortisol.

- This can cause an increase in androgenic and mineralocorticoid hormones resulting in hypertension, acne, and hirsutism.

- Nausea, vomiting, vertigo, headache, dizziness, abdomi- nal discomfort, and allergic rash have been reported after oral administration.

- **Aminoglutethimide** inhibits cortisol synthesis by blocking the conversion of cholesterol to pregnenolone early in the cortisol pathway.

- Side effects include severe sedation, nausea, ataxia, and skin rashes. Most of these effects are dose dependent and limit aminoglutethimide use in many patients. When used alone, aminoglutethimide is indicated for short-term use in inoperable Cushing's disease with ectopic ACTH syndrome as the suspected underlying etiology.

- Aminoglutethimide has limited efficacy as a single agent, with relapse occurring after discontinuation of therapy.

- ✓ Combination therapy with metyrapone and aminoglutethimide appears more effective than either agent alone for various etiologies of Cushing's disease with fewer side effects and is useful for inoperable patients.

- **Ketoconazole** inhibits a variety of cytochrome P450 enzymes, including 11-hydroxylase and 17-hydroxylase.

- It is highly effective in lowering cortisol in Cushing's disease, and patients can be maintained successfully on therapy for months to years.

- The most common adverse effects are reversible elevation of hepatic transaminases and GI upset. It can cause gynecomastia and lower plasma testosterone values.

- **Etomidate** is an imidazole derivative similar to ketoconazole that inhibits 11-hydroxylase. Because it is only available in a parenteral formulation, its use is limited to patients with acute hypercortisolemia awaiting surgery.

Adrenolytic Agents

- ✓ **Mitotane** inhibits the 11-hydroxylation of 11-desoxycortisol and 11- desoxycorticosterone in the adrenal cortex. The net result is reduced synthesis of cortisol and corticosterone.

- ✓ It decreases the cortisol secretion rate, plasma cortisol concentrations, urinary free cortisol, and plasma concentrations of the 17-substituted steroids.

- ✓ Because mitotane can severely reduce cortisol production, patients should be hospitalized before initiating therapy. The drug should be continued as long as clinical benefits occur.

- ✓ Nausea and diarrhea are common at doses >2 g/day and can be avoided by gradually increasing the dose and/or administering it with food. Lethargy, somnolence, and other CNS effects are also common. Reversible hypercholesterolemia can occur.

Neuromodulators of ACTH Release:

- None of the neuromodulatory agents has demonstrated consistent clinical efficacy for treating Cushing's syndrome. Combination therapy with these agents may prove more efficacious than any single agent.

- Cyproheptadine can decrease ACTH secretion; monitoring should include morning plasma cortisol and 24-hour urinary free cortisol concentrations. Side effects include sedation and hyperphagia.

- Cyproheptadine should be reserved for nonsurgical candidates who fail more conventional therapy. Because the response rate is no more than 30%, patients should be followed closely for relapses.

- **Tretinoin** can reduce ACTH secretion through inhibition of transcriptional activities. Its use has been limited to animal models, and efficacy in humans is undetermined.

- Other neuromodulatory agents include bromocriptine, cabergoline, val- proic acid, octreotide, and rosiglitazone.

Glucocorticoid-Receptor Blocking Agents

- **Mifepristone** (RU-486) is a progesterone-, androgen-, and glucocorticoid- receptor antagonist that inhibits dexamethasone suppression and increases endogenous cortisol and ACTH values in normal subjects.

- Limited experience in Cushing's syndrome suggests that mifepristone is highly effective in reversing the manifestations of hypercortisolism.