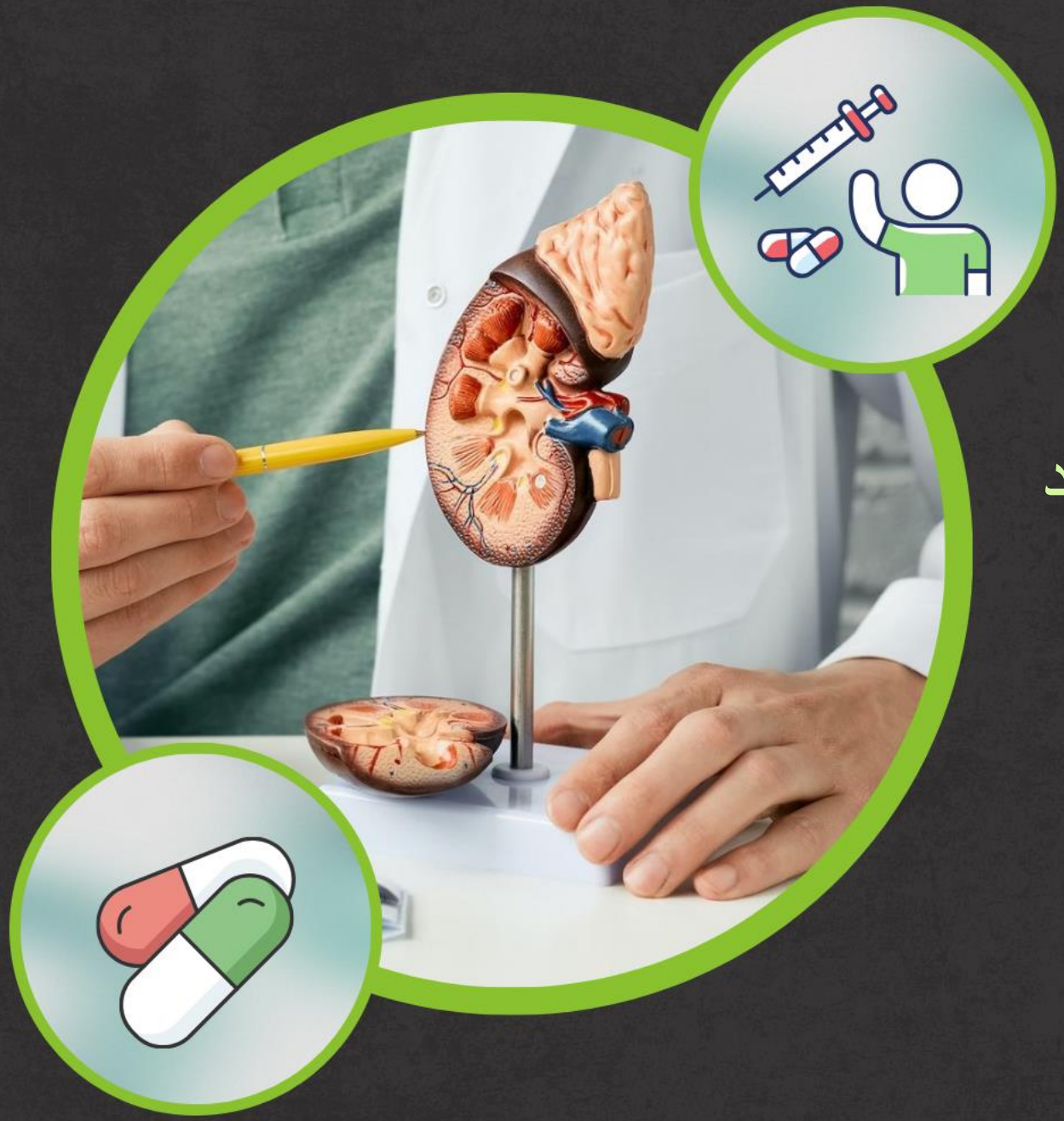


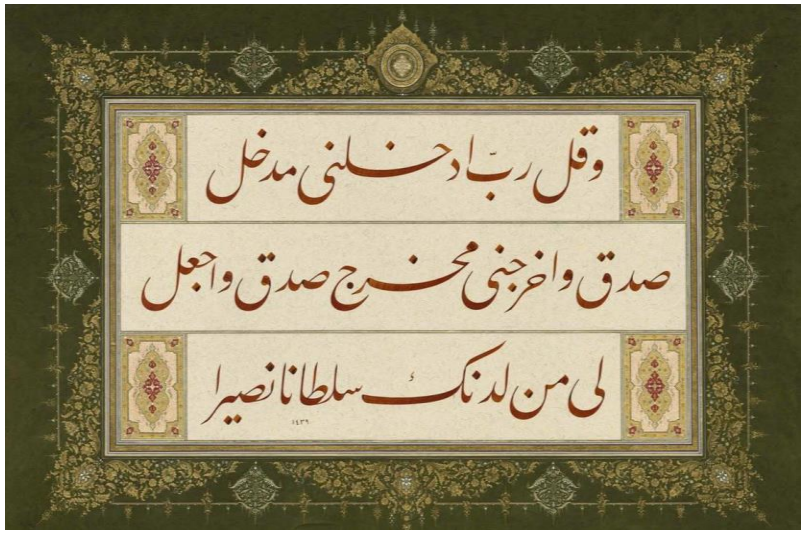
PHARMA

MODIFIED NO. 10

الكُتّاب: صهيب زعيتر، زهراء الحداد

المدققين: مالك عابدين

الدكتور/ة: يعقوب إرشيد



Male Hormones

Yacoub M. Irshaid, MD, PhD, ABCP
Department of Pharmacology

Color code

- Slides
- Doctor
- Additional info
- Important

Male Hormones

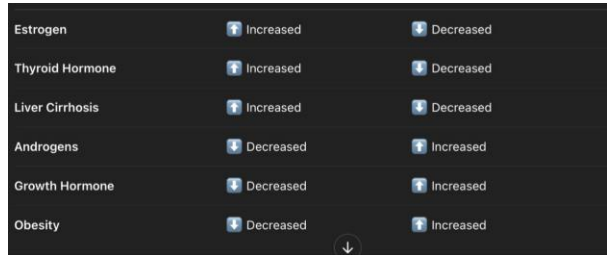
- **FSH controls gametogenesis, which also requires high local testosterone concentration.**
- **LH stimulates production of testosterone by interstitial or Leydig cells found in the spaces between the seminiferous tubules.**
- **Sertoli cells also secrete inhibin and activin.**
- **Activin stimulates pituitary FSH release.**
- **Inhibin, in conjunction with testosterone and dihydrotestesterone, inhibits FSH secretion.**

Androgens and Anabolic Steroids

- SHBG = Sex Hormone-binding Globulin

Testosterone and dihydrotestosterone:

- **65% of circulating testosterone is bound to SHBG, and most of the rest is bound to albumin. (~ 2% free).** The activity of testosterone and dihydrotestosterone in the body is primarily due to the **2% free (unbound) hormone**, as only the free form is biologically active.
- **SHBG is increased in plasma by estrogen, and thyroid hormone, and in patients with cirrhosis of the liver.** It is important because it enhances hormone binding, leading to a **lower free fraction of testosterone.**
- **It is decreased by androgen and growth hormone and is lower in obese individuals.**



Androgens and Anabolic Steroids

- **In target tissues (not in the testis), testosterone is converted to dihydrotestosterone (DHT) by 5α-reductase.** Most of the physiological actions of testosterone are actually mediated by **dihydrotestosterone (DHT)**, but:
- **Both are responsible for the changes that occur in puberty.**
- **DHT in peripheral tissues is the major active androgen.**

This is important because, in treating patients with **benign prostatic hyperplasia (BPH)**, we inhibit **5α-reductase** to reduce the formation of **dihydrotestosterone (DHT)**—the highly potent form of testosterone responsible for most of the androgenic activity in **peripheral tissues**.

- **Testosterone is metabolized by reduction and the metabolites are excreted in urine as conjugates.** Testosterone and DHT are also metabolized through **conjugation with glucuronic acid and sulfuric acid**, forming **glucuronide** and **sulfate conjugates**, respectively.

Androgens and Anabolic Steroids

Other androgens secreted by adrenal gland:

- **Androstenedione, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) are also produced in significant amounts in humans largely in the adrenal gland.**
- **They contribute slightly to the normal maturation process.**
- **They improve the sense of well-being and inhibit atherosclerosis.**

Androgens and Anabolic Steroids

- **DHEA may be of benefit in patients with SLE.** Systemic Lupus Erythematosus
  because It has an immunomodulatory effect and reduces circulating inflammatory 'drivers' such as interleukin-6 and upregulates the anti-inflammatory interleukin --> interleukin-2

This means that the balance between proinflammatory and anti-inflammatory interleukins shifts **in favor of the anti-inflammatory ones**.

Physiologic Effects:

- **They are responsible for the secondary sex characteristics and other changes that occur during puberty in males.**

Androgens and Anabolic Steroids

Metabolic effects:

1. **Reduction of sex hormone-binding proteins.**
2. **Increased liver synthesis of clotting factors, triglyceride lipase, α_1-antitrypsin, haptoglobin, and sialic acid.** each one has effect on the body.
3. **Increased renal erythropoietin secretion.**

   Androgens were previously used to treat anemia caused by bone marrow suppression (such as **aplastic anemia**) using **testosterone or its derivatives**. However, once **recombinant erythropoietin** became available and effective, it replaced androgens in this role.
4. **Reduction of HDL levels.** Which is a **risk factor for the development of atherosclerosis**.

Synthetic Androgenic and Anabolic Steroids

- **Testosterone has low oral bioavailability (~ 15%), Can't be given orally and is administered parenterally.**
- **Testosterone derivatives alkylated at the 17 position (methyltestosterone and fluoxymesterone) are active after oral administration.**

- Instead of using testosterone directly, we use **methyltestosterone** and **fluoxymesterone** orally—both of which are **17 alkylated derivatives of testosterone**.
- So, in therapeutic use, we primarily rely on **testosterone derivatives** rather than testosterone itself.

Synthetic Androgenic and Anabolic Steroids

This slide is important.
Read the next slide first

Oxymetholone, oxandrolone, nandrolone decanoate.

TABLE 40–5 Androgens: Preparations available and relative androgenic:anabolic activity in animals.

Drug	Androgenic Anabolic Activity
Testosterone	1:1
Testosterone cypionate	1:1
Testosterone enanthate	1:1
Methyltestosterone	1:1
Fluoxymesterone	1:2
Oxymetholone	1:3
Oxandrolone	1:3–1:13
Nandrolone decanoate	1:2.5–1:4

- These drugs are **synthetic androgens**, and it's important to understand that androgens have **anabolic effects**. This means they can be **misused by athletes**—both male and female—to **increase muscle mass and strength**.

- Synthetic androgens differ in their **androgenic-to-anabolic activity ratio**. For **testosterone**, this ratio is **1:1**, meaning its **androgenic** (masculinizing) and **anabolic** (tissue-building) effects are equal. The same applies to most of its derivatives—**except fluoxymesterone**, which has a ratio of **1:2** (i.e., **two-thirds anabolic, one-third androgenic**).

However, the following drugs have **stronger anabolic activity** compared to their androgenic effects:

- **Oxymetholone** → **1:3**
- **Oxandrolone** → ranges from **1:3 to 1:13**
- **Nandrolone decanoate** → ranges from **1:2.5 to 1:4**

- These drugs are considered to be **more anabolic**, and they are the ones commonly **misused by athletes** to enhance performance and physical appearance.

Androgenic and Anabolic Steroids

Anabolic steroid and androgen abuse in sports:

- **Usually used at 10-200 times larger dose than normal production**
- **The adverse effects of these drugs make their use inadvisable.**

Androgenic and Anabolic Steroids

Actions of anabolic steroids:

1. Increased in muscle mass and strength and increased training intensity

Increasing muscle mass on a weak bone structure is not ideal, but these drugs cause:

2. Growth and mineralization of bone

3. Improved competitive performance due to increased strength and aggressiveness. This has been seen only in women.

Androgenic and Anabolic Steroids

Anabolic steroids misuse:

- Misusers include athletes and body builders.

Long-term Adverse effects:

1. Cardiovascular complications
2. Liver disease
3. Reproductive organs toxicity
4. Severe mood swings
5. Aggressiveness

1- This **increased muscle mass** requires a **significantly higher cardiac output.**

2- This effect is **characteristic of 17 alkylated derivatives** of testosterone.

3- These compounds can cause **damage to the testes in males** and **ovaries in females**, potentially leading to **infertility** in both men and women.

Androgenic and Anabolic Steroids

🐱 👓 Therapeutic Uses:

1. **Androgen replacement therapy in hypogonadal men.**
   Can be used orally, sublingually, IM, TD, and topical gel.
   We use them in case of sex-organ failure (eg: testicular failure)

- **In the presence of pituitary deficiency, androgens are used rather than gonadotropins except when normal spermatogenesis is to be achieved.** In this case, the goal is not only to correct hypogonadal dysfunction but also to achieve normal spermatogenesis, which requires FSH (gonadotropin). However, if spermatogenesis is not desired, androgen therapy is given alone.

Androgenic and Anabolic Steroids

2. **In conjunction with dietary measures and exercise to reverse protein loss after trauma, surgery, prolonged immobilization and in patients with debilitating diseases.**
3. **Refractory anemias such as aplastic anemia and others (or any anemia that's associated with bone marrow suppression 🦴), Recombinant erythropoietin has largely replaced androgens for this purpose.**

Androgenic and Anabolic Steroids

IMPORTANT!!

🚨 **Adverse effects:** Some of these are due to the anabolic effect, others are by the androgenic effect

1. **Masculinizing actions in women: hirsutism, acne, amenorrhea, clitoral enlargement and deepening of voice.**
2. **Some exert progestational (progesterone-like) activity → withdrawal endometrial bleeding (shedding of the endometrium).**
3. **They also increase susceptibility to atherosclerosis in women.**
4. **Sodium retention and edema are not common. They might happen, but that's generally uncommon.**

Androgenic and Anabolic Steroids

5. **Masculinization or undermasculinization of the external genitalia of the female and male fetuses 👶, respectively, if given during pregnancy.**
6. **Administration of androgens in early life may have profound effects on maturation of central nervous system centers governing sexual development, particularly in the female.**

We mentioned earlier, the effects of androgens on the brain. 🧠

Androgenic and Anabolic Steroids

7. **Hepatic dysfunction (17-alkyl-substituted steroids,** synthetic, have high anabolic effects**): Cholestatic jaundice, and hepatomas and carcinomas.**
8. **Prostatic hyperplasia** in males.
9. **Increased LDL and lower HDL.** Facilitating atherosclerosis and ischemic heart disease, leading to heart failure. 🫀

Androgenic and Anabolic Steroids

10. Acne, sleep apnea, erythrocytosis, gynecomastia and azoospermia and decrease in testicular size (in high doses; as they are toxic to testes). May take months to recover after cessation of therapy.
11. Psychologic dependence (not physical, nor physiological); increased aggressiveness and psychosis.
12. Hepatocellular carcinoma.

Androgenic and Anabolic Steroids

🚦 Contraindications and Cautions:

1. **Pregnant women.**
2. **Male patients with carcinoma of the prostate and breast.**
3. **Infants and young children: special caution is required in giving them to produce a growth spurt (However, somatotropin is more appropriate). If they have a short stature and are predicted not to grow further, it's better to give them somatotropins rather than androgenic and anabolic steroids.**
4. **Patients with renal or cardiac disease predisposed to edema.**

Antiandrogens

A. **5α-reductase inhibitors:** they inhibit the conversion of testosterone to DHT, which is active in tissues, stimulates the prostate.

Finasteride:

- Is an orally active steroid-like drug.
- Decreases dihydrotestosterone levels that begins within 8 hours after administration and lasts for about 24 hours.
- Moderately effective (can be insufficient) in reducing prostate size in men with benign prostatic hyperplasia.
- ✅ Used for treatment of hirsutism in women and early male pattern baldness in men. (cosmetic cause, not all 5α-reductase inhibitors have this effect; it's special for Finasteride)

Antiandrogens

Dutasteride:

- **It is a similar orally active steroid derivative with a slow onset of action and a much longer half-life than finasteride.**
- **It is mainly approved for use in for benign prostatic hyperplasia.**

*** ❌Not approved to be used against hirsutism in women or male-pattern baldness in men.**

Antiandrogens

B. Receptor blockers:

1. Cyproterone and cyproterone acetate:

- Are effective antiandrogens that inhibit the action of androgens at the target organ.
- The acetate form has a marked progestational effect that suppresses the feedback enhancement of LH and FSH, leading to a more effective antiandrogen effect. When androgens are inhibited, the resulting positive feedback (or reduction of negative feedback) leads to increased secretion of FSH and LH. LH then stimulates androgen production and this compensatory increase in androgen synthesis is suppressed by cyproterone acetate.
- ✅ Used to treat hirsutism in women concurrently with an estrogen.
- Used in men to decrease excessive sexual drive.

Antiandrogens

2. Flutamide:

- **Nonsteroid antagonist at androgen receptors**
- **Potent antiandrogen.**
- **Used for treatment of prostatic carcinoma (which is usually androgen-dependent).**
- **Causes mild gynecomastia probably by increasing testicular estrogen production. Because when you inhibit the action of androgens on the testes, it might lead to increased estrogen production.**
- **Occasionally cause mild reversible hepatic toxicity.**
- **Also useful in the management of excess androgen effect in women.**

When treating certain cancers with monoclonal antibodies or hormone therapies, the approach is targeted; as these treatments act on specific molecules or pathways relevant to the cancer's pathophysiology. In contrast, **cytotoxic drugs are non-selective; they damage both cancerous and healthy cells equally, at the same time and to the same degree.** So, you need to keep this in mind. Additionally, these treatments can be extremely costly. 💰

Antiandrogens

3. Bicalutamide Enzalutamide and Nilutamide:

- Synthetic
- **Potent and orally active antiandrogens.**
- **Used in patients with metastatic carcinoma of the prostate.**
- **Bicalutamide is recommended for use in combination with a GnRH analog to reduce tumor flare.**

When administered in a sustained or non-pulsatile manner, they work as antagonists to reduce tumor flare.

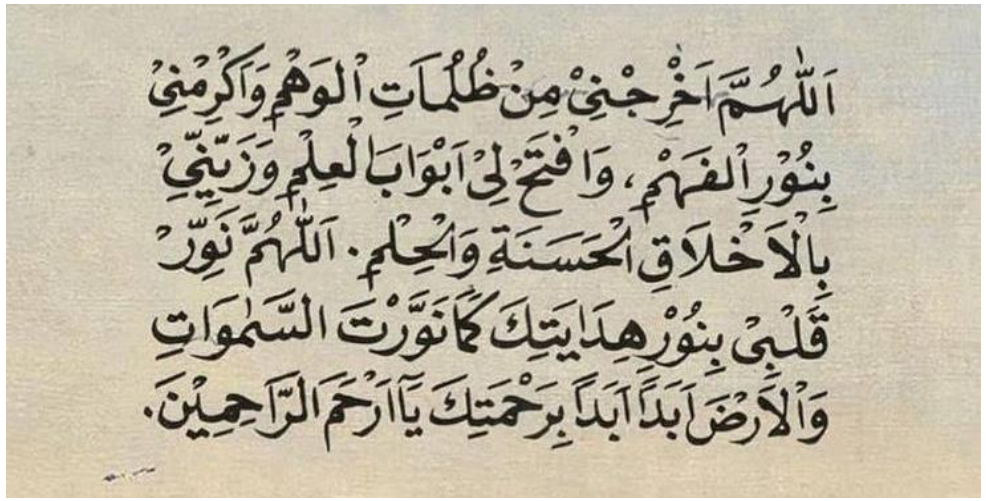
Antiandrogens

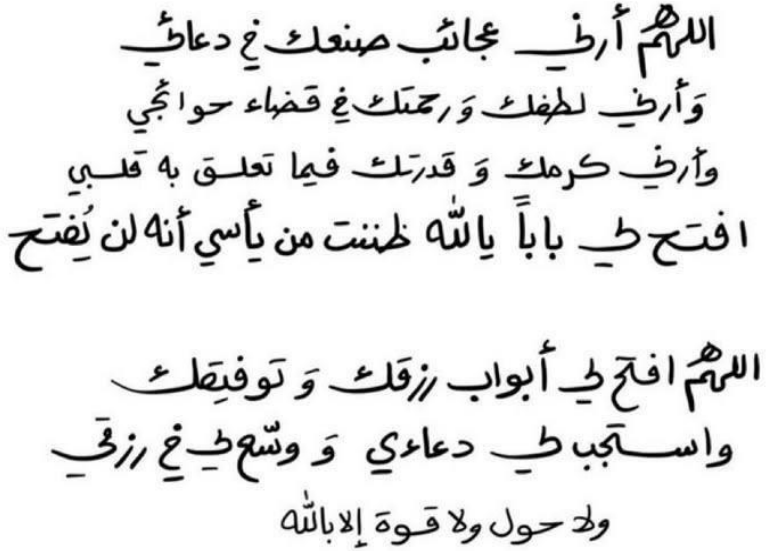
Last, but not least... our beloved spironolactone 🥳

4. Spironolactone: A potassium-sparing diuretic 🌟

- Aldosterone receptor antagonist.
- Also blocks androgen receptors, Leading to gynecomastia in males.
- Reduces 17α-hydroxylase activity → reduced plasma testosterone and androstenedione levels.
- So, it's of a dual function: blocks androgen receptors and prevents androgen formation by inhibiting 17α-hydroxylase enzyme.
- ✅ Used in treatment of hirsutism in women.

Good luck, half doc!!!





VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز وشاركنا بأفكارك لتحسين أدائنا!!