Sex hormones

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Androgens

- Have anabolic and/or masculinizing effects in both males & females.
- **Testosterone**, the most important androgen synthesized by Leydig cells in the testes & in smaller amounts, by thecal cells in the ovary & by the adrenal gland in both sexes.
- Testes secreted other androgens including 5α-dihydrotestosterone (DHT), androstenedione & dehydroepiandrosterone (DHEA) in small amounts. In males, **testosterone** secretion is controlled by GnRH, which stimulate FSH & LH secretion from anterior pituitary. [Note: LH stimulates steroidogenesis in the Leydig cells, whereas FSH is necessary for spermatogenesis.]

Testosterone or its active metabolite DHT inhibits production of FSH & LH through a negative feedback loop and thus, regulates **testosterone** production.

The androgens are necessary for:

1. Normal maturation in the male
2. Sperm production.
3. Increased synthesis of muscle proteins & Hb.
4. Decreased bone resorption.

Synthetic modifications of the androgen are designed to (1) modify solubility and susceptibility to enzymatic breakdown (thus prolonging the half-life of the hormone), and (2) separate anabolic and androgenic effects.

Mechanism of action:

Testosterone itself is the active ligand in muscle and liver,but in other tissues it must be metabolized to derivatives such as DHT. For example, after diffusing into the cells of the prostate, seminal vesicles, epididymis and skin, **testosterone** is converted by 5α-reductase to DHT.

Therapeutic uses

1. Androgenic steroid: indicated for primary hypogonadism (due to Leydig cell dysfunction) or, secondary hypogonadism (due to hypothalamic or pituitary failure) .

2. Anabolic steroids: used to treat chronic wasting associated with HIV or cancer. They may also be used as adjunct therapy in severe burns & to speed recovery from surgery or chronic debilitating disease.

Note: Unapproved use of anabolic steroids is to increase lean body mass, muscle strength and endurance in athletes & body builder. In some popular publications,

DHEA (**testosterone** & **estrogen** precursor) has been touted as the antiaging hormone as well as a "performance enhancer". With its ready availability in health food stores, the drug has been abused. There is no definitive evidence that it slows aging, or that it improves performance at normal therapeutic doses.

3. Endometriosis: **Danazol** (a mild androgen), is used for the treatment of endometriosis (ectopic growth of endometrium) & fibrocystic breast disease.

It inhibits release of FSH & LH but has no effect on the aromatase.

Weight gain, acne, decreased breast size, deepening voice, increased libido & increased hair growth are among the adverse effects.

Pharmacokinetics

1. Testosterone:

- Ineffective orally (first-pass metabolism).
- C17-esters of **testosterone** (eg. **testosterone cypionate** or **enanthate**) are administered I.M.

Note: addition of esters increase hormone lipid solubility & duration of action.

- Transdermal patches, topical gels & buccal tablets of **testosterone** are also available.
- **Testosterone** & its esters exhibit a 1:1 relative ratio of androgenic to anabolic activity.

2. Testosterone derivatives:

- Alkylation of **testosterone** allows its oral administration (e.g., **fluoxymesterone**)
- **Fluoxymesterone** is an orally effective agent with long half-life & it has a 1:2 androgenic to anabolic ratio.
- **Oxandrolone** is an orally active testosterone derivative with anabolic activity 3 to 13 times that of **testosterone**.
- Hepatic adverse effects are associated with 17 α -alkylated androgens.

Adverse effects

1. In females:

- Masculinization, acne, growth of facial hair, deep voice, male pattern baldness & excessive muscle development. Menstrual irregularities may also occur.
- **Testosterone** should not be used by pregnant women (virilization of female fetus may occur).

2. In males:

- Priapism, impotence, decreased spermatogenesis & gynecomastia.
- Cosmetic changes like those described for females may occur.
- Stimulate of prostate growth.

3. In children:

- Abnormal sexual maturation & growth disturbances due to premature closure of the epiphyseal plates.

4. General effects:

- Increase LDL & decrease HDL levels thus, LDL:HDL ratio & risk of premature CHD are increased.
- Fluid retention & edema.

5. In athletes:

- Anabolic steroids, (eg, DHEA) used by athletes can cause premature closing of the long bones epiphysis, which stunts growth & interrupts development.
- High doses taken by young athletes may result in (1) reduction of testicular size, (2) hepatic abnormalities, (3) increased aggression ("roid rage"), (4) major mood disorders & (5) other adverse effects described above.

Antiandrogens

- They either inhibit androgens synthesis or by blocking their receptors.
- **Finasteride** and **dutasteride**, are used for the treatment of BPH, they inhibit 5α-reductase decreasing DHT formation in the prostate & reducing its size.

- **Flutamide**, **bicalutamide**, **enzalutamide** and **nilutamide** act as competitive inhibitors of androgens & are effective orally for the treatment of prostatic cancer.

- **Cyproterone** is a progesterone derivative, it competes on testosterone receptors in peripheral organs reducing spermatogenesis that may even cause azoospermia (reversible over 4 months after drug discontinuation), it also compete on testosterone receptors in the CNS reducing sexual drive & thoughts resulting in impotence.
- Due to its progesterone activity, **cyproterone** inhibits gonadotrophin secretion decreasing testicular androgen production.

  Cyproterone uses:

  1. Reduce male hypersexuality.
  2. Prostatic CA.
  3. **Cyproterone-ethinylestradiol** combination (Dianette) is used to treat severe hirsutism & acne in female. This combination is also used as an OC (but should not be used primarily for this purpose).
- **Spironolactone** competes on DHT receptors, it is used to treat hirsutism in female.