Male Hormones

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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

Testosterone and dihydrotestosterone:

- **65% of circulating testosterone is bound to SHBG, and most of the rest is bound to albumin. (~ 2% free).**
- **SHBG is increased in plasma by estrogen, and thyroid hormone, and in patients with cirrhosis of the liver.**
- **It is decreased by androgen and growth hormone and is lower in obese individuals.**

Androgens and Anabolic Steroids

- **In target tissues, testosterone is converted to dihydrotestosterone (DHT) by 5α-reductase.**
- **Both are responsible for the changes that occur in puberty.**
- **DHT in peripheral tissues is the major active androgen.**
- **Testosterone is metabolized by reduction and the metabolites are excreted in urine as conjugates.**

Androgens and Anabolic Steroids

- **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. It has an immunomodulatory effect and reduces circulating inflammatory 'drivers' such as interleukin-6 and upregulates interleukin-2**

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.**
3. **Increased renal erythropoietin secretion.**
4. **Reduction of HDL levels.**

Synthetic Androgenic and Anabolic Steroids

- **Testosterone has low oral bioavailability (~ 15%) and is administered parenterally.**
- **Testosterone derivatives alkylated at the 17 position (methyltestosterone and fluoxymesterone) are active after oral administration.**

Synthetic Androgenic and Anabolic Steroids

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

Androgenic and Anabolic Steroids

Anabolic steroid and androgen abuse in sports:

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

Androgenic and Anabolic Steroids

Actions of anabolic steroids:

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

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**

Androgenic and Anabolic Steroids

Therapeutic Uses:

1. **Androgen replacement therapy in hypogonadal men. Can be used orally, sublingually, IM, TD, and topical gel.**

- **In the presence of pituitary deficiency, androgens are used rather than gonadotropins except when normal spermatogenesis is to be achieved.**

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. Recombinant erythropoietin has largely replaced androgens for this purpose.**

Androgenic and Anabolic Steroids

Adverse effects:

1. **Masculinizing actions in women: hirsutism, acne, amenorrhea, clitoral enlargement and deepening of voice.**
2. **Some exert progestational activity → withdrawal endometrial bleeding.**
3. **They also increase susceptibility to atherosclerosis in women.**
4. **Sodium retention and edema are not common**

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.**

Androgenic and Anabolic Steroids

7. **Hepatic dysfunction (17-alkyl-substituted steroids): Cholestatic jaundice, and hepatomas and carcinomas.**
8. **Prostatic hyperplasia.**
9. **Increased LDL and lower HDL.**

Androgenic and Anabolic Steroids

10. Acne, sleep apnea, erythrocytosis, gynecomastia and azoospermia and decrease in testicular size. May take months to recover after cessation of therapy.
11. Psychologic dependence, 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 (somatotropin is more appropriate).**
4. **Patients with renal or cardiac disease predisposed to edema.**

Antiandrogens

A. 5α-reductase inhibitors:

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 in reducing prostate size in men with benign prostatic hyperplasia.
- Used for treatment of hirsutism in women and early male pattern baldness in men.

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.**

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.**
- **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.**
- **Causes mild gynecomastia probably by increasing testicular estrogen production**
- **Occasionally cause mild reversible hepatic toxicity.**
- **Also useful in the management of excess androgen effect in women.**

Antiandrogens

3. Bicalutamide Enzalutamide and Nilutamide:

- **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.**

Antiandrogens

4. Spironolactone:

- **Aldosterone receptor antagonist.**
- **Also blocks androgen receptors.**
- **Reduces 17α-hydroxylase activity → reduced plasma testosterone and androstenedione levels.**
- **Used in treatment of hirsutism in women.**