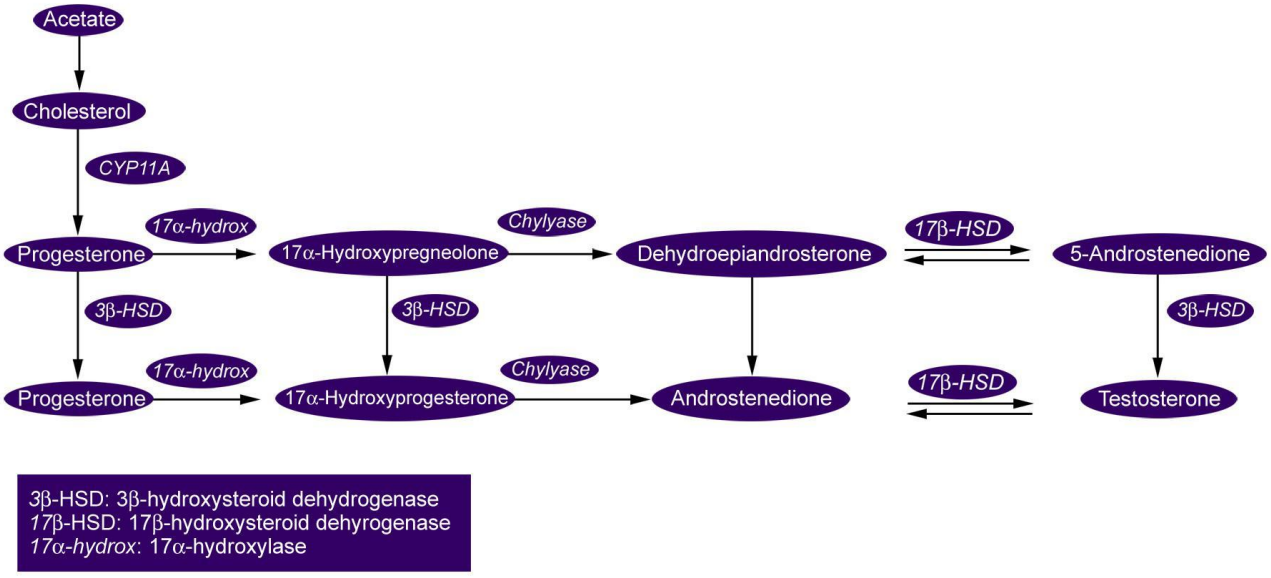
Androgen Excess

Background

Androgen excess is the most common endocrine disorder in women of reproductive age. Androgens are produced primarily from the adrenal glands and the ovaries. However, peripheral tissues such as fat and skin also play roles in converting weak androgens to more potent ones. Androgen excess can affect different tissues and organs, causing variable clinical features such as acne, hirsutism, virilization, and reproductive dysfunction. [1]

Sources and types of androgens in women

The endocrine glands secrete 5 androgens through a similar pathway: testosterone, dehydroepiandrosterone sulfate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione, and androstenediol, the latter of which has both androgenic and estrogenic activity. Testosterone and its biologically active metabolite dihydrotestosterone (DHT) are the only androgens with direct androgenic activity. DHEAS, DHEA, and androstenedione are all precursors of testosterone.



Ovarian androgens

The ovaries produce 25% of circulating testosterone, which is dependent on luteinizing hormone (LH) secreted by the anterior pituitary. The ovaries also secrete 50% of the androstenedione and 20% of DHEA. Testosterone is used as a marker of ovarian androgen secretion. However, the adrenals also contribute to circulating testosterone via peripheral conversion of androstenedione to testosterone.

Adrenal androgens

The adrenal glands produce all of the DHEAS and 80% of the DHEA. The adrenals also secrete 50% of androstenedione and 25% of circulating testosterone. DHEAS and 11-androstenedione are not secreted by the ovaries and, therefore, are used as markers of adrenal androgen secretion. Adrenal androgen secretion is dependent on adrenocorticotropic hormone (ACTH) secreted by the anterior pituitary. Both prolactin and estrogen can affect adrenal androgen production.

Peripheral conversion

Skin, fat, liver, and urogenital systems are important peripheral sites of androgen production. Androstenedione, and to some degree DHEA, are converted to testosterone in the skin.

Androgen metabolism

Of the circulating androgens, only testosterone and DHT are able to activate androgen receptors. In reproductive-aged women, 25% of the circulating testosterone comes from the adrenals; the

ovaries contribute another 25%. The rest of the testosterone is produced by the peripheral conversion of androstenedione in adipose tissue. [2] In healthy women, 80% of testosterone is bound to sex hormone binding globulin (SHBG), 19% is bound to albumin, and 1% circulates freely in the blood stream. The androgenicity depends mainly on the unbound fraction due to the high affinity of SHBG to the bound androgens. The levels of SHBG increase and decrease based on conditions and medications.

- SHGB levels are increased by the following:
  - Estrogens
  - Thyroid hormone
  - Pregnancy
  - Estrogen-containing preparations
- SHGB levels are decreased by the following:
  - Androgens
  - Synthetic progestins (norethindrone, norgestrel, desogestrel, norgestimate)
  - Glucocorticoids
  - Growth hormone
  - Insulin
  - Obesity
  - Acromegaly
  - Hypothyroidism
  - Hyperinsulinemia

The remaining androgens, DHEAS, DHEA, and androstenedione are almost entirely bound to albumin. Unlike SHBG; albumin has a low affinity for sex hormones, so the albumin-bound androgens are readily available to tissues.
Adrenal androgens increase in response to ACTH stimulation, while androgens do not influence the ACTH secretion. Also, LH stimulates theca cells of the ovaries to secrete androgens; however, there is no feedback regulatory loop that controls androgen secretion in women.
Most of the circulating testosterone is metabolized in the liver into androsterone and etiocholanolone, which are conjugated with glucuronic acid or sulfuric acid and execrated in the urine as 17-ketosteroids. Only 20-30% of urinary 17-ketosteroids are derived from testosterone metabolism; the rest originates from the metabolism of adrenal steroids. [3]

Androgen effects

Androgens induce virilization and are responsible for forming the male external genitalia in the fetus. Their absence or the absence of androgen receptors results in a female phenotype, despite the presence of a 46 XY karyotype (eg, androgen insensitivity syndrome). Androgens are also responsible for the development of the secondary sexual organs and ducts, the seminal vesicles, and the prostate.
Postnatal females are not as sensitive as the fetus to androgens, which induce the growth of sexual hair, temporal balding, acne, clitoral growth, sebum production, and a deepening of the voice.
Oral androgens decrease high-density lipoprotein (HDL) cholesterol and increase low-density lipoprotein (LDL) cholesterol. With androgen excess, the extent of these changes is dependent on the level of androgens in the blood.

Androgen effects on various tissues and systems

Androgens have direct effects on different body systems and also act as precursor hormones for ovarian and extragonadal estrogen synthesis. Androgen receptors are present in a variety of tissues like skeletal muscles, skin, gastrointestinal tract, genitourinary tract, bone, brain, cardiovascular system, placenta, and adipose tissues. Androgen actions are not completely understood in all of these tissues. [4]

Brain

Androgen receptors are distributed throughout the brain in close proximity to estrogen receptors. The highest concentrations are present in the preoptic area of the hypothalamus. Some areas contain 5α-reductase and aromatase and are able to convert testosterone to DHT or estradiol. [5] Androgen can have activational behavior on women and may have some negative effects on the cognitive functions of older women. [6]

Growing evidence supports the role of androgens in physiologic levels and sexual desire. Decreased sexual function has been reported in hyperandrogenic women receiving antiandrogens; on the other hand, administration of testosterone in women with hypoactive sexual desire disorder results in improvements in libido and sexual function. [7, 8]

Bone

Androgens have important roles in bone mineralization either directly or through aromatization to estrogen. Lower androgen concentrations have been associated with bone loss in various age groups. [9]

Breast

Androgen receptors are present in mammary epithelial cells in addition to estrogen and progesterone receptors. The proposed mechanisms include either direct stimulation of the androgen receptors or conversion to estradiol by the aromatase enzyme present in breast tissue. Androgens, particularly DHEA and testosterone, have been reported to protect against mammary epithelial proliferation in female monkeys. The reverse effect was reported when the antiandrogen flutamide was given to those animals. [10]

Few data are available regarding the effects of androgens on human breasts. Hyperandrogenemia in women with polycystic ovary syndrome (PCOS) doesn't appear to have significant risk of breast cancer. [11] In a prospective randomized controlled study in postmenopausal women evaluating breast cell proliferation and testosterone, the authors found no significant difference when testosterone was added to estrogen and progesterone, while they found a 5-fold increase in breast cell proliferation in women taking the placebo. [12]

Endometrium

Unopposed estrogen stimulation of the endometrium increases the risk of endometrial hyperplasia and eventually cancer. The proposed mechanism of androgen aromatization to estradiol may not be applicable because the aromatase expression has not been detected in normal endometrium and stromal cells. [13] In vitro studies have shown that androgens have an inhibitory effect on endometrial proliferation. [14]

Cardiovascular system

There is a great concern about the relation between sex hormones and cardiovascular events. Women with PCOS have hyperandrogenemia and are at higher risk of cardiovascular events. [15, 16, 17] However, the insulin resistance associated with PCOS is likely more relevant to the pathogenesis of cardiovascular disease. Moreover, the exogenous administration of testosterone for female to male transsexual has not been associated with the increased risk of cardiovascular disease. [18]

Mechanism of androgen action

In the target tissues, androgens enter the cell cytoplasm by simple diffusion across the cell membrane. Once inside the cell, the androgens bind and activate the androgen receptors. The androgen-receptor complex attaches to a specific DNA site and stimulates the production of messenger RNA, which, in turn, stimulates the production of the enzymes and proteins necessary to affect androgen action.

Pathophysiology

Androgen excess affects mainly the pilosebaceous unit (PSU) and the reproductive system. The PSU secretes sebum and is the unit from which hair grows. Three types of hair, lanugo, vellus, and

terminal hairs, exist. The fine hairs of the fetus are lanugo and the peach fuzz hair of adults is vellus hair. These hairs are fine, short, and nonpigmented. Thick and pigmented hair is referred to as terminal hair. Those hairs of the pubic, axillary, sternal, and facial areas are responsive to androgens and those in scalp, eyelashes, and eyebrows are androgen-independent. Their prevalence depends largely on genetics. As androgen levels rise, more vellus hairs in the androgen-sensitive areas are converted into terminal hairs, resulting in hirsutism.
Androgens prolong the growth phase of hair and promote their conversion from vellus to terminal type. Hirsutism affects 70-80% of women with androgen excess. Sebum production from the PSU is also increased by androgens. [19]
Acne vulgaris can be aggravated or initiated by increased androgen levels as the excess sebum production and the shedding of hyperkeratinized epithelium may occlude the hair follicle. *Propionibacterium acnes* proliferates and triglycerides of sebum are then hydrolyzed by the bacterial lipases to form glycerol and free fatty acids, which, together with other bacterial metabolites, cause inflammation. It is also commonly proposed that hypersensitivity of PSU to androgens is the cause of acne. [20] Sebum production increases markedly during the prepubertal period, a time when serum levels of DHEAS, a precursor to testosterone, are also elevated. Individuals who are insensitive to androgen have less active sebaceous glands and do not develop acne.
Although there has been some controversy over whether acne is common enough in androgen excess to be considered a sign of hyperandrogenemia, a study by Uysal et al indicated that it is indeed evidence of the condition. The study found that of 207 women aged 18-45 years suffering primarily from acne, 72% demonstrated clinical and/or biochemical hyperandrogenemia. [21]
Androgen excess is a common feature of PCOS, which is also the most common cause of anovulatory infertility. The ovarian theca cells increase their ovarian androgen production under the stimula Hyperinsulinemia due to peripheral insulin resistance is often present in women with PCOS and it promotes hyperandrogenemia through the binding of insulin to the insulin-like growth factor–1 (IGF-1) receptor. Insulin mimics the action of insulin growth factor 1 (IGF-1), which augments androgen production by the theca cell in response to LH. Since insulin decreases levels of SHBG, the circulating levels of free testosterone are also increased.tory activity of the raised LH levels, and in many cases, raised insulin levels.

Epidemiology

Frequency

United States

The prevalence of androgen excess is 8%.

International

The international incidence rate is dependent on the particular culture, but, essentially, it is similar to that of the United States.

Mortality/Morbidity

Androgen excess per se does not cause mortality or morbidity, but it is associated with insulin resistance, dyslipidemia, hypertension, and vascular diseases; therefore, it is a forerunner of cardiovascular disease.

- In premenopausal African-American women, relative androgen excess is associated with insulin resistance and increased risk for development of type 2 diabetes. [22]
- Impaired glucose tolerance and type 2 diabetes affect about 40% of women with PCOS.
- The presence of PCOS is an independent cardiovascular risk factor. Women who have anovulatory PCOS have greater cardiovascular risk compared with women who have ovulatory PCOS and idiopathic hyperandrogenism.
- Androgen-secreting tumors are rare and about 30% of them are malignant.

Race

Androgen excess occurs equally in all races. Congenital adrenal hyperplasia prevalence due to 21-hydroxylase deficiency is greater among those of Ashkenazi Jewish descent.

Sex

Congenital adrenal hyperplasia occurs equally in both sexes; however, this article focuses on females.

Age

The most common causes of hyperandrogenism begin in early adolescence or in childbearing age. Androgen-producing tumors may rarely affect postmenopausal women.

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