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Physiological Effects of Androgens in Women

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SUMMARY

Androgens are important sex steroid hormones for women as well as men. Previously, the focus of androgen research in women was almost exclusively on issues of excess. Only recently have we become aware that androgens play an important role in many aspects of the health and well-being of women. From sexual orientation to brain development to bone health, androgens are closely intertwined with estrogens, and only by understanding the former can we have a full understanding of women's health and their medical care issues. This chapter focuses on the normal physiology of androgens in women—what we know and what we have yet to learn.

Key Words: Androgens; DHEA; intracrinology; pilosebaceous unit; sex steroid hormones; sexual differentiation; SHBG; testosterone.

1. INTRODUCTION

Androgens are the most abundant of the sex hormones in women; while their concentrations are measured in nanomoles, estrogens are measured in mere picomoles *(1)*. Many of the major biological events of a woman's life—adrenarche, menarche, sexuality, fertility, parturition, lactation, and menopause—are mediated in part by sex hormones. Yet we know relatively little about the effects of androgens in women. Much of what we do know is deduced from our understanding of conditions of androgen excess or insufficiency in men and women, from mutations involving the genes for the androgen receptor and for key enzymes in the steroid sex hormone pathways, and from extrapolation of the results of in vitro studies and experiments in other animal species *(2)*. Although sex hormones are gender-typical, they are not gender-limited *(3)* —males and females use the same pathways, hormones, and enzymes for synthesis and metabolism. Where there is sexual dimorphism, the different response may result from differences in (a) concentration, (b) duration of exposure, (c) tissue-specific receptivity or sensitivity, and (d) the presence or absence of other modulating hormones, growth or inhibiting factors, or enzymes.

2. BACKGROUND

2.1. Androgen Physiology

The sex hormones dehydroepiandrostenedione (DHEA) and its sulfated form, DHEAS, androstenedione (A4), testosterone (T), dihydrotestosterone (DHT), estrone (E1), and estradiol (E2) are produced in the adrenal glands, the gonads, and in numerous peripheral sites. Although adrenal androgen secretion increases in response to adrenocorticotropic hormone (ACTH), androgens do not influence ACTH secretion, and ACTH plays a primarily permissive role in adrenal androgen physiology. In fact, a specific regulator of adrenal androgen secretion has been proposed, but, so far,

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has eluded isolation *(4)*. Ovarian androgen secretion increases following stimulation of the theca cells by luteinizing hormone (LH). However, unlike the situation in men in which testosterone inhibits the secretion of LH, either directly or through aromatization to estradiol, there is no known feedback regulatory loop controlling androgen secretion in women, at least not at the levels normally observed.

Most of the circulating androgens are bound to sex hormone-binding globulin (SHBG) or albumin. SHBG has a high affinity for the biologically active sex hormones DHT, T, A4, E2, and E1, whereas DHEA and DHEAS exhibit little or no binding *(5)*. The role of SHBG in the regulation of sex hormone action has yet to be fully elucidated. It is thought to regulate the concentration of circulating steroid hormones, act as a reservoir for ready-made hormones, and serve as a partner for nongenomic steroid action. Between 0.5 and 7.5% of the androgens in women exist in the free or unbound state and are available to freely act upon cells *(6)*. Unlike SHBG, albumin has a low affinity for sex hormones; therefore, the albumin-bound steroids may be readily available to the tissues. The free and albumin-bound fractions of sex steroid hormones together are termed *bioavailable*.

Although serum measurements of the sex steroid hormones are generally relied upon to diagnose androgen excess or deficiency, most of the androgens produced in women are made in peripheral tissues, which contain the enzymes to convert DHEAS to DHEA (which can then be transformed into A4 and then T) or 5α-reductase (where T may be further converted to the potent androgen DHT). Alternatively, in selected tissues such as liver, skin, fat, muscle, kidney and bone, T can undergo aromatization to E2, which in turn may be converted to E1 in those tissues that contain 17β-hydroxysteroid dehydrogenase. These locally produced hormones can act on neighboring cells in a paracrine fashion or on the cell of origin in an intracrine manner. The extent of the intracrine process can be appreciated by measurements of androgen metabolites, such as androsterone glucuronide, androstane-3α,17β-diolglucuronide, androstane-3β,17β-diolglucuronide, and androsterone sulfate *(7)*.

2.2. Mechanisms of Action

The classic model of sex steroid hormone action is a nucleus-based, ligand/receptor-mediated event that acts on DNA to bring about transcription and translation (i.e., a genomic effect). This complex pathway is well suited for routine maintenance of sex hormone action, such as protein synthesis. However, its relative slowness (minutes to hours) means that it is unable to respond to rapid shifts in physiological demands. Although not the first to describe the effect, Tchernitchin was the first to use the term *nongenomic* to describe a hormonal action sequence that could not otherwise happen if it were regulated by classic genomic processes *(8)*. Nongenomic effects differ from genomic effects in at least three ways: (a) they are more rapid (from seconds to minutes), (b) they do not rely on an operational nucleus and can be shown to take place in nonnucleated cells, and (c) they are not sensitive to the effects of inhibitors of transcription or translation *(9)*. It has taken the better part of three decades to begin to understand the nongenomic actions of sex steroids, yet many controversies (well reviewed by Lösel and colleagues *[10]*) remain to be settled.

It is possible that some of the nongenomic actions of androgens are the result of direct action by the hormone on cell membrane fluidity through their interaction with the membrane phospholipids. Other evidence suggests that nongenomic actions are possibly mediated by receptors— either cell surface receptors that generate signals across the plasma membrane or androgen receptors without associated transcription action *(9,11)*. Triggers for nongenomic reactions include calcium ions, which act as a second messenger to stimulate transmembrane cascades or stimulation of the mitogen-activated protein kinase or cyclic adenosine monophosphate (cAMP) pathways *(11)*.

SHBG has been shown to have a role in the nongenomic action of sex hormones. SHBG receptors have been found on the cell surface of the testes, prostate, breast, and liver, and represent either a G protein-coupled receptor or a closely related one. SHBG devoid of steroids binds to this receptor, and sex steroids then interact with the SHBG–receptor complex, resulting in the generation of cAMP, either directly or by stimulating an influx of calcium into the cell *(11)*.

Megalin is a member of the family of low-density lipoprotein receptors, and there is evidence that it may serve as a helper molecule in nongenomic steroid hormone action *(12)*. It is known that certain tissues require more steroid hormones than can be supplied by the classic pathway. Not only is the stimulatory process too slow, but the classic paradigm does not allow for the local storage of steroid hormones. Tissues needing large quantities of steroid hormone—and in which abundant megalin receptors have been found—are the breast, uterus, prostate, and epididymis. Lipophilic molecules such as megalin may help these cells store large amounts of sex hormones *(13)*.

Although the mechanisms for the nongenomic effects of androgens remain controversial, their cellular effects have been clearly demonstrated. The principal androgen within follicular cells of the ovary, A4, can cause a rapid, dose-related increase in calcium ion concentrations in granulosa-lutein cells of humans and in ovarian granulosa cells of pigs. No such effect has been noted for T. Likewise, osteoblasts of male, but not female, rats experience a rapid increase in calcium ion concentration in the presence of T. The nongenomic effects of progesterone, E2, T, and A4 have been studied in vitro and in vivo in granulosa, endometrial, and Sertoli cells as well as in the oocytes and spermatozoa of various animal models, including humans *(9)*. However, it is yet to be determined whether the nongenomic pathways for androgens have any physiologically important effect in humans.

2.3. Overview of Androgen Action Throughout the Female Life Span

2.3.1. Prenatal

2.3.1.1. Differentiation of Internal Genital Ducts and External Genitalia

Primordial germ cells formed in the dorsal endoderm of the yolk sac migrate into the undifferentiated, bipotential, embryonic gonads at the urogenital ridge—a process that is well underway by 6 weeks of gestation. In a male fetus with a normal Y chromosome, the sex-determining region Y gene (SRY), SOX9, and other genes initiate the differentiation of the gonad into testes at 6–7 weeks. The Leydig cells, which appear by 8–9 weeks, contain functional LH/human chorionic gonadotropin (hCG) receptors. They are stimulated initially by hCG secreted by placental trophoblasts, then later by fetal pituitary LH. The result is T production. Between 9 and 14 weeks of gestation, T stimulates the wolffian duct structures to differentiate into the epididymis, vas deferens, and seminal vesicles. The normal fetal testes also secretes anti-müllerian hormone (AMH), which results in the local regression of the müllerian duct between 8 and 12 weeks of gestation. The external genitalia remain undifferentiated until about 8 weeks. The urogenital tubercle, urogenital sinus, and labioscrotal tissue contain type 2 5α-reductase, which converts T into DHT. The DHT effects the fusion of the labioscrotal folds to form a scrotum and penile urethra, stimulates the growth of the genital tubercle to form a glans penis, and enhances prostate differentiation and growth *(14)*. That DHT is required for the normal formation of the male external genitalia is most clearly demonstrated by patients with the autosomal recessive 5α-reductase, type 2 deficiency (pseudovaginal perineal-scrotal hypospadias). These genetic males, whose testes secrete ample quantities of T, are unable to form normal amounts of DHT. At birth, affected individuals have ambiguous genitalia, with a phallus that resembles a clitoris, bifid, empty scrotum, and a urogenital sinus that contains the urethra and a blind vaginal pouch opening into the perineum. Wolffian duct structures are present, having developed under the influence of T, while the prostate is underdeveloped, and the müllerian duct-derived structures are absent *(15)*.

The female fetus begins her process of sexual differentiation when the bipotential embryonic gonad begins to develop oocytes—between 11 and 12 weeks of gestation. In the absence of gonadal T production, the wolffian duct structures regress, and, lacking AMH, the müllerian ducts differentiate into the fallopian tubes, the uterus, and the upper third of the vagina. Because T levels are low, the 5α-reductase, type 2 at the genital ridge lacks the substrate to form DHT. Therefore, there is no "zipping up" of the labioscrotal folds, resulting in formation of open labia, a perineal vaginal orifice, and a perineal urethra. The regression of the wolffian duct structures, the differentiation of the

müllerian duct structures, and the maintenance of open labioscrotal folds along normal female lines does not require a gonad, nor does it require the fetus to be a genetic female. XX or XY fetuses with dysgenetic or streak gonads also exhibit development of the internal and external genitalia along female lines *(14)*. XY fetuses with complete androgen insensitivity resulting from mutations in the androgen receptor gene (complete testicular feminization) have functional testes that produce T and AMH. However, as a result of the inability of T or DHT to act and the presence of AMH, the fetus does not develop wolffian or müllerian duct structures, respectively, and the external genitalia develop along female lines *(15,16)*.

Although the prenatal female internal and external genital development appears to be a passive process, the tissues of the female fetus are capable of responding to T. This is well demonstrated by patients with congenital adrenal hyperplasia (CAH) who have mutations in the *CYP21* gene that cause a deficiency of 21-hydroxylase. This enzyme deficiency results in reduced cortisol production, which leads to an elevation of ACTH and, in turn, increases the conversion of cholesterol to pregnenolone in the adrenals. The buildup of cortisol precursors results in increased quantities of 17-hydroxyprogesterone, A4, and T. The high T levels result in fusion of the labioscrotal folds and clitoral enlargement. The responsiveness of the external genitalia to T is time dependent; labioscrotal fusion only takes place when the fetus is exposed to high T and DHT before 12 weeks gestation. After 12 weeks, high T levels only result in clitoral enlargement. Of interest, the wolffian ducts in affected females regress normally, suggesting that the T levels achieved are not sufficient to stimulate their growth and differentiation *(17)*.

2.3.1.2. Brain Imprinting

The concept that the sex steroid milieu of the brain during gestation and shortly after birth can permanently influence the reproductive cycles and sexual behavior emanates from studies in nonhuman mammals, especially rats *(2,18)*. During species-specific critical periods, androgen administration to females masculinizes the brain, leading to anovulatory infertility and loss of sexual responsivity to males. Administration of androgens to female rhesus monkeys during gestation also leads to masculinized sexual behavior, play, and grooming. It is much more difficult to determine what role, if any, prenatal androgen exposure has on human behavior. Sex differences in childhood play behaviors, including playmate preferences and types of activities and objects chosen for play, can be detected by 12 months of age in normal children. Girls born to women who were given androgenic progestins during pregnancy demonstrated increased male-typical play behavior. In addition, a longitudinal study of the relationship between endogenous maternal serum T levels and the sex-type behavior of the offspring at 3.5 years of age failed to show a correlation in males, but did in female children; the higher the maternal T during pregnancy, the more likely the girls were to exhibit male-type play behavior. Females with the 21-hydroxylase deficiency form of CAH exhibit more male-typical activities during childhood, adolescence, and adulthood than do control females. Spatial orientation, visualization, and targeting are higher in women with CAH than controls, more closely resembling the male pattern. Finally, and in contrast to their unaffected sisters, females with CAH have a greater likelihood of being sexually attracted to women *(19,20)*. Other evidence that prenatal androgen exposure is important for subsequent masculine behavior comes from studies of males with complete androgen insensitivity, who exhibit female-type behavior in regards to interests, gender identity, and sexual orientation *(21,22)*.

2.3.2. Postnatal, Prepubertal Period

In the first 4 months of life, the neonate experiences brief increases in the levels of sex hormones. The male neonate experiences surges in LH and T, in part because the maternal-placental estrogens are no longer suppressing the hypothalamic–pituitary–testicular axis. The hormone levels peak at 1–2 months and then decline, and by age 6 months they are at a nadir, remaining low until adrenarche. In females, the postnatal hormone activity is less dramatic than in the males, but more complex.

There is a modest increase in LH, which stimulates ovarian E2 secretion for 2–4 months, whereas the follicle-stimulating hormone (FSH) rise, which peaks at 3–6 months, brings about maturation of the ovarian follicles. FSH then steadily decreases but is measurable up to 2 years of age. All neonates experience a precipitous decrease in circulating DHEA secondary to the disappearance of the adrenal fetal zone. By age 1, the two-zone fetal adrenal gland has been replaced by an adrenal with three zones (granulosa, fasciculate, and reticularis), which initially produce little DHEA *(23)*.

The physiological roles, if any, of androgens in the neonatal or preadrenarchal female are unknown. Unlike female rats administered androgens in the postnatal period, high androgen exposure during this time in females with CAH does not suppress subsequent menstrual cyclicity in gonadotropins or sex steroids *(24)*. As noted above, females with CAH may exhibit an increased rate of attraction to females, and this may be secondary to the prenatal or postnatal exposure to high androgen levels, as well as other factors such as psychological issues arising from their ambiguous genitalia and their social milieu.

It is also unknown whether physiological levels of androgens are important for bone health in childhood *(25,26)*. Girls with untreated CAH show rapid growth of the long bones with early epiphyseal maturation, resulting in the individual being tall for her age during childhood and shorter as an adult than would have been predicted based on parental height. In this instance, it is possible that the elevated androgens were serving as substrate for estrogen production in the bone and that it is this estrogen, and not the androgens, that stimulates bone growth. Evidence for this comes from a female with aromatase deficiency, a defect that prevents the conversion of T to E2. This patient was virilized but was shorter than expected and had a delay in bone age despite marked elevations in androgens *(27)*.

2.3.3. Adrenarche

The adrenal sex hormones remain suppressed following the regression of the fetal adrenal zone. The zona reticularis forms at about 3 years, but DHEA and DHEAS secretion from this region does not begin to rise until about age 6 years, which marks the biochemical onset of adrenarche. By about age 8 years, there is sufficient peripheral conversion of the adrenal androgens into T and DHT to stimulate axillary and pubic (ambisexual) hair growth. Androgen stimulation of the apocrine glands in these areas may result in a change in body odor. The child also may experience a transient growth spurt at this time *(28)*.

2.3.4. Puberty

The onset of puberty is heralded by an increase in gonadotropin-releasing hormone secretion, which initially induces a nocturnal rise in LH and then pulsatile increases in both LH and FSH throughout the day and night. The gonadotropins stimulate gonadal growth and development, and sex steroid hormone production in both sexes. The effects of increased pubertal androgen secretion in males is dramatic and easily observed: growth of the penis, increased pubic and axillary hair, development of body and facial hair, growth of the larynx with deepening of the voice, skeletal muscle enlargement and increase in muscle strength, growth spurt, increase in bone mass, increased erythrocytosis, increased malodorous perspiration, acne, and an increase in libido and aggressive behavior *(29)*.

Pubertal girls also experience a rise in T, which follows a diurnal variation with higher levels in the morning than evening. When menstrual cycles are established, there is a midcycle rise of T and A4 that is concordant with the rise in E2 and follows the peak in LH secretion. One of the physiological roles of T in females is to serve as the major prohormone for the production of E2, a hormone essential for secondary sexual development and the pubertal growth spurt. Other physiological actions of androgens during normal female puberty are more difficult to discern, although they likely have a role in the increased activity of sudoriferous glands, a further increase in the amount and thickness of ambisexual hair (axilla, pubis), and enhanced sebum production with the likelihood of concurrent acne.

2.3.5. Adulthood

Peak levels of androgens and androgen precursors in women are achieved between ages 20 and 30 years, followed by a steady decline. Between the ages of 21 and 40 years, there is approximately a 50% drop in T, DHEA, and DHEAS levels *(30,31)*. There is a further decline of close to 25% between the ages of 42 and 50 years *(32)*. Several longitudinal studies have demonstrated that there is no significant change in T levels during the menopausal transition, and, in fact, free T may actually increase owing to the reduction in SHBG levels that occurs following the profound decline in estrogen production by the ovaries *(32,33)*. That the theca cells in the postmenopausal ovary are steroidogenically active in androgen production has been demonstrated by studies carried out in postmenopausal women undergoing bilateral oophorectomy, in which serum T and A4 levels were reduced by 50% *(34)*. DHEA, DHEAS, T, A4, and DHT continue to decrease between ages 60 years and 70 years, but at a slower rate than prior to age 50. Thus, adrenal and ovarian secretion of androgens decrease over time with age.

The physiological role of androgens in women during adulthood is unclear. Women with hyperandrogenic disorders may develop hirsutism, acne, deepening of the voice, androgenic alopecia, clitoromegaly, malodorous perspiration, increased muscle mass, and aggressive behavior—essentially confirming the fact that female androgen target tissues can respond in a manner similar to those in men when exposed to a high enough concentration of androgens for a sufficient duration. Low free T levels have been found in women with hypopituitarism, adrenal insufficiency, oophorectomy, or premature ovarian failure and after institution of oral estrogen therapy in menopausal women *(6)*. Based upon observations in such women, a consensus panel developed the clinical construct of the female androgen insufficiency syndrome: low libido with a global decrease in sexual desire, fantasy, or arousability; persistent, unexplained fatigue; decreased sense of well-being; blunted motivation; flattened mood; thinning or loss of pubic hair; decreased lean body mass; and osteopenia or osteoporosis *(35)*. Thus, it is likely that androgens play at least a permissive role in female sexuality, mood, and body composition in adulthood, although unassailable direct support for this concept is currently lacking.

2.4. Androgen Effects on Specific Target Tissues in Women

The sites of sex hormone production are also, in most cases, the sites of tissue-specific action. Following is a brief review of these sites and their functional aspects.

2.4.1. Brain

Functional differences in some aspects of brain function exist between males and females, and studies in rodents and nonhuman primates indicate that sex steroid hormones are important contributors to these differences. Hormonal effects are categorized as organizational or activational *(2)*. Organizational refers to the hard wiring by which a male or female phenotype is actualized. Activational refers to those effects that are malleable and respond to current conditions. Each of these effects may be structural, or functional, or both *(2,36)*. Androgen receptors are distributed throughout the brain and are generally within close proximity to estrogen receptors *(37)*. High concentrations of the receptors are present in the preoptic area of the hypothalamus, with smaller numbers located in the amygdala, hippocampus, and cerebral cortex. Areas of the brain also contain 5α-reductase and aromatase and are thus able to convert T to DHT or E2, which may mediate some of the effects of T. In addition, as well demonstrated in rat studies, myelinating glial cells in the central and peripheral nervous system can synthesize DHEA directly from cholesterol as well as from precursors of extraneural origin *(38)*. At present it is unknown whether local androgen synthesis in the human brain is physiologically relevant. Small trials of DHEA given orally to patients have not shown a clear effect on cognitive function, mood, sense of well-being, perimenopausal symptoms, or memory *(10,39)*. These negative studies may indicate a lack of physiological importance of DHEA in brain function, an inadequate achievement of brain DHEA concentrations following oral administration, or that the locally pro-

duced neurosteroids have exerted their maximal physiological effects and that the exogenous DHEA can exert no additional effect.

As previously noted, the prenatal exposure of female rats and monkeys to androgens during the critical prenatal and early postnatal periods results in masculinized behavior and, in the rats, inhibits the cyclicity of the hypothalamic–pituitary–ovarian axis. CAH represents the clinical correlate in humans, and affected females do demonstrate more male-typical activities than controls *(2)*. In contrast, males with complete androgen insensitivity have female-typical behavior, suggesting that in the absence of androgen action, the default behavior is female. It is clear that androgens can have an activational effect on behavior in women. In some studies, women who fulfill the criteria for the female androgen insufficiency syndrome note an improvement in their overall sense of well-being when given exogenous T, increasing their serum T concentrations into the physiological or slightly supraphysiological range for women in their reproductive age group *(40–43)*. In addition, an increase in the scores for aggression has been noted in women receiving T injections that result in supraphysiological levels *(41,44)*. These studies suggest that androgens may be a modulator of mood and behavior in women.

The relationship between androgens and libido and sexual function in women has been an active area of investigation. In reproductive-age women, there is a correlation between the midcycle increase in T and libido, the ability to become sexually aroused, and frequency of sexual activity *(45–49)*. Within the normal range for women, those that have the highest T levels across the menstrual cycle have less depression and more sexual gratification than do the women with the lowest levels of T *(46)*. Some, but not all, cross-sectional populations studies have also shown correlations between serum T concentrations and desire, arousal, responsiveness, and frequency of sexual activity *(6)*. Although a recent cross-sectional study failed to show a relationship between T levels and self-reported sexual function in women, it did note that there was a significant association between reduced sexual desire, arousal, and responsiveness, and low DHEAS levels *(50)*. Since DHEAS serves as a prohormone for tissue production of A4, T, and DHT, it is likely that the tissue concentrations of these more potent androgens were also low in these women. Decreased sexual function has been noted in women with hyperandrogenic disorders given antiandrogens, such as cyproterone acetate *(51)*. Finally, the administration of T to women with hypoactive sexual desire disorder results in an improvement in libido and sexual function. The levels of free T achieved in these studies were within the high physiological range to slightly supraphysiological range for premenopausal women. Of interest, there is a positive, though not robust, correlation between the change in T levels and improvement in sexual desire and other parameters of sexual function in women *(6,52–55)*. Thus, the relationship between physiological levels of androgens and female sexual desire is well established and most likely reflects an action of T on the brain *(56)*.

2.4.2. Bone

Androgen receptors are present on osteoblasts and, to a lesser extent, on osteoclasts and osteocytes. Osteoblasts from young bone have greater expression of androgen receptors than in older bone, and the receptors are more expressed in osteoblasts from cortical bone than from cancellous bone *(57)*. In vitro, androgens stimulate osteoblast proliferation, enhance their differentiation, and prevent osteoblast apoptosis, while stimulating osteoclast apoptosis *(25,57)*. Estrogen receptors and aromatase are also present in bone. Thus, it is difficult to dissect out the physiological role that androgens play directly vs indirectly through conversion to estrogen in bone development, growth, and health.

Endogenous serum T levels are correlated with bone mineral density in adolescent females and premenopausal women; in pre- and perimenopausal women, there is also an inverse correlation between bone density and SHBG levels. Conflicting data exist regarding the relationship between endogenous T levels and bone density in postmenopausal women *(57)*. Women with hyperandrogenism resulting from polycystic ovary syndrome (PCOS) have increased bone mass, and the bone mineral

density correlates with the T and A4 levels *(25,57)*. Patients with complete androgen insufficiency syndrome exhibit a reduction in bone mineral density of the spine, but not of the hips, compared to normal females *(58)*. Administration of androgens along with estrogens to women with postmenopausal osteoporosis increases bone mass in the spine and hips to a greater extent than with estrogen alone *(25,56,59)*. That this is not merely a result of aromatization of the T to E2 in the bone arises from two observations in women. First, women who receive norethindrone acetate or nandrolone decanoate, compounds related to T, but which are not aromatized to estrogen, exhibit significant increases in bone mineral density *(60,61)*. Second, in a study that compared the effects of esterified estrogens alone or with methyltestosterone on serum and urine markers of bone formation and resorption, estrogen or estrogen plus methyltestosterone both decreased the markers of osteoclastic bone resorption, while only the estrogen plus methyltestosterone combination increased the levels of markers of osteoblastic bone formation *(62)*.

Androgens stimulate growth plate closure during puberty, but this action is mediated through aromatization to estrogens and binding to the estrogen receptor. Men and women with aromatase deficiency have an absent pubertal growth spurt and delayed epiphyseal closure, as do men with a mutation in the estrogen receptor-α gene *(25,27)*.

2.4.3. Breast

Normal mammary epithelial cells contain androgen receptors in addition to estrogen and progesterone receptors. To date there is a paucity of in vitro studies of the effect of androgens on normal human breast cells. In breast cancer cell lines, androgens antagonize the proliferation induced by estrogens and increase cellular apoptosis. Studies in animals also have generally shown that T and DHEA inhibit mammary carcinoma development. Dimitrakakis and coworkers examined the effects of estrogen alone, estrogen plus progesterone, estrogen plus T, and vehicle control in oophorectomized rhesus monkeys. These investigators observed that the addition of T significantly decreased mammary epithelial proliferation, altered the ratio of type of estrogen receptor (α or β) expressed, and reduced mammary epithelial estrogen receptor signaling *(63)*. The administration of the androgen receptor antagonist flutamide to intact, cycling female monkeys led to an increase in mammary epithelial cell proliferation, indicating that physiological levels of T in female monkeys protect the breast from the proliferative effects of estrogen *(63)*.

Few well-controlled clinical studies in women have examined the relationship between endogenous androgen levels and breast health. Some, but not all, studies have found that women with higher total T levels have an increased risk of breast cancer. In contrast, women with hyperandrogenemia resulting from PCOS do not appear to have an increased risk of breast cancer *(64)*. A recent retrospective, observational study in women receiving hormone therapy found that women who were given a combination of estrogen, progestin, and T had a lower rate of breast cancer development than historical control women who received only estrogen and progestin and was actually similar to that found in women who had never used hormones *(65)*. The limited data available at this time support the notion that endogenous T has a protective role in the breast, counterbalancing the effects of estrogens and progesterone.

2.4.4.Pilosebaceous Unit

Skin is an important site for peripheral conversion of androgens; at least 50% of a woman's androgen production occurs here as DHEAS is converted to DHEA to A4, A4 to T, and T to DHT. Hair is produced by the pilosebaceous unit (PSU), which extends outward from the hypodermis. The PSU is composed of a hair and a sebaceous gland component, which can differentiate into a terminal hair follicle or to a sebaceous follicle with a fine, vellus hair and an active sebaceous gland. Prior to puberty, the hair in the androgen-sensitive areas of the body is primarily vellus with small sebaceous glands. During puberty, the increased androgens stimulate vellus hairs to develop into terminal hairs. The growth of hair in sexual areas (i.e., hair that is terminal primarily in males, such as that of the upper lip, chin, chest, abdomen, back, thighs, or upper arms) depends upon the sensitivity of the PSU

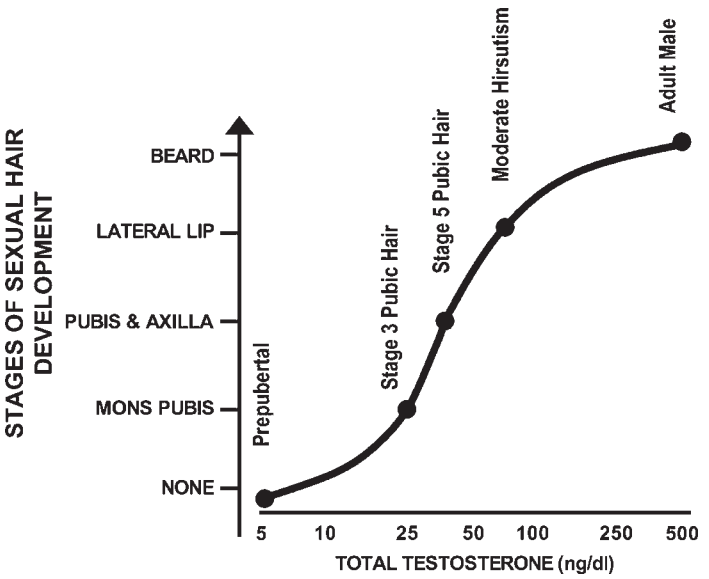

Fig. 1. Relationship of stages of sexual hair development to T circulating levels (log scale): **(A)** prepubertal; **(B)** stage 3 pubic hair; **(C)** stage 5 pubic hair (adult female); **(D)** moderate hirsutism; **(E)** adult male. (From ref. *72*.)

to androgens, the level of androgens they are exposed to, and the duration of exposure. p illustrates the relationship between plasma T levels and the degree of sexual hair development, demonstrating that the sensitivity of hair follicles to T is greatest in the pubic region and less in the beard area *(66)*. Androgen receptors present in the dermal papilla, sebaceous, and eccrine sweat epithelium have the highest concentration in the genital skin, followed by the pubic area, and then the nonsexual areas (e.g., lateral aspects of the scalp, eyebrows, etc.). The concentration of 5α-reductase in the skin follows the same pattern, and the fact that men with the 5α-reductase deficiency syndrome have sparse body and facial hair growth suggests that local production of DHT from T is important for hair growth in some areas of the body. Hirsutism—growth of excessive hair in the androgen responsive hair follicles in sexual areas of the body—can occur in women whose PSUs are exquisitely sensitive to normal serum androgen levels or may occur when androgen production increases above normal.

The sebaceous glands also are sensitive to androgen action. Sebum production increases with increasing concentrations of T, as shown in Fig. 2 *(66)*. Androgens stimulate the prepubertal vellus follicles to form large sebaceous glands in the acne-prone areas of the body *(67)*. The presence of acne in women correlates best with free T concentration. Again, there appears to be a large degree of variability in the sensitivity of the sebaceous glands to the effect of androgens. The sebocytes contain both 3β-hydroxysteroid dehydrogenase and 5α-reductase, allowing DHEA to serve as a prohormone for the local production of DHT *(67)*. Acne initially arises when there is overproduction of sebum by the sebaceous glands. The result is a noninflammatory process that produces simple blackheads and whiteheads. Acne becomes pathological when the lining of the sebaceous follicle is overstimulated by androgens. The cells slough off faster than the follicle can expel them, and they begin to adhere to one another. This accumulation blocks egress from the follicle, and a comodone (pimple) develops. If the condition continues, the follicle may become infected with *Propionibacterium acnes* (*P. acnes*). If the lesions (papules, pustules, nodules, and cysts) become rampant, the condition is termed acne vulgaris, a potentially devastating condition that can leave lifelong physical and psychological scars.

Pattern alopecia is thinning or loss of hair that accelerates with age in genetically susceptible men and women and is the result of miniaturization of scalp hairs (i.e., conversion of terminal hairs to vellus hairs) *(67)*. Although the two patterns of balding are labeled male pattern (temporo-occipital)

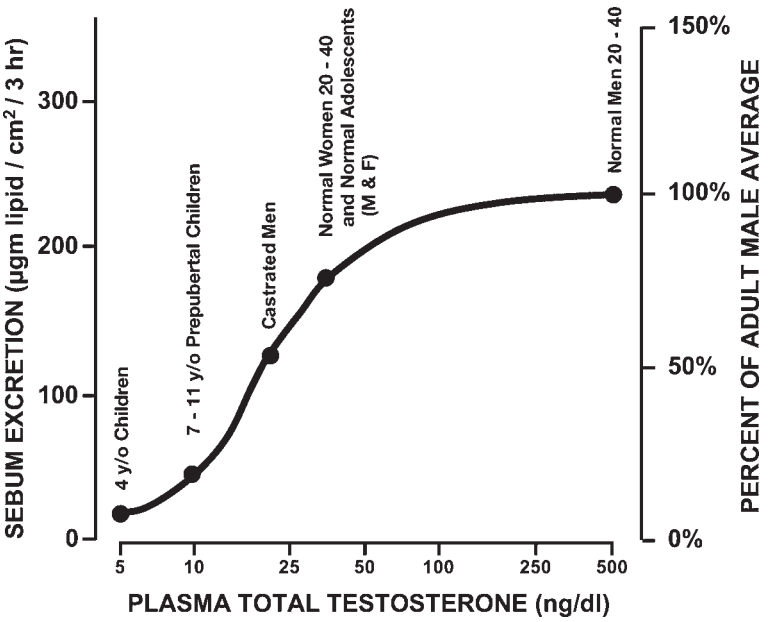

Fig. 2. Relationship of stages of sebum output and T (log scale): **(A)** 4-year-old children; **(B)** 7- to 11-year-old prepubertal children; **(C)** castrated men; **(D)** normal adult women, 20–40 years as well as average sebum level of normal 15- to 19-year-old males and females; **(E)** normal adult men, aged 20–40. (From ref. *72*.)

and female pattern (crown of scalp or diffuse), women can have male-pattern alopecia and men the female type. DHT appears to be the most important androgen involved in the process in males, because the 5α-reductase, type 2 isoenzyme is located in the hair follicles in the scalp. Patients with the 5α-reductase deficiency syndrome lack this isoenzyme and do not develop male pattern baldness. Also, men with male pattern baldness may respond to inhibitors of the 5α-reductase type 2 enzyme activity, such as finasteride. However, women with female pattern alopecia usually have normal androgen levels, and they do not generally respond to finasteride, suggesting that this pattern is not androgen sensitive *(68)*. Women with severe hyperandrogenism more often display a male pattern of hair thinning, which may respond to antiandrogens.

2.4.5. Cardiovascular System

There is a high degree of interest in the role of sex hormones in cardiovascular disease (CVD), the leading cause of death in both men and women. A few studies have examined the relationship between endogenous T and A4 levels and the presence of CVD in women, with conflicting results *(69)*. The largest prospective cohort study to date did not observe a correlation *(70)*. Conflicting data also exist concerning the risk of heart disease in patients with hyperandrogenism. These studies have examined women with PCOS and have amply demonstrated an adverse risk profile (metabolic syndrome) for CVD. However, it is likely that the insulin resistance associated with the syndrome is more relevant to the pathogenesis of CVD than are the elevated androgen levels. For example, exogenous administration of T to women or to female-to-male transsexuals has not been associated with an increased risk of CVD *(69)*. Thus, at present, there is no evidence for either a physiological or a pathological effect of androgens on the cardiovascular system.

3. CONCLUSIONS

Table 1 summarizes the areas where physiological functions of androgens in women have been demonstrated through a collection of observational and investigational studies, as well as the areas

Table 1
Physiological Actions of Androgens in Females

Demonstrated

- Prohormone for E2 production
- Axillary and pubic hair growth in adrenarche and puberty
- Stimulation of sebum production in adrenarche and puberty
- Bone health
- Sexuality

Probable but not conclusively demonstrated

- Imprinting of behavior in prenatal or early postnatal period
- Influence on mood and behavior
- Influence on some aspects of cognition
- Antagonize physiological concentrations of E2 in some tissues

where data supporting a role exist, but are not yet proven. It is clear that DHEA, DHEAS, A4, and T serve as prohormones for the production of estrogens in the adrenals, ovaries, and a variety of peripheral tissues. Therefore, the physiological effects of estrogens in women indirectly reflect a role for androgens, for if there were no androgens, there would be no estrogens. The rise in androgens during adrenarche and puberty directly stimulates axillary and pubic hair growth, as well as increased sebum production. In addition to serving as an important prohormone for estrogen synthesis in the bone, androgens directly influence osteoblastic and osteoclastic function. The importance for androgens in female sexual desire has been well demonstrated; studies of postmenopausal women with low sexual desire and low T levels demonstrate an increase in desire and sexual activity when their T levels are increased to within the reference range for premenopausal women. Areas in which there are suggestive but inconclusive data concern the physiological roles on the organizational and activational aspects of brain function, including the issues surrounding prenatal imprinting of behavior and postnatal influence on mood and behavior. The roles of androgens in the breast and the cardiovascular system remain to be better determined.

4. FUTURE AVENUES OF INVESTIGATION

Several areas concerning the normal physiological effects of androgens in women warrant additional study. These include:

1. Determining the role of androgens and estrogens in the sexual dimorphism of brain structure and function.
2. Understanding the steroid-specific effects in relation to the enzymatic conversion of the sex steroids in tissues, i.e., discerning which hormone is responsible for which effect.
3. Developing sensitive and specific assays for measurement of androgens and their metabolites in women, as well as methods to accurately access the tissue production and intracrine action of androgens.
4. Determining the physiological contribution of androgens to body composition, muscle mass, and strength.
5. Ascertaining if androgens contribute to the development of the metabolic syndrome in hyperandrogenic women or if the increased cardiovascular risk is a result of other factors such as hyperinsulinism.
6. Understanding the relationship of the immune system and autoimmune diseases to androgens. Although not discussed in the text, an important aspect of sexual dimorphism is that females are much more likely to develop autoimmune diseases than men. Further investigation is required to understand the role of physiological concentrations of androgens in the normal function of the immune system and possible protection against the development of autoimmune disorders (*see* ref. *71*).

KEY POINTS

- DHEA, DHEAS, A4, and T are prohormones for the production of estrogens in the adrenals, ovaries, and peripheral tissues.
- Androgens directly stimulate the pilosebaceous unit, stimulating axillary and pubic hair growth and increasing sebum production at puberty.

- Androgens influence osteoblastic and osteoclastic function in the bone.
- Androgens influence female sexual desire.
- Androgens may have a physiological role in the organizational and activational aspects of brain function.

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