Review

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# The Role of Androgens in Health and Disease in Females: A Narratıve Review

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ABSTRACT

Androgens play a key role in maintaining women's and men's health. They act on the ovary, endometrium, vagina, and vulva to maintain a balanced reproductive system, and have regulatory and protective effects on almost every part and function of the body, such as the heart, brain, bone, muscle, skin, and metabolism. As with many other substances, the effects of androgens are dose-dependent and pathological when present in excessive amounts. Although the role of androgen therapies in pre- and postmenopausal women's female has been better understood in recent years with increasing studies, there is still a need for studies in terms of side effects, patient selection, and standardization in terms of laboratory tests.

**Keywords:** Androgens, women, reproductive health, menopause, testosterone therapy

## INTRODUCTION

In discussions of women's reproductive health, estrogens are typically associated with women's health, while androgens are often contextualized within their related diseases. This perspective stems largely from the high clinical prevalence of androgen-related disorders. However, it is important to acknowledge the increasing recognition of the significance of androgenic well-being throughout a woman's life span. This review examines the role of androgens in both health and disease from an explanatory perspective.

## Physiology of Androgens in Females

### Androgen Synthesis and Measurement in Women

The main androgens in female are dehydroepiandrostenedione sulfate (DHEAS), dehydroepiandrostenedione (DHEA), androstenedione, testosterone and dihydrotestosterone (DHT), based on their concentration in serum.[1] DHEAS is a non-potent pro-androgen synthesized from zona reticularis in the cortex of the adrenal gland under the influence of adrenocorticotropic hormone. The secretion begins during adrenarche, peaks in mid-reproductive adulthood, and gradually declines before plateauing in later life. The rate of synthesis does not change during the menstrual cycle or is not affected by the transition to menopause.[2] DHEAS is an important source of androgen produced in the ovary.

DHEA is produced intracellularly, mainly from the zona reticularis by conversion in ovarian theca cells and from circulating DHEAS.[3] Serum concentrations decrease with age.[4,5]

Androstenedione is synthesized in the zona fasciculata of the adrenal cortex and stromal cells of the ovary. Serum concentrations are affected by circadian rhythm and menstrual cycle. It rises in the middle of the menstrual cycle in parallel with an increase in estrogen levels. A significant decrease in serum concentration has been observed in postmenopausal women undergoing oophorectomy.[1]

Testosterone is synthesized from both the zona fasciculata in the cortex of the adrenal gland and ovarian stromal cells. However, most is formed from androstenedione via peripheral conversion. It has been detected at higher concentrations in the ovarian vein than in the peripheral veins, and its serum concentrations decrease significantly in patients after oophorectomy. The level of testosterone is affected by the circadian rhythm.[6] The highest blood levels were observed in the early morning. It is the lowest in the early follicular phase of the menstrual cycle, peaks in the mid-cycle, and decreases in the luteal phase, although not as much as in the follicular phase.[7] Ten years after the onset of menopause, testosterone and androstenedione concentrations fell to half of those in the perimenopausal period.[1,8,9]

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DHT is derived from peripheral conversion of testosterone and is present in very low concentrations in the female body. A very small amount is produced by the adrenal zona fasciculata. Of note, testosterone can aromatize to estradiol, whereas DHT cannot.[1]

Liquid or gas chromatography and tandem mass spectrophotometry are reliable and reproducible methods for measuring total testosterone levels.[10] Direct immunoassay measurements are less reliable. However, salivary measurements are still far from being used clinically in terms of accuracy and they are considered investigational.[11]

### Androgen Receptors in Women

Androgen receptors (ARs), which belong to the nuclear receptor family, are located in many organs of the female body, such as the ovaries, brain, endometrium, bone, and heart, and they mediate important metabolic activities. AR-ligand interactions have been observed in the prostate, breast, ovary, and pancreas, and AR deficiency leads to dysfunction in follicle development, ovulation, and fertility. Studies have also suggested that ARs are located in the endometrium of women and provide uterine hemostasis.[5,12,13]

## Androgens and Reproductive Health

### Ovarian Function

Understanding the specific role of androgens in the ovary is highly dependent on AR knockout animal models, as completely androgen-resistant individuals cannot arise through natural reproduction. These models have elucidated the stimulatory role of androgens in early follicle development and their subsequent use in communication between follicles to maintain follicle health and induce late-phase growth.[14] Therefore, an increasing number of studies in recent years have focused on the use of pro-androgenic or aromatase inhibitor drugs in patients who respond poorly to hyperstimulation in in vitro fertilization centers.[15] However, it should be remembered that the positive effects of androgen on follicular development are actually only possible within an optimal concentration range. At increasing concentrations, individuals may abruptly begin to show clinical symptoms similar to polycystic ovary syndrome (PCOS), and evidence has shown that AR-related signaling pathways are responsible for the development of PCOS.[16]

### Endometrial Effect

Androgens can initiate both regulatory and reparative physiological mechanisms in the endometrium as well as pathological processes that can occur through AR-based pathways and aromatization to estrogen.[5] AR expression changes significantly throughout the menstrual cycle.[2,17] It is increased in epithelial cells during the proliferation phase and decreased in the secretory phase. It is suggested that ARs provide repair and durability in endometrial tissue. DHEA is thought to stimulate endometrial stromal fibroblasts in women of late reproductive age, causing decidualization, thus contributing positively to fertility.[12,18] In animal models, DHEA has also been shown to increase endometrial receptivity by exerting antioxidant effects on the endometrial stroma.[19,20]

There is no strong evidence that exogenous testosterone increases endometrial cancer. In a group of female-to-male patients, after long-term testosterone use, the endometrium underwent a process of atrophy similar to that observed in long-term progesterone users. In a large study comparing endometrial cancer risk according to the type of intrinsic androgen, pre-disease total and free testosterone levels were associated with endometrial cancer risk, whereas androstenedione and DHEAS levels were not.[21]

### Vulvo-vaginal Effects

The efficacy of estrogen in vulvovaginal tissues by increasing superficial cells and lowering pH has long been known and has been used in the treatment of certain diseases such as the genitourinary syndrome of menopause (GSM). Recent studies in animal and human tissues have shown that ARs are also present in the labium and clitoris of the vulva, predominantly in all three layers of the vagina.[22,23] To understand whether these receptors work as predicted, it is necessary to understand the mechanisms of up- and down-regulation properties and more than 1000 receptor mutations have occurred. These mutations have mostly been found in androgen insensitivity syndrome or female-looking XY individuals. In animal studies, androgenic treatments have been shown to lead to positive improvements in many areas, including vaginal weight, which is a measurable parameter in mice.[24] However, androgens have not yet entered routine therapeutic use for these beneficial their effects on vulvovaginal tissue.[25] In addition, as with estrogen, there is no clear consensus on the benefits and harms of their systemic or local use.

## Clinical Conditions Associated with Androgen Imbalance

### Conditions Associated with High Androgen

High androgen levels in women are primarily associated with PCOS, which affects approximately 20% of young women. PCOS is characterized by several reproductive and metabolic abnormalities. From a reproductive perspective, women with PCOS often experience oligomenorrhea, ovulatory dysfunction, and infertility. The metabolic implications of PCOS are significant and largely driven by hyperandrogenism.[26] Elevated androgen levels predispose women with PCOS to obesity, insulin resistance, and metabolic syndrome. These metabolic disturbances can have far-reaching consequences. For instance, about half of obese women with PCOS develop metabolic syndrome, highlighting the strong interaction between androgens and insulin. Furthermore, metabolic derangements associated with PCOS may progress to more severe conditions, with approximately 40% of women with PCOS developing impaired glucose tolerance, which may eventually evolve into Type 2 diabetes mellitus. Additionally, women with PCOS often exhibit an unfavorable lipid profile, characterized by increased triglyceride and total and low-density lipoprotein cholesterol levels. Thus, high androgen

levels, particularly in PCOS, have significant implications for both reproductive function and metabolic health in women.[27,28]

### Conditions Associated with Low Androgen

Screening for low androgen levels in women is not routinely recommended, as there is no well-defined syndrome of "female androgen insufficiency" that reliably correlates with serum androgen levels. The Endocrine Society advises against diagnosing "female androgen deficiency" or using testosterone to treat low-androgen states in women.[29] This is because low serum androgen levels do not consistently correlate with clinical symptoms, even among oophorectomized women.[30] Understanding the conditions that can lead to low androgen levels in women is important, however these conditions include reduced ovarian androgen production (caused by chemotherapy, radiation, ovarian failure or insufficiency, and oophorectomy), decreased adrenal androgen production (adrenal insufficiency), issues with the hypothalamic-pituitary axis (such as malnutrition, anorexia, and hypopituitarism), and the use of specific medications (corticosteroids, hormonal contraceptives, antiandrogenic agents, oral estrogen therapy, and opioids).[8] When considering these conditions, clinicians should focus on the patient's clinical presentation rather than solely relying on serum androgen levels, as the interpretation of these levels and their physiological effects are complex.

To address the necessity and timing of oophorectomy separately, the oophorectomy approach, which in the past was customarily performed prophylactically during hysterectomies for benign causes, is now considered unfavorable from the perspective of androgen metabolism and its effects.[31] Although many of the metabolic and cardiovascular disadvantages of oophorectomy-induced menopause in premenopausal women are mostly attributed to estrogen deprivation, oophorectomy in postmenopausal women causes similar findings. Therefore, studies have shown that in women with no ovarian indication and an average familial risk of ovarian cancer, the decision to perform prophylactic oophorectomy should be made with much more caution.[32]

### Interpretation of Sex Hormone-Binding Globulin

Active testosterone circulates in the blood either free or bound to albumin. Testosterone measurements also measure the circulating inactive testosterone bound to sex hormone-binding globulin (SHBG) in the blood. SHBG is a protein synthesized in the liver and shows a high affinity for sex steroids. Factors that increase or decrease SHBG levels directly affect the amount of active testosterone circulating in the blood. For example, with menopause, SHBG decreases slightly, leading to increased levels of active testosterone in the blood. Exogenous estrogen therapy increases SHBG levels, which has the opposite effect. When transdermal estrogen preparations are used, this effect is not observed, unless very high doses are used.

SHBG functions beyond its role as a simple transport protein It serves as a metabolic marker. It is a parameter that warrants consideration in the evaluation of PCOS due to its direct association with hyperinsulinemia, Type 2 diabetes, and metabolic syndrome.[33] Low concentrations of SHBG in postmenopausal women without elevated testosterone levels have been associated with unfavorable lipid profiles, visceral fat and diabetes risk. Genetic factors (single nucleotide polymorphisms) in the investigation of low SHBG levels were only informative in a small group.[34] Fatty liver disease, especially in the presence of dietary fructose, was sufficient to significantly lower SHBG levels in animal models. This effect is thought to be insulin independent. The free androgen index (FAI), calculated using total testosterone and SHBG levels, is associated with increased metabolic syndrome and cardiovascular risk in postmenopausal women, whereas this cannot be said for testosterone alone.[35] The conclusion from these studies is that SHBG may be important for screening women of various ages for metabolic diseases.[36]

## Androgens in Non-Reproductive Health

### Cardiovascular Effects

Many studies have examined the effects of androgen levels or lifetime exposure, on cardiovascular health in women. Women exposed to low androgen levels during reproductive age have been observed to have an increased risk of cardiovascular disease in the postmenopausal period.[37] This effect was supported by findings in another study that indicated that appropriate androgen levels help maintain an antiatherogenic lipid profile in women.[38] At the other end of the equation are women with hyperandrogenemia, the most common example being women with PCOS. In these women, total androgen overload appeared to increase atherosclerosis in the postmenopausal period. FAI is one of the methods used to monitor the effects of androgens in such patients. Insulin resistance, hypertension, impaired lipid profile, and central obesity are commonly observed in women with increased FAI. Based on these findings, it may be conclude that one of the conditions required to maintain cardiovascular health in women is maintaining androgen levels at physiological levels.[39,40]

### Metabolic Effects

The difference in fat distribution in the male and female bodies suggests that androgens act on fat cells. Androgens do this by affecting the differentiation of adipose stem cells into mature adipocytes. Testosterone also reduces lipolysis by inhibiting adipose-sensitive lipases in women. Visceral obesity increases insulin resistance, leading to hyperinsulinemia and increased insulin-like growth factor-1 synthesis, which in turn increases ovarian androgens and decreases SHBG synthesis from the liver.[41] Thus, increased androgen levels lead to insulin resistance, which in turn leads to increased androgens, resulting in a cycle of PCOS and metabolic syndrome. The same effect can occur after menopause when testosterone levels increase due to decreased estrogen and SHBG.[42]

### Neuroprotective and Cognition Regulating Effects

Like many other organs, the brain is influenced by the withdrawal of ovarian hormones, particularly during menopause. Estrogen and testosterone exhibit anti-inflammatory and neuroprotective effects in the brain, contributing to the regulation of cognition and mood.[43] ARs are distributed throughout the central nervous system and play a role in processes such as sexual desire,

thermoregulation, sleep, visuospatial skills, and language. In addition, testosterone appears to reduce oxidative stress, limit the accumulation of amyloid beta, and accelerate nerve regeneration, highlighting its potential protective effects against neurodegenerative conditions, such as Alzheimer's disease.[44]

Although the majority of women transitioning through menopause do not experience major cognitive changes, some encounter significant disruptions that impair their quality of life, particularly in younger women undergoing oophorectomy.[32] Observational and interventional studies suggest a relationship between physiological concentrations of testosterone and improvements in verbal learning and memory in postmenopausal women when administered exogenously. The simulation of male testosterone levels in premenopausal women has been shown to enhance visuospatial performance; however, its effects on verbal learning and memory in this population remain unstudied.

Randomized controlled trials investigating the cognitive effects of testosterone therapy in postmenopausal women are limited and are often constrained by small sample sizes or concurrent estradiol therapy. The current data suggest that testosterone therapy has no adverse effects on cognition, mood, or overall well-being in postmenopausal women. Research has indicated that postmenopausal women who applied 300 $\mu$g/day of testosterone gel transdermally for a duration of 26 weeks demonstrated marked improvements in verbal learning and memory functions.[45] However, no noteworthy effects on overall well-being were observed. In a contrasting investigation, hysterectomized women, regardless of whether they had undergone oophorectomy, received intramuscular testosterone at both physiological and supraphysiological levels in conjunction with transdermal estradiol. This study reported no significant alterations in cognitive function among participants.[46]

Notably, the cognitive benefits of testosterone in postmenopausal women appear to be independent of aromatization to estradiol. While these findings suggest that testosterone therapy may enhance verbal memory or delay cognitive decline, current evidence does not warrant its routine use for these purposes.[47]

### Osteoprotective Effect

ARs and estrogen receptors (ER) are both important receptors regulating bone metabolism.[48] Androgens and estrogen-aromatized helices trigger significant effects on osteoblasts and osteoclasts through AR and ER.[49] AR activation stimulates osteoblast proliferation and inhibits osteoclast activity. In addition, ER activation inhibits osteoclast proliferation and activates osteoclast apoptosis. This results in an inhibitory effect on bone resorption.[50] In the female body, the second estrogen-dependent mechanism is more effective. In one study, low free testosterone levels in women of late reproductive age were associated with a more rapid decrease in bone density in the future.[51] Another study found that, among older patients, those with lower endogenous testosterone levels also had lower lumbar and hip bone densities.[36] In the Women's Health Initiative observational study, higher endogenous bioavailable testosterone concentrations were associated with lower hip fracture rates, independent of estradiol and SHBG.[36] It is important to note that studies in which an effect was observed have always compared endogenous testosterone values. Studies into whether testosterone treatment increase bone mineral density have been inconclusive, and the findings are conflicting. Although there are studies showing better results in women given testosterone in combination with estrogen compared to estrogen alone[52], there are also studies showing the opposite, and androgen therapies are still far from being used primarily to contribute to bone density.[53]

### Effects on Skin and Hair

Although the adrenal glands and ovaries are the main centers of androgen production, the skin is also an organ where potent androgens such as DHT are formed, and ARs are involved in this mechanism. ARs are found in sebocytes, dermal papilla cells, root sheaths of hair follicles, sweat glands, vascular endothelial smooth muscle cells, and epidermal and follicular keratinocytes.[54] AR activation causes proliferation and sebum production in sebaceous glands. In the frontal region and vertex of the head, it shortens the anagen phase of hair follicles in genetically predisposed individuals and causes hair loss, whereas in other parts of the body, it transforms the vellus into terminal follicles.[55] Although it plays a role in the pathogenesis of acne, patients with acne vulgaris are rarely hyperandrogenic. Hirsutism is caused by androgen action, and androgens are elevated in most hirsute women. In female pattern hair loss, the pathogenesis of AR disorders is being investigated, although the causes are not fully understood.[56] Endocrinological tests and a multidisciplinary approach are important to ensure treatment success in androgen-mediated skin diseases.[56,57]

### Effects on Muscle Mass and Performance

It is well known that androgens increase muscle mass and performance in both sexes. Many professional and recreational athletes worldwide use testosterone derivatives as well as anabolic steroids to enhance athletic performance or physique. In addition to external use, a study among athletes with PCOS showed a significant correlation between muscle mass and androgen levels. This gives some athletes a significant advantage over others.[58,59] The athlete's biological passport is used for such cases, and androgen levels are recorded after taking ethnicity, menstrual status, and oral contraceptive use into account. In addition, studies on postmenopausal women using exogenous androgen derivatives have shown increases in both muscle mass and athletic performance.[60,61] These therapies are currently being used for the treatment of neuromuscular diseases, dystrophies, and myositis.[62]

## Therapeutic Applications of Androgens

### Genitourinary Syndrome of Menopause

Up to 70% of women who have gone through menopause experience GSM, a condition previously referred to as vulvovaginal atrophy. It encompasses urinary, genital, and

sexual dysfunctions resulting from declining sex hormone levels.[63] The clinical presentation typically encompasses dyspareunia, vaginal dryness, irritation, dysuria, increased urinary frequency and urgency, recurrent urinary tract infections, and a shift towards alkalinity in vaginal pH. While non-hormonal therapies, such as vaginal moisturizers and lubricants, can provide some relief, they do not restore genitourinary tissue integrity. Hormonal therapies, particularly vaginal estrogen and DHEA, are considered to be the most effective treatments for GSM.[39,64] The Food and Drug Administration has approved intravaginal DHEA 6.5 mg for GSM treatment, which has shown improvements in cell maturation, vaginal pH, dyspareunia, and sexual function with neutral effects on the endometrium.[9,65]

### Hypoactive Sexual Desire Disorder

Women's sexual behavior is inherently multifactorial and influenced by many organic and psychological factors. In addition, there are many variations in androgens, their receptors, and their pathways, and it is almost always very difficult to perform true androgen measurements in the laboratory. Despite this, it is now well-established that sexual function in women is regulated by androgens.[52,66] Testosterone and its precursors significantly affect sexual function, desire, and arousal.[52,67,68] There is a relationship between testosterone levels and sexual function pre- and post-menopause.[69] Although hypoactive sexual desire disorder (HSDD) is a controversial condition in some communities, it has become the focus of research for testosterone treatment in some countries.

Although research indicates potential sexual health advantages, testosterone formulations have not been approved for women in many countries. Based on existing safety information and adverse effect profiles, the preferred method of administering testosterone to women is through short-term, low-dose transdermal applications. The Endocrine Society Guideline recommends six months of transdermal testosterone for HSDD.[29] When prescribing testosterone to women, clinicians should use caution and typically prescribe a tenth or less of the recommended male dose to avoid supraphysiological dosing. Topical products should be applied to the inner thigh, buttocks, abdomen, or vulva, avoiding the breasts and arms.[25] Oral testosterone is discouraged due to first-pass metabolism in the liver and associated side effects.[70] Intramuscular and pellet therapies should also be avoided because of their potential for prolonged exposure and supraphysiologic dosing.[70] Although safe and successful results have been obtained in the short term, long-term studies are required.[9,67,71]

### Monitoring During Treatment

Once testosterone therapy is initiated, careful monitoring is essential. The Endocrine Society and global consensus position statement recommend checking baseline testosterone levels before starting therapy. Monitoring of follow-up levels is recommended 3-6 weeks post-initiation and semi-annually thereafter to prevent side effects and excessive dosing.[25,29] It is essential to recognize that clinical response is not correlated with serum hormone levels; testing serves only to ensure treatment safety. Subsequent steps should focus on a clinical evaluation of perceived benefits versus risks, with the aim of enhancing sexual desire, arousal, orgasmic function, satisfaction, or responsiveness to sexual cues, while concurrently addressing sexual anxieties and distress. If there is no response after six months of consistent use, treatment should be discontinued. Regular monitoring should also include assessment of potential side effects, such as mild increases in acne or hirsutism, although significant adverse effects are rare when serum testosterone levels remain within normal physiological ranges.[9,67]

### Androgens and Breast Cancer

Breast cancer is the most common cancer in women worldwide. ARs can be positive or negative in breast cancer tissue regardless of the ER. Those who are positive have shown better response to treatments and longer survival times.[72,73] The effect of androgen hormones on the development of cancer itself is still unclear. Some researchers suggest protective effects, while others suspect that they promote tumor growth.[25,73] Studies measuring androgen concentrations in the blood during the postmenopausal period have shown an increased incidence of cancer at higher concentrations, similar to estrogens. Currently, there are studies on the use of selective AR mediators in the treatment of some types of breast cancer.[73,74] For other reasons, the use of testosterone is not recommended in women with a history of breast cancer because of the risk of aromatization to estrogen.[25]

### Emerging Research and Future Directions

Research on the effects of androgens on women's health will undoubtedly continue to be published and new studies will be planned in the coming years. We will continue to learn about the effects of androgens and their receptor behaviors on the health of individuals in reproductive and non-reproductive systems, in premenopausal and postmenopausal ages, and even in adolescence. On the reproductive side, studies examining androgens and ovarian eserve, receptor polymorphisms, and reproduction from conception to sexual behavior will continue to be examined in depth. On the non-reproductive side, we will see more oncological studies, especially in the endometrium and breast, and studies to discover the effect on pain perception, which has perhaps not received much attention so far. In the field of cosmetic gynecology, the results of studies examining androgens and their safety in complementary and preventive therapies will continue to be published, and undoubtedly more will be said about androgen excess and reproductive metabolic syndromes. Although androgens and their effects after gender-affirming surgery were not mentioned in this review, it seems that there will be results that will be of interest to both this group and non-transgender people.

## CONCLUSION

Androgens play important roles in women's reproductive and systemic health, supporting ovarian function, endometrial repair, bone strength, neuroprotection, and metabolic balance. When dysregulated, they contribute to disorders: excess androgens, as in PCOS, lead to metabolic and reproductive

problems, while deficiency is linked to conditions like HSDD and GSM. Their systemic impact is shaped by interactions with estrogen and SHBG, influencing cardiovascular, cognitive, and musculoskeletal health. However, a major limitation to effective androgen therapy is the lack of reliable biomarkers to assess tissue-level androgen activity. Current treatments aim to maintain total testosterone within physiological ranges, but no strong evidence supports initiating therapy solely based on low levels. HSDD remains the only established indication for androgen replacement, underscoring the urgent need for standardized measures and long-term safety data.

**Footnote**

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