Androgen insufficiency in women

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Abstract

Androgens are directly secreted by the ovaries and adrenals in women, and androgen precursors from these glands are converted in a variety of peripheral tissues into androgens. The major androgen in women is testosterone, and its action in target tissues can be mediated through the androgen receptor or through the estrogen receptor after aromatization to estradiol. Low sexual desire that causes personal distress (or hypoactive sexual desire disorder [HSDD]) is the most common form of female sexual dysfunction, and androgen insufficiency is one cause of this problem. In addition to a low libido, the clinical construct of the female androgen insufficiency syndrome includes the presence of persistent, unexplained fatigue and a decreased sense of well-being. Although there is conflicting information about the relationship between serum testosterone concentrations and sexual desire, multiple randomized, double-blind, placebo-controlled treatment trials have demonstrated that testosterone improves libido significantly more than placebo. Doses that provide physiologic to slightly supraphysiologic serum free or bioavailable testosterone concentrations are safe and associated with only mild androgenic side effects of acne and hirsutism. Oral, but not parenteral or transdermal, testosterone may decrease high-density lipoprotein cholesterol. At present, no testosterone preparation has been approved by the FDA for the treatment of low sexual desire (HSDD), so all such therapy is considered to be off-label use at this time.
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1. Introduction

In 2003, 21% (approximately 145,000) of all prescriptions for commercially available male testosterone products were written for women [1]. In addition, between 2002 and 2003, women were given 1,315,000 prescriptions for compounded or generic androgen preparations [1]. Thus, a large number of women are prescribed androgens for "off-label indications," primarily for the treatment of sexual dysfunction. What are the data supporting androgen therapy for women? What are the risks of such use? This review will address these issues.

2. Androgen physiology

Androgens are produced by the ovaries, by the adrenals, and in the peripheral tissues from androgen precursors of ovarian and, especially, adrenal origin. Although a number of different androgens are produced, testosterone is the major moiety taking into account the serum levels, the amount free to enter target tissues, and potency. In the premenopausal state, approximately 25% of endogenous testosterone is secreted by the ovaries and 25% by the adrenals, and 50% is produced in peripheral tissues. After menopause, approximately 50% is produced by the ovaries, 10% by the adrenals, and 40% from peripheral conversion. This reflects the marked reduction in the production of adrenal androgen and androgen precursors, primarily dehydroepiandrosterone [DHEA] and its sulfate [DHEAS] [2].

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Testosterone serum levels follow a circadian rhythm, with levels being higher in the morning than in the evening. In premenopausal women with normal menstrual cycles, there is a midcycle rise in testosterone that coincides with a peak in serum luteinizing hormone. Testosterone levels decline with age, such that serum levels in women in their 40s are approximately one half of those in women in their 20s. In contradistinction to what is observed with estradiol, ovarian testosterone production does not decrease at the time of menopause, and serum testosterone levels during the menopausal transition do not change [2].

Measurements of total serum testosterone levels reflect the presence of both of protein-bound and free testosterone in the circulation. The primary testosterone-binding protein is sex hormone-binding globulin (SHBG), which binds approximately two thirds of the testosterone with a high affinity, essentially rendering the hormone unavailable to tissues. Approximately one third is bound to albumin; in this state, testosterone can readily diffuse away from its binding site. The remaining 1–2% exists in the free state and can easily enter target tissues. The combination of albumin-bound and free testosterone is commonly referred to as *bio-available testosterone*.

When taken up by the tissues, testosterone can either directly bind to the androgen receptor and elicit androgen action, or it can be metabolized to dihydrotestosterone (DHT) through the action of 5α-reductase, or to estradiol by aromatase. DHT, which on a molar basis is more potent than testosterone, binds to the same androgen receptor as testosterone. Estradiol binds to the estrogen receptor in tissues. Therefore, the actions of testosterone in different tissues may reflect both androgen and estrogen effects.

3. Relationship of androgens to female sexual dysfunction

Female sexual dysfunction has been classified into four main categories: desire disorders, arousal disorders, orgasm disorders, and pain disorders [3,4]. The most common is hypoactive sexual desire disorder (HSDD), which is defined as the persistent or recurrent deficiency (or absence) of sexual fantasies, thoughts, and/or desire for, or receptivity to, sexual activity, which causes personal distress. HSDD accounts for approximately 85% of all female sexual dysfunction. Based upon worldwide data, approximately 5–10% of women report that they frequently experience low sexual desire [5].

The relationship between serum testosterone levels and sexual function is not clear-cut. While some studies have correlated testosterone levels with midcycle sexual activity and overall sex drive, arousability, frequency of masturbation, and frequency of intercourse [6–13], other studies have failed to demonstrate an association

[14–21]. Moreover, the administration of antiandrogens, such as cyproterone acetate, has been shown to decrease libido [22]. Clinical trials of testosterone replacement in women with HSDD have shown that increases in testosterone levels correlate with increases in the frequency of satisfying sexual activity and improvement in desire, as well as a decrease in personal distress [23–25].

4. The female androgen insufficiency syndrome

Based upon expert opinion, a clinical construct of the female androgen insufficiency syndrome was developed at a recent consensus conference [26]. The signs and symptoms most commonly associated with this syndrome are listed in Table 1. Other potentially related signs and symptoms include bone loss, decreased muscle strength, and alterations in cognition or memory. The onset of these signs and symptoms generally relates to an event or condition associated with a decline in androgen production, but other causes for these symptoms, such as depression, thyroid disease, or chronic fatigue syndromes, should be explored. It is important to note that androgen insufficiency is only one cause of HSDD, and HSDD can result from depression, relationship issues, acute or chronic illnesses, and medications.

Conditions widely known to be associated with low testosterone production and HSDD include hypothalamic–pituitary abnormalities, bilateral oophorectomy, adrenal insufficiency or glucocorticoid therapy, and the administration of exogenous estrogens. Hypothalamic and pituitary disorders that result in diminished secretion of gonadotropins and ACTH lead to inadequate production of ovarian and adrenal androgens and androgenic precursors [27]. Bilateral oophorectomy has been shown to reduce serum testosterone levels by approximately 50%, while abnormally low production of adrenal androgens due to adrenal insufficiency or suppression from exogenous glucocorticoids also results in low testosterone levels [28–36].

It is important to distinguish between HSDD due to androgen insufficiency and that related to dyspareunia, which contributes to the avoidance of sexual activity

Table 1
Female androgen insufficiency syndrome

Symptoms
Low libido with global decrease in sexual desire or fantasy
Persistent, unexplained fatigue
Decreased sense of well-being
Blunted motivation
Flattened mood

Signs
Thinning or loss of pubic hair
Decreased lean body mass
Osteopenia/osteoporosis

Table adapted from Bachmann et al. [26].

and a secondary diminution in desire. The loss of ovarian estrogen production that accompanies menopause results in a decreased volume of vaginal secretions and, hence, vaginal lubrication, which may lead to pain during intercourse. Therefore, the physician should ensure that women with HSDD have adequate vaginal estrogenization before concluding that the HSDD is caused by androgen insufficiency. The route of estrogen administration is also important. Due to a first-pass effect on the liver, oral estrogens stimulate hepatic SHBG production, often resulting in supraphysiologic levels of this protein. Since SHBG avidly binds circulating testosterone, and since testosterone production in women is not tightly regulated through the hypothalamic–pituitary–gonadal or adrenal axis, this enhanced binding reduces the free and bioavailable forms of testosterone [37,38]. Thus, oral estrogen administration may precipitate symptoms of androgen insufficiency. In contrast, transdermal estrogens do not significantly alter SHBG levels, and thus, their use markedly reduces the risk of inducing HSDD by this mechanism.

5. Results of testosterone treatment trials on sexual function in women

The first randomized, placebo-controlled testosterone treatment trial was reported by Greenblatt and associates in 1950 [39]. Subsequently, as shown in Table 2, a multitude of trials have examined the effects of testosterone on sexual function in pre- and post-menopausal women [23–25,39–55]. Together, these trials indicate that testosterone treatment which results in high (premenopausal) physiologic or slightly supraphysiologic testosterone levels increases arousability, desire, fantasy, frequency of sexual activity, frequency of orgasm, sexual satisfaction, and pleasure, and decreases personal distress. However, several limitations of these studies must be considered. As shown in Table 2, most clinical studies were conducted for less than 1 year, so the long-term effects of testosterone on sexual desire are unknown. In addition, the majority of women studied also received estrogens and, in some cases, progestogens. Therefore, it is unclear whether testosterone is efficacious in the absence of estrogen. Studies designed to elucidate the effect of testosterone alone are currently in progress. Finally, the randomized, double-blind, placebo-controlled trials have uniformly demonstrated a marked placebo effect, which makes the efficacy assessment of any open-label trial difficult to interpret.

6. Safety of testosterone in women

The major safety concerns surrounding testosterone treatment in women include the risk of androgenic effects, cardiovascular disease, endometrial hyperplasia, breast carcinoma, liver dysfunction, sleep apnea, and aggressive behavior. There is a clear association between an increased rate of androgen production and acne and hirsutism and, with further increases, signs of virilization, including temporal hair recession, deepening of the voice, and clitoromegaly [56]. In addition, a concentration-dependent effect has been established for the development of sexual hair production of sebum [57]. Thus, it is not surprising that the most common testosterone-related adverse effects are hirsutism and acne, which are found in about 3–8% of patients receiving low doses of oral, parenteral, or transdermal testosterone [2]. In some studies, the incidence of these side effects is similar between testosterone- and placebo-treated women [23–25,50,53]. When such androgenic effects occur, they are usually mild, dose- and duration-dependent, and generally reversible. Virilization is rare, but can occur with high doses of testosterone, such as those used to treat female-to-male transsexuals [58].

In terms of cardiovascular safety, testosterone treatment in women does not adversely alter vascular reactivity, blood viscosity, or coagulation parameters, nor does it induce polycythemia, insulin resistance, or the metabolic syndrome [59]. Oral intake of testosterone decreases high-density lipoprotein and triglycerides, whereas testosterone administered by other routes has no significant effect on the lipid profile [2,59]. Finally, no increase in cardiovascular morbidity or mortality has been reported in women treated with testosterone, even with the markedly supraphysiologic levels used by female-to-male transsexuals [60].

Unopposed estrogen stimulation of the uterus can result in the development of endometrial hyperplasia and neoplasia. Because testosterone may be aromatized to estrogens in target tissues, including the uterus, there is concern that testosterone therapy may lead to uterine stimulation. Indeed, in one study, 12 of 19 female-to-male transsexuals treated with large doses of testosterone exhibited evidence of a proliferative endometrium [61]. However, no increase in endometrial hyperplasia has been observed in prospective studies utilizing more physiologic doses [53]. Additionally, no uterine cancers have been reported to date.

The increased risk of breast cancer reported in the estrogen plus progestin arm of the Women's Health Initiative trial has raised concern that testosterone administration may have a deleterious effect on the breast. Indeed, both the aromatase enzyme complex and androgen receptors are present in the breast tissue. Epidemiological studies suggest a relationship between elevated endogenous testosterone levels and the development of breast cancer, although frequently, the 95% confidence limits reported for these odds ratios include 1, yielding a clinically nonsignificant association [62]. Of interest, there is no increased risk of

Table 2
Review of clinical trials of androgen therapy in women with HSDD

Clinical trial	Study design	Population (n)	Therapy	Duration	Treatment effect
Greenblatt et al. [39]	DB, RCT, crossover	Peri- and postmenopausal women (102)	Placebo vs DES 0.25 mg/MT 5 mg TID vs DES 0.25 mg TID vs MT 5 mg TID	10 mo	↑ Libido
Dow and Hart [40]	Parallel, double-blind RCT	SMP and NMP (40)	E 50 mg pellet vs E 50 mg/T 100 mg pellet	4 mo	↑ Orgasm frequency (at 2 mo in low dyspareunia pts only) ↑ Psychological factors (in low dyspareunia pts only)
Burger et al. [41]	Open study	SMP and NMP (17)	E 40 mg/T 100 mg pellet	6 mo	↑ Libido
Sherwin et al. [42] and Sherwin and Gelfand [43]	Crossover RCT	SMP (53)	Control hysterectomy vs placebo vs E 10 mg vs E 8.5 mg/T 150 mg IV vs T 150 mg IM	3 mo	↑ Desire[a] ↑ Fantasy[a] ↑ Arousal[a] ↑ Well-being[a] ↑ Energy level[a] ↑ Sexual appetite
Sherwin and Gelfand [44]	Parallel, nonrandomized controlled trial	SMP (44)	Placebo vs IM E2 vs IM E2/T	2 yr	↑ Sexual desire[b] ↑ Sexual fantasy[b] ↑ Sexual arousal[b] ↑ Orgasm[b] ↑ Sexual activity[b]
Burger et al. [45]	Single-blind, randomized	SMP and NMP (20)	E2 40 mg pellet vs E 40 mg/T 50 mg pellet	6 mo	↑ Libido ↑ Enjoyment
Myers et al. [46]	Parallel, double-blind RCT	SMP and NMP (40)	Placebo vs CEE 0.625 mg vs CEE 0.625/MPA 5 mg vs CEE 0.625/MT 5 mg vs MT 5 mg	2 mo	↑ Masturbation ↑ Orgasm with no difference in – pleasure with intercourse – dyspareunia – sexual desire
Davis et al. [47]	Parallel, single-blind trial	SMP and NMP (32)	E2 50 mg pellet vs E2 50 mg/T 50 mg pellet	2 yr	↑ Activity ↑ Satisfaction ↑ Pleasure ↑ Orgasm ↑ Relevancy
Tuiten et al. [48]	Crossover, double-blind RCT	Premenopausal women with hypothalamic secondary amenorrhea (16)	Placebo vs 40 mg testosterone undecanoate	2 mo	↑ Genital vasocongestion No difference – sexual fantasy – sexual excitement – lust
Sarrel et al. [49]	Placebo lead-in: parallel, double-blind RCT	SMP and NMP (20)	EE 1.25 vs EE 1.25/MT 2.5	2 mo	↑ Sexual sensation ↑ Sexual desire ↑ Sensation No change – vaginal moisture/pain – rates of sexual fantasy
Shifren et al. [50]	Crossover, double-blind RCT	SMP (75)	Placebo vs 150 µg T patch vs 300 µg T patch	3 mo	↑ function[c] ↑ Sexual desire[c] ↑ Frequency of sexual[c] ↑ Activity[c] ↑ Orgasm[c]
Floter et al. [51]	Crossover, double-blind RCT	SMP (44)	Placebo vs E valerate 2 mg vs E valerate 2 mg/T undecanoate 40 mg	6 mo	↑ Lubrication ↑ Interest in sex ↑ Sexual thoughts and fantasies

Table 2 (continued)

Clinical trial	Study design	Population (n)	Therapy	Duration	Treatment effect
					↑ Arousal ↑ Orgasm ↑ Frequency of sex ↓ Dyspareunia
Davis et al. [52]	Parallel, double-blind RCT	SMP (77)	Placebo vs 300 µg T patch	6 mo	↑ Sexual desire ↑ Frequency ↑ Orgasm ↑ Sexual arousal ↑ Sexual responsiveness ↑ Sexual self-image ↓ Distress
Lobo et al. [53]	Parallel, double-blind RCT	NMP and SMP (218)	EE 0.625 vs EE 0.625/1.25 mT	4 mo	↑ Desire ↑ Responsiveness
Goldstat et al. [54]	Crossover, double-blind RCT	Premenopausal (31)	Placebo vs 10 mg of 1% testosterone cream daily	3 mo	↑ Sexual interest ↑ Activity ↑ Satisfaction ↑ Pleasure ↑ Fantasy ↑ Orgasm
Warnock [55]	Parallel, double-blind RCT	SMP (102)	EE 1.25 mg vs EE 1.25 mg/MT 2.5 mg	2 mo	↑ Sexual desire in 1 of 2 questionnaires
Braunstein et al. [23]	Parallel, double-blind RCT	SMP (447)	Placebo vs 150 µg T patch vs 300 µg T patch vs 400 µg T patch	6 mo	↑ Total satisfying[c] sexual events ↑ Desire[c]
Buster et al. [24]	Parallel, double-blind RCT	SMP (533)	Placebo vs 300 µg T patch	6 mo	↑ Satisfying sexual activity ↑ Desire ↑ Arousal ↑ Orgasm ↑ Pleasure ↑ Responsiveness ↓ Personal distress
Simon et al. [25]	Parallel, double-blind RCT	SMP (562)	Placebo vs 300 µg T patch	6 mo	↑ Satisfying sexual activity ↑ Desire ↑ Arousal ↑ Orgasm ↑ Pleasure ↑ Responsiveness ↓ Personal distress

Table adapted from Cameron and Braunstein [2].

E, estrogen; CEE, conjugated equine estrogen; EE, esterified estrogens; DES, diethylstilbestrol; E2, estradiol; T, testosterone; MT, methyltestosterone; MPA, medroxyprogesterone acetate; IM, intramuscular; TID, three times daily; ↑, increased/improved; ↓, decreased; SMP, surgical menopause; NMP, natural menopause.

[a] In T group vs both placebo and E alone.

[b] Compared to placebo and E only; significant in first 3 weeks of injection, but not in week 4.

[c] With 300 µg dose only.

breast cancer in women with endogenous hyperandrogenism associated with polycystic ovarian syndrome. In vivo studies in oophorectomized rhesus monkeys given physiologic concentrations of estradiol, estradiol plus progesterone, or estradiol plus testosterone have shown that testosterone partially inhibits the enhanced breast proliferation induced by estradiol and progesterone [63]. A recent retrospective analysis showed that postmenopausal women who received testosterone concomitantly with usual hormone replacement (estrogen alone or combined with progesterone) had breast cancer rates similar to or below that observed in women who had never used sex steroid hormones for menopause [64]. Finally, female-to-male transsexuals who received large amounts of testosterone showed no pathologic differences in breast tissue as compared to that obtained from normal women undergoing reduction mammoplasty [65]. Thus, at present there is no evidence that

testosterone administration adversely affects the breast, and, in fact, most of the evidence suggests that co-administration of testosterone with estrogens may offer some protection from the development of breast cancer.

Other safety concerns, including liver abnormalities (ranging from elevated liver enzymes to peliosis hepatitis and benign or malignant tumors), sleep apnea, and aggressive behavior, have not been seen in women receiving testosterone in physiologic to slightly supra-physiologic doses.

7. Patient evaluation

When evaluating a patient who fulfills the criteria for HSDD, it is important to rule out dyspareunia as a cause of low sexual desire. Thus, an adequate amount of estrogen should be provided to enhance vaginal mucus production. If estrogen administration is indicated, the transdermal or vaginal routes are preferred to avoid the increased SHBG levels that occur with oral use. Other causes of HSDD need to be considered and investigated, as outlined in a recent position statement from the North American Menopause Society (Table 3) [66]. Once these conditions are ruled out or treated, a therapeutic trial of testosterone may be given for persistent signs and symptoms of HSDD.

Testosterone serum concentrations are not useful in the diagnosis of testosterone-responsive HSDD for multiple reasons. Most of the commercially available assays involve direct immunoassay methodologies that are standardized for male levels of testosterone, which are normally 10–20 times higher than female concentrations. Therefore, levels measured by these methods overestimate total testosterone concentrations, and the direct methods used to measure free testosterone tend to underestimate actual levels in women [67,68]. Also, free testosterone levels in women who fulfill the criteria of HSDD without relationship, psychological, or other medical issues are low and do not add valuable information to the clinical decision-making process [23–25].

8. Testosterone preparations

No testosterone preparations are currently FDA approved for the treatment of women with HSDD. Methyltestosterone combined with esterified estrogens (Estratest® and Estratest-HS®, Solvay Pharmaceuticals, Marietta, GA) is only available for the treatment of vasomotor menopausal symptoms that are not responsive to estrogens alone. In a study by Lobo and colleagues, Estratest-HS was shown to increase desire in postmenopausal

women with HSDD [53]. As described, limitations of this oral preparation include mild androgenic side effects and reductions in HDL cholesterol. Testosterone esters (testosterone enanthate, cypionate, and mixed esters) administered intramuscularly every 2–4 weeks, have also been shown to improve sexual function in women. The major drawback related to this route of administration is the fluctuation in androgen levels, with peaks in the supraphysiologic range within a few days after administration and a trough for several days prior to the next injection. These fluctuations in serum concentrations may be accompanied by mood swings. Subcutaneous implants have been used in Australia and Europe, but have not been popular in the United States. They require a skin incision and subcutaneous placement of a testosterone-containing pellet through a large-bore needle at 3–6-month intervals. As with injectable testosterone, there are fluctuations in testosterone concentrations throughout the dosing interval. Testosterone also can be administered through the transdermal route via patches, creams, and gels; this route has been demonstrated to be an effective means of ensuring stable, physiologic concentrations of testosterone to women with HSDD.

9. Monitoring testosterone therapy in women

The efficacy of testosterone replacement is monitored by interviewing the patient regarding sexual desire, fantasy and arousal, pleasure from sexual activity, receptivity to sexual advances, amount of sexual activity with partner and/or self, energy level, sense of well-being, and overall mood. Because of the marked placebo effect noted in clinical studies, it is sometimes difficult to discern an active treatment effect from a placebo effect in patients who know that they are receiving testosterone. Clinical assessment of the risk versus benefit must be performed at each visit, allowing the identification of any possible androgen-related adverse reaction.

As noted, the major adverse reactions to testosterone administration are androgenic side effects, primarily acne and hirsutism. Therefore, a clinical assessment of these dose- and time-related effects should be performed at each visit. Hirsutism can be evaluated by means of the Ferriman-Gallwey or Lorenzo scales, and acne through use of the Palatsi scale [69–71]. Measurements of serum testosterone are generally not necessary unless a patient is receiving a compounded preparation or using a product developed for men. In that case, testosterone measurements may reveal that the therapy failed to raise testosterone into the normal range for a young woman or that the testosterone level is excessive. However, the problems associated with testosterone measurements in women need to be kept in mind, as the information

Table 3
Potential causes of HSDD in postmenopausal women

Psychosocial issues
Previous attitudes toward sex
Social customs and religious beliefs regarding sex
Poor partner relationship
Feelings toward partner
Length of relationship
Partner's decreased capacity for sexual activity
Partner's loss of interest in sex
No available partner
Life stressors from work, family, relationships
Negative body image

Psychological disorders
Depression
Anxiety
Other psychiatric illness

Medical conditions
Menopause
  Vaginal atrophy
  Vasomotor symptoms
Age-related decline in sexual drive
Fatigue
Incontinence
Chronic illness, including cardiovascular disease, diabetes, arthritis,
  renal failure
Cancer, particularly gynecologic or breast cancer

Pharmacologic agents
Psychotropics: selective serotonin-reuptake inhibitors, tricyclic
  antidepressants, benzodiazepines, barbiturates, anxiolytics, sedatives
Cardiovascular: beta-blockers, clonidine, methyldopa, spironolactone
Hormones: gonadotropin-releasing hormone agonists and antagonists,
  corticosteroids, antiandrogens
Recreational drugs: alcohol, marijuana, cocaine, heroin, methadone

Table adapted from North American Menopause Society [66].

is only as good as the method used to obtain it. Additionally, breast exams and yearly mammograms should be performed to monitor breast safety. Women receiving oral testosterone should also undergo an evaluation of the serum lipid panel 3–6 months after starting therapy. Women who have a uterus should be monitored by endometrial ultrasound before initiation of, and periodically during, testosterone therapy to detect endometrial hyperplasia, should it occur.

10. Is female androgen insufficiency a construct of the pharmaceutical industry?

In recent editorials, Moynihan has posited that female androgen insufficiency and HSDD are constructs of the pharmaceutical industry designed to create a market for new therapies [72,73]. He raises several points to support his thesis: sexual activity normally waxes and wanes with stress, medications, and social issues; and these normal life situations should not be capitalized upon. He further states that testosterone levels do not effectively discriminate between

women with normal and low libido and that data supporting the efficacy and safety of testosterone treatment are tainted by investigator conflict of interest. He also emphasizes the ever-increasing market for lifestyle drugs.

However, it should be noted that low libido causing distress is not a new construct and has been defined as a disorder in the International Classification of Disease and the American Psychiatric Association's Diagnostic and Statistical Manual; worldwide prevalence studies have shown that 5–10% of women indicate that they frequently have low libido [5]. In addition, it should be emphasized that: (1) medical conditions associated with low androgen production result in a loss of libido; (2) currently available testosterone assays are not optimized for the low levels observed in older women; and (3) testosterone was used well before the pharmaceutical industry was interested in using it as a treatment for HSDD [74].

11. Summary

Despite the available data supporting the existence of a female androgen insufficiency syndrome and the efficacy and safety of testosterone replacement therapy, a better understanding of the role of androgens in the health and well-being of women is needed. Future research efforts should focus on the development of reliable assay methodologies to establish normal ranges for women by age, life-cycle stage, and ethnicity; to detect low levels of testosterone; and to characterize the relationships between testosterone levels and clinical status. In addition, clinical trials are encouraged to examine the short- and long-term efficacy and safety of specific androgens administered in physiologic doses and to identify therapeutic markers that can be used to optimize treatment outcomes for affected women.

Acknowledgements

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