Formulations and Use of Androgens in Women

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The physiology of normal androgen production in women has been poorly understood. Defining an androgen insufficiency state in women, in the absence of adrenal suppression and/or bilateral oophorectomy, has been difficult. Nevertheless, beneficial effects of androgen on many organ systems, including bone and the brain, are well documented. This review discusses the definition of androgen insufficiency, anticipated effects of androgen treatment on several factors of health, and treatment options for women with androgen insufficiency.

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DHEA = dehydroepiandrosterone; SHBG = sex hormone–binding globulin

The physiology of normal androgen production in women has been poorly understood. Aging accounts for much of the reduction in both ovarian and adrenal androgen production, but natural menopause does not result in an abrupt decline in testosterone production. Therefore, defining an androgen insufficiency state in women, in the absence of adrenal suppression and/or bilateral oophorectomy, has been difficult. Because androgens affect many organ systems, including bone, muscle, and the brain, there are beneficial effects of androgen therapy for documented androgen insufficiency.

Some of the difficulty in accepting that androgen insufficiency may be a valid entity in women is the confusion surrounding measurements. In most perimenopausal women, testosterone and free testosterone levels are considered normal, but there is a wide range in values for testosterone and unbound testosterone in individual perimenopausal women.[1] In addition, some women with low levels (eg, after oophorectomy) do not report having symptoms. Finally, because testosterone is efficiently aromatized to estrogen in many tissues, including the brain, it has been argued that the effects attributed to testosterone may be due to estrogen and that estrogen replacement alone may be sufficient.

Nevertheless, several arguments favor the legitimacy of a clinical syndrome of androgen insufficiency in women: (1) symptoms are highly individual; (2) even with estrogen deficiency, there is no direct correlation with blood levels; (3) with aging, testosterone production decreases, although it is a relative decrease; and (4) alter-

ations in factors of mood and well-being are difficult to quantify.[2]

An international consensus conference on androgen insufficiency in women was convened in Princeton, NJ, in 2001. Because of the lack of sufficient epidemiological data and limitations of current laboratory assays, a conservative definition of androgen insufficiency in women (Table 1) was proposed on the basis of 3 essential criteria. First, clinical symptoms of androgen insufficiency should be clearly present. Symptoms of androgen insufficiency most often reported in the literature include a diminished sense of well-being or dysphoric mood; persistent, unexplained fatigue; and sexual function changes, including decreased libido, sexual receptivity, and pleasure. Second, because estrogen effects are also strongly linked to mood, psychological well-being, and sexual function in women, androgen insufficiency should be diagnosed only in women with adequate estrogen status. Third, in the absence of a sufficiently sensitive assay or absolute threshold for androgen insufficiency in women, free testosterone values should be at or below the lowest quartile of the reference range for reproductive age (20-40 years) in conjunction with the presence of clinical symptoms and adequate estrogen status.[3] To assist clinicians in making a diagnosis and initiating therapy, a simple management algorithm was proposed (Table 2).[3]

PHILOSOPHY OF ANDROGEN TREATMENT

The concept of using androgen in women, with or without estrogen, to enhance various factors of well-being dates to the 1940s. These prospective studies primarily used methyltestosterone, and it was considered beneficial for menopausal symptoms and general well-being and for libido, in particular.[2] In the 1960s, methyltestosterone was added to esterified estrogens and received class approval from the Food and Drug Administration only for menopausal symp-

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Table 1. **Definition of
Female Androgen Insufficiency Syndrome***

Decreased libido, sexual receptivity, and pleasure
Low energy and persistent, unexplained fatigue
Dysphoric mood
Diminished psychological well-being
Blunted motivation
Bone density
Muscle mass and strength
Adipose tissue redistribution
Sexual hair
Changes in cognition or memory

*Based on the pattern of clinical symptoms and signs in the presence of
decreased bioavailable testosterone and normal estrogen status.
Data from Bachmann et al.[3]

toms such as hot flashes that did not respond adequately to estrogens alone. More recent studies[2] have focused on symptoms and well-being, in addition to assessing bone mass changes. The first studies[2] to clearly show benefit used testosterone injections. Subsequently, testosterone implants, transdermal testosterone, and oral methyltestosterone were found to be effective in combination with estrogens. The instruments used to assess well-being and sexual function have not been standardized, and thus some studies that showed no beneficial effect may be criticized on this basis. Additionally, there is controversy regarding whether the improvements observed in prospective studies are because of pharmacological rather than physiological testosterone replacement. Indeed, data suggest that levels of testosterone near or above the normal physiological range are necessary to document significant improvement.[2]

Part of the difficulty in determining whether androgen levels are normal, increased, or decreased is related to the

Table 2. **Decision-making Algorithm for Initiating
Androgen Therapy in Women***

Q. Does the woman have symptoms consistent with female androgen
   insufficiency (eg, low libido, decreased energy, and well-being)?
A. *If yes, initiate evaluation.*
Q. Is there an alternative explanation or cause for these symptoms (eg,
   major depression, chronic fatigue syndrome)?
A. *If yes, manage as appropriate. If no, evaluate further.*
Q. Is the woman in an optimum estrogen state?
A. *If yes, continue evaluation. If no, initiate estrogen replacement.*
Q. Does the woman have laboratory values consistent with a diagnosis of
   androgen insufficiency?
A. *If yes, continue evaluation. This should include assessment of at least
   two of three measures of total T, free T, or SHBG. Androgen values
   should be in the lowest quartile of normal ranges for reproductive
   age women. If no, consider alternative treatments or referral.*
Q. Does the woman have a specific treatable cause for androgen
   insufficiency (eg, oral estrogens, oral contraceptive use)?
A. *If yes, treat the specific cause (eg, change medications). If no,
   consider a trial of androgen replacement therapy.*

*SHBG = sex hormone–binding globulin; T = testosterone.
From Bachmann et al,[3] with permission from the American Society for
Reproductive Medicine.

variability in measurements. Methods used to measure testosterone vary substantially, and even standardized methods such as radioimmunoassay vary depending on whether serum is extracted and/or undergoes chromatography before radioimmunoassay is performed. Upper normal ranges of testosterone vary from 50 to 100 ng/dL. This has challenged the notion of what constitutes a low level in perimenopausal and postmenopausal women. In general, testosterone levels are considered low if they are less than 20 ng/dL, and values are usually lower than 10 ng/dL after oophorectomy. However, women taking oral estrogen have higher levels of total testosterone because of the increase in sex hormone–binding globulin (SHBG) levels. In this setting, bioavailable or free testosterone levels are decreased, and this is the preferred moiety to measure. The most sensitive measurement of testosterone bioavailability is unbound or free testosterone. Commercial assays for free testosterone are extremely inconsistent, especially at the lower ranges of measurement, and therefore, many investigators prefer to use the free testosterone index, a calculated value, usually the ratio of testosterone to SHBG.[4]

Classic studies in the mid-1980s provided evidence of a significant effect of injected testosterone vs the effect of estrogen alone in women who had undergone oophorectomy.[5-7] This model of premenopausal women who have undergone oophorectomy provides the most extreme example of androgen insufficiency. In addition, injected estrogen and testosterone combined provide a rapid pharmacological peak effect of both sex steroids, with values often higher than 150 ng/dL for testosterone, as well as high levels of estrogen. This form of therapy typically results in an accumulation of steroids, with even higher levels reached with repeated dosing. With prolonged therapy, symptoms precipitating the need for another injection precede normalization of testosterone levels. However, these studies have shown that testosterone enhances sexual motivation, the sense of well-being, and the energy level in this cohort of women.

These studies showing benefit used regimens that led to pharmacological levels of testosterone. Some evidence shows that androgen replacement at near-physiological levels may also be efficacious for symptoms of sexual dysfunction and dysphoria. In women who have undergone oophorectomy, replacement of estradiol and testosterone with use of 50-mg implants has been shown to improve well-being, sexual function, and bone mass.[8] Testosterone levels were above the reference range (approximately 90 ng/dL) yet clearly lower than those observed with injectable testosterone. In a recent study that compared 2 doses of transdermal testosterone for 12 weeks in addition to oral estrogen,[9] serum testosterone levels averaged 64 and 102
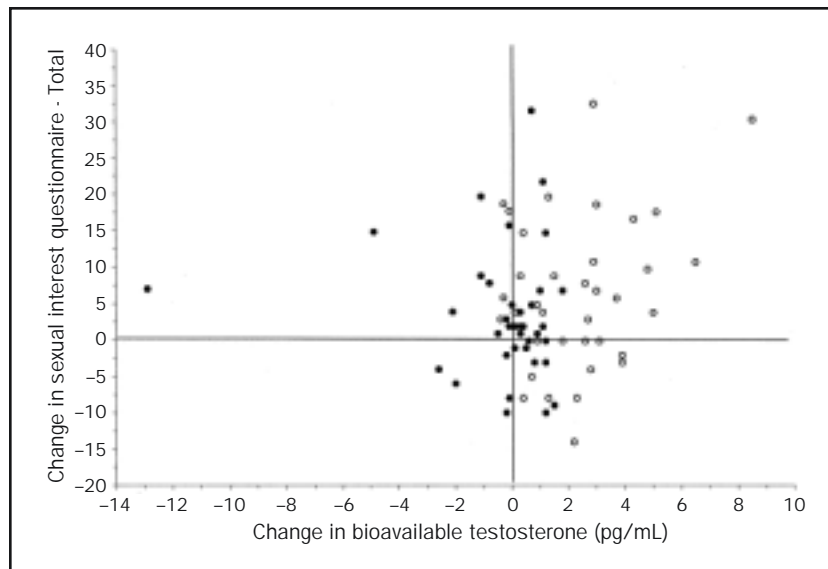
Figure 1. Association between change in score on sexual interest questionnaire and change in bioavailable testosterone concentrations from baseline to week 16. Each open circle and closed circle represents a single participant receiving esterified estrogen and methyltestosterone or esterified estrogens alone, respectively. Most open circles cluster in the right upper quadrant of the graph, indicating a significant correlation between an increase in bioavailable testosterone and improvement in score on sexual interest questionnaire for those who received combination therapy. From Lobo et al,[12] with permission from the American Society for Reproductive Medicine.

ng/dL with the 150-μg and 300-μg testosterone patches (reference range, 14-54 ng/dL), respectively, with concomitant use of oral estrogen. However, bioavailable testosterone was not elevated and was in the upper-normal range with the 300-μg patch (11.4±9.5 ng/dL; reference range up to 12.7 ng/dL). Only the 300-μg dose resulted in statistically beneficial effects on sexual function and well-being.[9]

Data on the use of esterified estrogen and methyltestosterone are difficult to interpret regarding physiological vs pharmacological intervention. Although benefits are attributed to the addition of lower doses of methyltestosterone (1.25 and 2.5 mg/d), the circulating levels of methyltestosterone are relatively low, in the range of 20 to 30 ng/dL. Because methyltestosterone is at least as potent as testosterone, some androgenic biological effect is anticipated.[10] Possibly a more significant androgen effect may be attributable to the increase in unbound testosterone with methyltestosterone because of the reduction in SHBG levels. Despite concomitant oral estrogen use, SHBG levels are suppressed by approximately 45%.[11] Thus, the testosterone-SHBG ratio has been shown to increase by 25% to 50%, which would put unbound testosterone levels into the upper-normal range. In our recent study,[12] the increase in unbound testosterone with 0.625 mg/d of esterified es-

trogen and 1.25 mg/d of methyltestosterone correlated statistically with improvement in sexual interest in postmenopausal women (Figure 1).

Various other androgen preparations are potentially viable for use in women (Table 3). In general, injected testosterone is not recommended because of the pharmacological nature of this approach, the peaks and valleys associated with this therapy, and the risk of steroid accumulation. However, intramuscular testosterone has been shown to be efficacious in women who have undergone oophorectomy.[7]

Methyltestosterone or fluorinated testosterone in large doses (as used occasionally in men) should not be used. In lower doses, methyltestosterone (1.25-2.5 mg/d) with esterified estrogens (as mentioned previously) has been shown to be beneficial for menopausal symptoms, bone mass, and possibly sexual function and quality-of-life variables. The long-term safety of this product has also been reported.[13]

Testosterone undecanoate, an oral form of replacement, is available in Europe and Canada, and it is believed to be efficacious in that it is absorbed via the lymphatic system, particularly if ingested with a liquid high in fat (eg, milk). Absorption and turnover are rapid, and high testosterone levels have been observed with 40 mg/d.[14] In one study,[15] the addition of testosterone undecanoate improved specific

Table 3. **Androgen Replacement Potentially Viable for Women***

Method	Dose
Injectable (IM) approximately every 4 wk	
Nandrolone decanoate	25-50 mg
Mixed testosterone esters	50-100 mg
Testosterone enanthate	25-50 mg
Testosterone cypionate	25-50 mg
Oral (daily)	
Methyltestosterone	1.25-2.5 mg
Testosterone undecanoate	40-80 mg
Subcutaneous and transdermal	
Testosterone implant	50 mg every 4-6 mo
Transdermal	150-300 µg every 3.5 d
Testosterone gel	1 mg/d
Other options	
DHEA (oral)	25-50 mg/d
Other androgens (androstenedione, DHT)	
Other routes (vaginal, sublingual, and buccal)	

*DHEA = dehydroepiandrosterone; DHT = dihydrotestosterone; IM = intramuscular.
From Lobo,[2] with permission from Lippincott Williams & Wilkins.

aspects of sexual function more than treatment with estrogen alone.

Testosterone implants, also known as pellets (50 mg), are required to be inserted at 4- to 6-month intervals with a trocar (same as used with estradiol pellets). Monitoring is necessary with this therapy, and testosterone levels should be determined before a repeated insertion. Although values vary considerably among subjects, values remain fairly constant for each individual, a characteristic of this method of hormonal therapy. As stated earlier, values are usually at the upper level of the reference range, 70 to 90 ng/dL.[16]
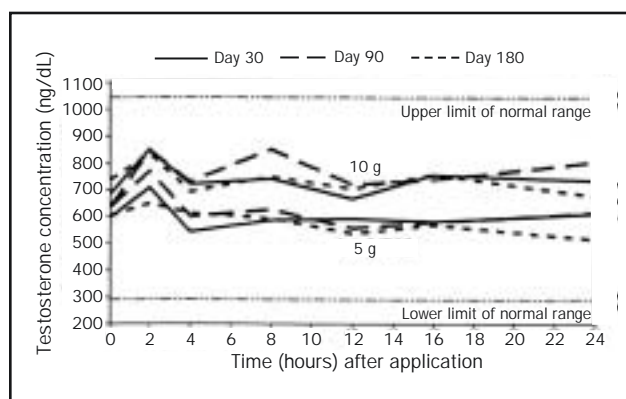

Figure 2. Mean steady-state testosterone concentrations in patients who used testosterone gel (AndroGel, Unimed Pharmaceuticals, Inc, a Solvay Pharmaceuticals, Inc, company, Deerfield, Ill) once a day. Testosterone concentrations were maintained as long as the patient continued to apply the prescribed treatment properly.[21]

Transdermal testosterone patches have become well accepted in the treatment of testosterone deficiency in men and are currently being developed in appropriate dosage strengths (150-300 µg/d) for androgen therapy for women. Short-term studies have shown efficacy with the 300-µg dose, and testosterone values are generally in the physiological range with no adverse findings.[17] The investigational testosterone matrix patch at 300 µg/d is now in phase 3 clinical trials for the treatment of sexual dysfunction in women who have undergone oophorectomy and in women who have experienced natural menopause.[18]

The hydroalcoholic gel of testosterone has been approved for men in whom the pharmacokinetics have been well established, and its efficacy has been shown for sexual function, mood, muscle strength, and body composition.[19,20] In men, the 5-g dose provides physiological replacement with steady-state levels of approximately 600 ng/dL (Figure 2).[21] By extrapolation, the dose required in women would be approximately 1 g/d or less, although this has not been established. A recent study evaluated the pharmacokinetics and metabolism of 14 days of daily morning application of a topical gel containing 1 mg of micronized testosterone in 5 women who had undergone oophorectomy and were taking estrogen. Although the hormone and metabolite profile achieved with the testosterone gel had desirable pharmacokinetics, the 1-mg dose appeared excessive.[22]

Oral micronized dehydroepiandrosterone (DHEA) has been used in various clinical trials.[23-25] Although not the most efficient or efficacious way to deliver testosterone, this approach is an option because serum testosterone levels may double, while DHEA and DHEA sulfate levels are higher than the reference range. However, a recent study did not confirm the benefit of 50 mg/d for quality-of-life measures.[25] Because DHEA can lower high-density lipoprotein cholesterol levels and potentially affect hepatic function, vaginal or transdermal administration of DHEA could be considered.

Other treatment approaches include administration of testosterone vaginally, buccally, or sublingually. A sublingual form (testosterone cyclodextrin) has been developed for men. Because cyclodextrin is a carbohydrate, this method is thought to be useful since testosterone is transported across mucous membranes.[26] We have also used hydroalcoholic gels of androstenedione and dihydrotestosterone in various trials in women to assess androgen metabolism.[27,28] However, these approaches have not been subjected to efficacy trials.

FUTURE CONSIDERATIONS

The only product available in the United States for women with androgen insufficiency is esterified estrogen in com-

bination with 1.25 or 2.5 mg/d of methyltestosterone; however, no indication has been approved by the Food and Drug Administration for androgen insufficiency syndrome. Although some data suggest safety and efficacy with this regimen,[13,29] other nonoral routes are being investigated. Currently, physicians are prescribing androgen replacement therapy, including testosterone supplements or DHEA, on an "off-label" basis. Ideally, treatment recommendations should be based on the results of large randomized, placebo-controlled clinical trials. The goal of androgen treatment should be to achieve normal premenopausal levels of testosterone, thus limiting adverse effects and adverse experiences. To determine the safety and effectiveness of such treatment, sensitive androgen assays are required as well as appropriate instruments to assess efficacy.

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