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Current perspectives on testosterone therapy for women

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Testosterone therapy is widely prescribed for postmenopausal women in the United States.[1] No testosterone product, however, is FDA approved for use in women. In this article, we briefly review why testosterone might be prescribed for postmenopausal women, the potential benefits of therapy, and the safety data available on testosterone use in this population.

Testosterone physiology

Testosterone production is critical for women. Testosterone is a major precursor for estradiol production, and it acts directly on androgen receptors throughout the body. In healthy premenopausal women, circulating testosterone levels are approximately 10-fold greater than circulating estradiol levels. Testosterone levels decline with age across the reproductive years; by the time women reach their late 40s, their blood testosterone levels are approximately half what they were in their 20s.[2] Importantly, testosterone levels do not decline across the natural menopausal transition.[2]

Two major challenges have been (1) determining which symptoms reflect testosterone deficiency in women and (2) establishing a serum testosterone level cutpoint for testosterone deficiency. As in men, symptoms of testosterone deficiency in women overlap with other medical conditions. For example, while testosterone insufficiency may underpin loss of libido, flat mood, and fatigue, these symptoms may also be explained by depression, iron deficiency, and hypothyroidism. Debate continues regarding the lower limit of "normal" testosterone for men. For women, an absolute cutoff level that defines serum testosterone deficiency is unlikely to be established.

Conditions characterized by low testosterone levels include bilateral oophorectomy, adrenal insufficiency, hypopituitarism, use of combination oral contraceptive pills or systemic glucocorticosteroids, and premature ovarian failure. Hysterectomy has also been associated with lower circulating testosterone levels. There is debate as to whether the postmenopausal ovary continues to produce testosterone; some studies provide supportive evidence,[3,4] while others do not.[5,6] Most likely, interindividual variability exists among women regarding ovarian testosterone production after menopause.

Testosterone plays multiple roles

Testosterone is thought to be the key hormone underlying sexual desire in both men and women. Some studies have reported a direct relationship between serum testosterone levels and sexual desire and coital frequency. In healthy young women, free testosterone levels, but not estradiol or progesterone, have been correlated with sexual desire and masturbation,[7] and antiandrogen therapy has been associated with loss of sexual desire.[8] However, more recent studies have shown conflicting results. A large community-based cross-sectional study failed to demonstrate a relationship between total or free testosterone and sexual desire, arousal, or responsiveness in women.[9]

Inadequate sexual arousal may partly be due to decreased blood flow to the sexual organs. Androgen receptors identified in the vagina may play a role in vaginal health. Testosterone appears to exert vasomotor effects in the vagina, enhancing vaginal blood flow and lubrication.[10,11]

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Testosterone as magic bullet

Women in menopause continue to ask their health care providers for the "magic bullet" that will bring back their sexual desire. It is commonly believed that testosterone is the answer, since this hormone declines with age. But what are the risks of testosterone therapy for women, and what is the potential benefit? Clearly, other issues may also play a role in decreased sexual desire and should be considered, including increased demands from work and family, depression, and the onset of health problems such as hypothyroidism.

In this issue of *Menopausal Medicine*, Susan R. Davis, MBBS, FRACP, PhD, and Sonia L. Davison, MBBS, FRACP, PhD, of Monash University in Melbourne, Australia, provide a focused review on the role of endogenous testosterone in female physiology and sexual health and the current evidence on testosterone therapy for menopausal women with low sexual desire.

While clinicians in Australia and some European countries can prescribe a testosterone cream, a transdermal patch, or a subcutaneous implanted pellet for women, clinicians in the United States are limited to off-label testosterone preparations, since no testosterone product is FDA approved for use in women. Ongoing studies focused on testosterone gel treatment and breast and cardiovascular safety may provide new treatment options in the future.

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Testosterone may also be important for the maintenance of bone and muscle mass. Observational studies have reported that low serum testosterone is associated with lower bone mineral density and increased fracture risk in postmenopausal women. Testosterone is a vasodilator.[12] Despite a perceived link between increased testosterone and cardiovascular disease, most studies do not show that higher testosterone contributes to cardiovascular disease risk in postmenopausal women.[13] A large study has reported an increased risk of coronary heart disease events in women who had low levels of total and bioavailable testosterone.[14]

Research evaluating the effect of testosterone therapy on cognitive performance in postmenopausal women is under way.

Effects of testosterone treatment on sexual parameters

The use of testosterone therapy for women is not based on an established link between symptoms and biochemistry, but rather on clinical evidence that exogenous testosterone improves commonly reported sexual problems, such as diminished sexual desire and arousal, pleasure, and overall satisfaction. For most women, these problems are part of a continuum of the sexual experience and are inextricably related. Recent studies evaluating the efficacy of testosterone for the treatment of female sexual dysfunction (FSD) have required participants to fulfill the diagnostic criteria for hypoactive sexual desire disorder (HSDD), defined as "persistent or recurrent deficiency or absence of sexual thoughts and fantasies and/or desire for, or receptivity for, sexual activity causing personal distress or interpersonal difficulties."[15]

Women who report being dissatisfied with their sexual life continue to engage in sexual activity; frequency of sexual engagement is therefore a poor measure of sexual well-being. Evidence supports this finding: postmenopausal women who self-identified as being dissatisfied with their sexual well-being still recorded a median of 5 sexual events per month.[16,17] Substantial evidence suggests that testosterone therapy improves sexual well-being in postmenopausal women with loss of libido.[18] Improvements have been reported in the number of sexual events reported as satisfactory; sexual desire, pleasure, arousal, and frequency of orgasm; and reduction in personal distress. Benefits were observed initially in studies of testosterone implants and oral methyltestosterone and, subsequently, with the use of transdermal testosterone therapy. The testosterone transdermal patch, which delivers 300 µg of testosterone per day, improved sexual function in naturally and surgically menopausal women using either concurrent oral or transdermal estrogen.[19-21] Efficacy has also been demonstrated in postmenopausal women who were not on estrogen therapy.[17]

Regarding the local vaginal effects of testosterone, preliminary data indicate that the vaginal application of testosterone, 300 µg per day, may alleviate dyspareunia in women with breast cancer without raising circulating testosterone blood levels.[22] This merits further evaluation.

Safety issues

The potential virilizing effects of exogenous testosterone include development of acne, hirsutism, deepening of the voice, and androgenic alopecia. These effects are dose related and are uncommon if supraphysiologic hormone levels are avoided. Various studies have shown that women treated with transdermal testosterone, compared with placebo, reported a higher rate of androgenic adverse events; these were mainly attributable to increased hair growth, mostly reported as mild, and were not associated with discontinuation of therapy.[17] Hirsutism, androgenic alopecia, and/or acne are relatively strong contraindications to androgen therapy.

There is no evidence from randomized controlled trials that testosterone therapy, in formulations designed for women, adversely affects lipid levels, carbohydrate metabolism, blood pressure, coagulation parameters, or hematocrit.[13] No adverse endometrial effects have been observed with testosterone use in women who were not receiving concurrent estrogen therapy.[17] Small studies have shown that testosterone treatment increases vertebral and hip bone mineral

TABLE Approach to addressing sexual dysfunction in postmenopausal women

AREAS FOR ASSESSMENT

Biopsychological

- Partner status
- Social circumstances
- Past sexual experiences
- Adequacy of sexual stimulation, both contextual and physical
- Contribution of partner's mental and physical health

Medical

- Health history, medications, drug use
- Physical examination, including genital and pelvic examination, particularly for loss of sensitivity or pain disorders
- Exclude iron deficiency, hypothyroidism

MANAGEMENT CONSIDERATIONS

Address psychosocial components

- Relationship issues: consider referral for relationship counseling
- Sexual health knowledge, ie, individual and partner's understanding of anatomy and sexuality and whether the woman is experiencing sexual stimulation; consider referral for sexual counseling

Identify and manage health-related factors

Mental health

- Body image and self-esteem
- Experience of sexual abuse/trauma
- Negative attitudes, inhibitions, and anxieties
- Depression

Physical health

- Vaginal atrophy
- Other menopausal symptoms
- Any identified medical conditions
- Medication side effects, particularly antidepressants and antipsychotics

Consider testosterone therapy

density in postmenopausal women and in women with hypopituitarism. Testosterone therapy increases lean mass and reduces body fat in postmenopausal women. In a small study of women with congestive cardiac failure, testosterone improved strength and function.[23]

Whether testosterone therapy raises breast cancer risk is a concern. There is no evidence that past users of testosterone have an increased risk of breast cancer or that duration of exposure to testosterone therapy influences breast cancer risk. Analysis of data from the Nurses' Health Study suggests that methyltestosterone users may be at increased risk of breast cancer.[13] However, other studies of methyltestosterone use have not shown an increased risk.

Although there is no evidence to date that transdermal testosterone therapy influences the risk of breast cancer in postmenopausal women, randomized controlled trials have not been of sufficient size or duration to permit clear conclusions.[13] In the United States, a longitudinal study involving more than 3600 women is currently investigating the cardiovascular and breast safety of transdermal testosterone gel in postmenopausal women.

Treating women with testosterone

Although surgically menopausal women may be the most likely group to benefit from testosterone therapy, women with natural menopause are equally likely to benefit.[17] Women who have experienced premature ovarian failure, particularly secondary to chemotherapy or radiotherapy, should also be considered for testosterone therapy.

An array of physical, psychological, cultural, and relationship factors influence sexual well-being and sexual function. Hence, women presenting with diminished sexual interest with or without impaired sexual responsiveness need to be assessed for general psychological, physical, and social health. Stress, fatigue, relationship issues, depression, and medication side effects commonly contribute to diminished sexual interest. Medical conditions that might cause fatigue and low well-being, such as iron deficiency and hypothyroidism, should be ruled out. While the presence of such factors and conditions should not exclude a woman from testosterone treatment, they need to be concurrently managed. The **TABLE** lists aspects to consider in assessing and managing a postmenopausal woman presenting with sexual dysfunction.

The need for an approved testosterone product formulated for women is clear. Women in America are seeking out testosterone therapy, and gynecologists are supporting them by prescribing either compounded testosterone creams and troches or testosterone products that deliver doses appropriate for male testosterone replacement. Off-label use exposes women to the risks of supraphysiologic testosterone levels.

Neither oral testosterone undecanoate nor methyltestosterone can be recommended for women, as both may adversely affect lipid levels, and testosterone undecanoate may induce insulin resistance. Available data indicate that the most physiologic mode of delivery of testosterone is parenteral, and primarily as a transdermal formulation.

Putting it all together

Physicians have been treating women with testosterone for decades. Testosterone-treated women who experience symptom improvement and improved sexual well-being generally wish to continue therapy. Large, robust randomized controlled trials have demonstrated efficacy of testosterone therapy compared with placebo for multiple parameters of sexual function. Other possible beneficial effects of testosterone therapy, such as reduced fracture risk and favorable effects on cognitive function and cardiovascular function, require further investigation.

When considering initiating testosterone treatment, only doses appropriate for women should be prescribed. Women should be fully informed that although the combined findings of the randomized trials of testosterone conducted to date have not demonstrated an increased risk for breast cancer or cardiovascular disease, evidence is not yet available regarding safety of long-term testosterone use. ■

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