Testosterone supplementation: For whom and when?

Reviewing issues in use after surgical or natural menopause

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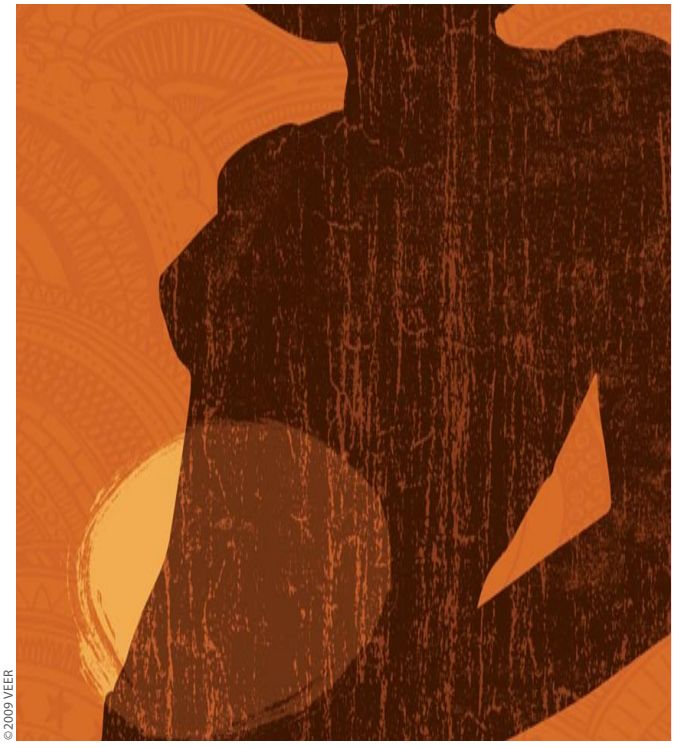

Evidence shows that testosterone, added to estrogen therapy (ET), improves sexual function in women[1-3] and may improve bone health.[4] However, without an FDA-approved agent, off-label use raises questions about patient selection, dosing, and safety. Approval of testosterone-containing preparations has been deferred pending confirmation of long-term safety assessments (2-5 years).

Assessing low testosterone

Testosterone status is assessed primarily by the signs, symptoms (**TABLE 1**),[5] and known causes of deficiency (**TABLE 2**). Diagnosis of female androgen deficiency syndrome requires (1) serum testosterone levels below or within the lower quartile of the female normal range (15-70 ng/dL) (2) impaired well-being or decreased libido, and (3) adequate estrogenization[6] (decreased estrogen levels can impair sexual function).[1] Hypoactive sexual desire disorder is defined as the persistent or recurrent deficiency (or absence) of sexual fantasies, thoughts, and/or desire for, or receptivity to, sexual activity that causes personal distress.[7]

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Assays designed for men lack sensitivity in low ranges, and only about 2% of the total in women is biologically active.[8] The remainder binds primarily to sex-hormone binding globulin (SHBG). Ovarian testosterone production declines within 2 to 4 years of menopause. After menopause, testosterone production continues in the ovaries (50%), adrenals (10%), and peripheral tissue (40%).

Studies: Testosterone ± estrogen

A few trials describe testosterone's role in improving total satisfying sexual activity and sexual desire and decreasing sexual distress in estrogen-deficient women.[1,3,9] Benefits on bone development have also been described.[10-12] (For detailed information on randomized controlled trials, go to www.srm-ejournal.com.)

KEY POINT

Testosterone use does not appear to increase cardiovascular risk in women.

TABLE 1

Indications of testosterone deficiency

Signs	Symptoms
Decreased lean body mass	Decline in sexual motivation or libido
Increased body fat	Fatigue, lack of energy
Pubic hair thinning/loss	Impaired sense of well-being
Osteopenia/ Osteoporosis	

TABLE 2

Causes of low testosterone in women

Increased age

Iatrogenic causes
- Surgical menopause (bilateral oophorectomy)
- Chemotherapy
- Radiation
- Treatment with glucocorticosteroids

Conditions resulting in elevated SHBG levels
- Pregnancy
- Oral contraceptive pills
- Hyperthyroidism
- Estrogen replacement therapy
- Age
- Cirrhosis
- Anorexia nervosa

Certain disease states
- Addison's disease
- Hypopituitarism
- Premature ovarian failure

Testosterone formulations

Women require about 5% to 10% of a man's daily testosterone dose (2.5 to 5 mg/d). The only FDA-approved product for women, Estratest (estrogen, 0.625 mg; methyltestosterone, 1.25 mg), is indicated only for moderate to severe menopausal vasomotor symptoms unresponsive to estrogen alone. However, on March 13, 2009, Solvay discontinued distribution of this product; when all supplies are gone, it will no longer be available in the United States. Other options include oral testosterone undecanoate, absorbed mainly by the lymphatic system, avoiding first-pass liver metabolism.[13] Its short half-life may require multiple daily doses. Testosterone patches, available in Europe, are applied 2 times per week and offer stable pharmacokinetics and demonstrated efficacy.[9,14] Testosterone gels and creams are associated with less skin irritation than the patches. Subcutaneous testosterone pellets are self-dissolving; new implants are placed every 4 to 6 months and have been used successfully.

Levels of dehydroepiandrosterone-sulfate (DHEA-S), converted to testosterone by peripheral tissue, begin to decline at age 40. Evidence shows that supplementation can significantly improve a woman's libido and sexual function.[15-17] DHEA-S is available without a prescription in the United States.

Adverse effects of testosterone therapy

The most commonly reported side effects of testosterone therapy are acne (6%), unwanted hair growth (5.7%), alopecia (3.2%), and voice deepening (2.5%).[9] Discontinuation reverses acne and hirsutism; many clinicians observe effects to monitor the efficacy of testosterone therapy.

Evidence suggests that testosterone supplementation does not increase the risk of breast cancer; it may have a protective effect on breast tissue.[18,19] A longer time to disease progression and a higher response rate is observed when androgens are added to anti-estrogen therapy.[18] Long-term androgen administration does not have significant, adverse effects on female breast tissue.[20] Nevertheless, testosterone can still be aromatized to estrogen; patients with a history of estrogen-sensitive breast cancer should be discouraged from treatment.

No convincing data suggest that testosterone use increases the risk of cardiovascular events in women. Although oral methyltestosterone has been shown to reduce HDL and raise LDL levels in women, this effect is not seen in association with other forms of testosterone.[2,21] Finally, no evidence indicates that testosterone supplementation increases the risk of endometrial cancer. In vitro studies have thus far demonstrated that androgens actually inhibit human endometrial cell growth and secretory activity.[22] ■

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