Androgen therapy in women, beyond libido

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ABSTRACT

Objective The aim of this review was to summarize the literature regarding the potential role of testosterone therapy for women.

Methods The author conducted a search of the literature using Medline (Ovid, 1946–present) and PubMed (1966–2013) for English-language studies that included the following search terms: ‘testosterone’ or ‘androgen’ combined with ‘women’, ‘therapy’ or ‘treatment’.

Results Randomized, placebo-controlled trials have consistently shown that transdermal testosterone therapy improves sexual desire, arousal, orgasm frequency and satisfaction in premenopausal and postmenopausal women presenting with sexual desire/arousal problems. No adverse metabolic effects have been observed in these studies. In postmenopausal women, testosterone therapy has also been associated with favorable effects on body composition, bone, cardiovascular function and cognitive performance.

Conclusions Although androgens have many varied roles, the focus of testosterone therapy for women has been on improving sexual desire. Not only do testosterone effects on sexuality extend beyond libido, but testosterone has other key physiological actions. Issues that urgently need to be addressed include approval of a testosterone formulation that delivers a female dose such that physicians refrain from prescribing compounded testosterone or modifying doses of testosterone formulated for men and regulation of prescription of compounded androgens for women.

INTRODUCTION

Androgen therapy for women in current usage includes testosterone, administered as an oral transdermal or implanted formulation, and the pre-androgen, dehydroepiandrosterone (DHEA), mostly as an oral preparation. Both are also being extensively prescribed as individually compounded creams and troches (oral lozenges). This review focuses on the therapeutic use of testosterone as the use of DHEA for women has been recently comprehensively reviewed elsewhere.

Testosterone was first isolated in 1935, with the name being derived from its testicular origin: testo = testes, ster = sterol, one = ketone. Shortly after this, the German scientists, Butenandt and Hanisch, reported synthesizing testosterone from cholesterol. Initially thought of as a primarily male hormone, testosterone levels across the menstrual cycle were documented by Engstrom and Munson in 1951. Its initial reported clinical applications in women were for the treatment of disseminated breast cancer and migraine. The first report of the use of androgen therapy for sexual ‘frigidity’ in women pertained to the use of a synthetic androgenic preparation. Dr Robert Greenblatt subsequently noted in 1987 that ‘The use of androgens in the treatment of gynecic disorders has had few adherents because of the belief generally held that androgen administration to the female patient is antiphysiologic and antipharmacologic’. This myth primarily underpins the fear of the use of testosterone therapy for women today.

A BRIEF PHYSIOLOGICAL REVIEW

Circulating testosterone levels arise from direct ovarian secretion and peripheral conversion of pre-androgens produced by the adrenal glands, with the adrenals also being the main site of production of dehydroepiandrosterone sulfate (DHEAS). In women, testosterone circulates in nanomolar concentrations, contrasting with the picomolar concentrations of estradiol. Testosterone has direct actions through the androgen receptor (AR) throughout the body. In addition, testosterone...
and the pre-androgens (androstenedione and DHEA produced by the adrenals and ovaries) are essential for the biosynthesis of estrogens. In postmenopausal women, when the ovaries cease to produce estrogens, estrogen production is from testosterone and adrenal pre-androgen precursors in extraglandular tissues. These tissues include adipose tissue, osteoblasts and chondrocytes of bone, vascular endothelium and aortic smooth muscle cells, and numerous sites in the brain. Thus, adequate levels of testosterone are important throughout the female lifespan for the maintenance of musculoskeletal health and possibly healthy vascular and brain function. The intracellular actions of androgens and estrogens on their respective receptors in different tissues are complex and beyond the scope of this review. It is, however, important to note that a multitude of co-regulators with diverse actions regulate the transcriptional consequences of each of testosterone and the estrogens interacting with their respective receptors. Thus, circulating sex steroid levels, even when measured with precision, do not necessarily correlate with tissue effects.

Under normal physiologic conditions, only 1–2% of total circulating testosterone in women circulates unbound to plasma proteins. The rest is bound by sex hormone binding globulin (SHBG) and albumin, with SHBG binding 66% of total circulating testosterone in healthy women. Therefore, variations in the plasma levels of SHBG influence the amount of unbound testosterone.

Circulating androgen levels decline with age prior to the menopause, such that by menopause most women have half the levels of circulating testosterone and pre-androgens, androstenedione and DHEA that they had in their twenties. The cause of this decline is not understood and the consequences merit further investigation. Other causes of lowered testosterone include ovarian suppression, most commonly by systemic hormonal contraception, surgical menopause, pathological or iatrogenic adrenal insufficiency, adrenal suppression by systemic glucocorticosteroid therapy and hypopituitarism.

TESTOSTERONE SUPPLEMENTATION AND IVF

A significant proportion of women undergoing in vitro fertilization (IVF) respond poorly to ovulation induction. Poor response to ovarian stimulation usually indicates a reduction in follicular response, resulting in a reduced number of retrieved oocytes. Consequently, poor ovarian response results in fewer embryos, reduced implantation rates, decreased pregnancy rates and high cycle cancellation rates. Delaying childbirth until the late reproductive years increases a woman’s risk of being a poor responder to ovarian stimulation. Although several approaches have been considered for the management of poor responders, this remains a challenging issue.

Ovarian androgens are produced by the thecal cells under the control of luteinizing hormone (LH). Whereas androgen excess is characterized by the ovarian production of multiple follicles, androgen insufficiency appears to be associated with inadequate follicular development. In rhesus monkeys, treatment with dihydrotestosterone or testosterone augments expression of follicular follicle stimulating hormone (FSH) receptors in ovarian granulosa cells. Androgens also have a synergistic effect to FSH in promoting initiation of primordial follicle growth, increasing the number of growing preantral and small antral follicles and increasing granulose cell proliferation. Therefore, testosterone supplementation might increase the number of follicles available to enter the recruitment stage as well as the process of follicle recruitment itself. Pretreatment with transdermal testosterone has been reported in a meta-analysis to be associated with significant increases in clinical pregnancy (risk difference (RD) +15%, 95% confidence interval (CI) +3 to +26%) and live birth rates (RD +11%, 95% CI +0.3 to +22%) in poor responders undergoing ovarian stimulation for IVF. In contrast, the same meta-analysis reported no beneficial effect on pregnancy rates after IVF in poor responders treated with DHEA or aromatase inhibitors during pre-stimulation. To date, the studies evaluating the use of testosterone therapy to enhance responsiveness to IVF cycles have been small and have employed supraphysiological doses of testosterone. As there is biological plausibility for a beneficial effect of testosterone pretreatment for poor IVF responders, further clinical trials using physiologic doses of testosterone are warranted.

TESTOSTERONE FOR MANAGEMENT OF SEXUAL DYSFUNCTION

In line with the decline in testosterone from the mid reproductive years, a subset of premenopausal women experiences a decline in their sexual interest and responsiveness at this time. Efficacy of transdermal testosterone over placebo has been demonstrated in two separate randomized, placebo-controlled trials (RCTs) in premenopausal women aged 35 years or more. Hence, testosterone therapy may be of benefit to older premenopausal women presenting with diminished sexual interest and responsiveness.

Testosterone therapy has been consistently shown to be more effective than placebo for improving sexual well-being in women with low sexual desire in RCTs of surgically menopausal women taking oral estrogen and non-oral estrogen, naturally menopausal women on estrogen therapy and postmenopausal women not using estrogen. Women with elevated SHBG levels may experience little or no benefit. In these studies, the benefits over placebo were not limited to improved sexual desire, but included significant increases in orgasm frequency and sexual pleasure. These studies all involved the continuous use of testosterone therapy. Studies are now underway to evaluate the effects of intermittent testosterone therapy for women with anorgasmia and transdermal testosterone for the treatment of antidepressant-associated sexual dysfunction.
When considering the use of any therapy to treat female sexual difficulties, the clinician always needs to be mindful that sexual function is complex and that a full clinical assessment is prerequisite to any therapeutic intervention. Potentially contributing factors such as dyspareunia, depression, medication side-effects, relationship issues and other health problems need to be identified and managed.

TESTOSTERONE AND VAGINAL HEALTH

The AR is expressed throughout the vaginal mucosa and stroma. The density of the AR in vaginal mucosa, but not the stroma, declines with age. Systemic testosterone therapy is associated with an increase in AR expression in both the mucosa and stroma of the vagina. Well before identification of the AR in vaginal tissues, Leiblum and others reported higher levels of circulating testosterone and androstenedione, but not estradiol, to be correlated with less vaginal atrophy. In a pilot study, Witherby and co-workers observed normalization of vaginal cytology and reduced dyspareunia with daily intravaginal testosterone (300 μg) after 28 days in women on aromatase inhibitor therapy. These studies provide a sound basis for further study of intravaginal testosterone for the treatment of vaginal atrophy.

TESTOSTERONE AND THE MUSCULOSKELETAL SYSTEM

Androgens exert anabolic effects in skeletal muscle through genomic and non-genomic pathways. Testosterone therapy in postmenopausal women has been associated with increased lean mass and reduce percentage fat. In women with hypopituitarism, testosterone therapy has also been shown to increase lean mass. Studies of women with anorexia nervosa have shown that low testosterone is associated with lower lean mass and lower bone density, independent of low body mass index. Various non-steroidal selective androgen receptor modulators which exhibit selective anabolic action in bone and muscle, but do not cause virilization or prostate growth, are being investigated as therapies to prevent/treat sarcopenia, as an alternative to testosterone therapy for this problem.

ARs have also been demonstrated in human osteoblast-like cell lines, and androgens have been shown to directly stimulate bone cell proliferation and differentiation. Low endogenous testosterone is associated with lower bone density in women with anorexia nervosa and a greater rate of bone loss in women approaching menopause. Analysis of data from the Women’s Health Initiative observational study revealed that older women with higher levels of non-SHBG-bound testosterone had a lower rate of hip fracture, independent of other hormones, including estradiol, and other risk factors. Postmenopausal testosterone has been associated with increased bone mineral density at the hip and the spine, but evidence of fracture prevention with testosterone therapy remains lacking.

TESTOSTERONE AND CARDIOVASCULAR FUNCTION

Observational studies consistently demonstrate that both endogenous testosterone and SHBG are inversely associated with increased cardiovascular disease (CVD) risk in women. In postmenopausal women, endogenous testosterone has been positively associated with better endothelial function and inversely associated with carotid intima-media thickness. Both total and free testosterone are inversely associated with internal carotid artery atherosclerosis. CVD in older women has been associated with lower levels of androgen precursors and a higher estradiol to testosterone ratio. Polycystic ovarian syndrome (PCOS) is a common condition characterized by hyperinsulinemia and androgen excess. The largest observational study reporting the morbidity and mortality associated with this condition did not find an increase in coronary heart disease morbidity or mortality in women with PCOS, despite these women having more CVD risk factors.

The vasodilatory effects of testosterone were first reported in dogs. Subsequently, testosterone has been shown to exhibit acute and chronic vasodilation in postmenopausal women. In an open-label, pharmacokinetic study of inhaled testosterone involving 12 postmenopausal women, systolic blood pressure fell for all three doses studied at all time points following dose administration. At 5 min post-dose, there was a mean drop of 10 mmHg systolic (standard deviation ± 12 mmHg) blood pressure with seven women having a fall of 10 mmHg or more at this time. In an RCT of transdermal testosterone versus placebo in women with documented congestive cardiac failure (mean ejection fraction 32.9 ± 6%), testosterone therapy was associated with improved brachial artery flow-mediated dilatation, evidence of improved endothelial function, and improved exercise tolerance.

Studies of testosterone administered by subcutaneous implant, transdermal patch, spray or gel do not show any adverse effects in terms of altered lipid levels, C-reactive protein, glycosylated hemoglobin or insulin sensitivity. However, high density lipoprotein (HDL) cholesterol and apolipoprotein A1 levels decrease significantly when oral methyltestosterone is administered with oral estrogen. Estrogen and methyltestosterone therapy is also associated with reduced plasma concentrations of apolipoprotein B, reduced low density lipoprotein (LDL) particle size, and increased total body LDL catabolism. Similarly, oral testosterone undecanoate adversely affects lipoproteins and increases insulin resistance.

There is no evidence from the published RCTs completed to date that transdermal testosterone therapy increases the risk of CVD in women.

TESTOSTERONE AND THE METABOLIC SYNDROME

Testosterone and dihydrotestosterone are strongly bound to the protein SHBG. A low SHBG level is a robust and
independent marker for increased risk of type 2 diabetes. SHBG levels vary substantially in women, with endogenous levels inversely linked to central adiposity and insulin levels. The free androgen index (FAI; total testosterone (nmol/l)/SHBG (nmol/l) × 100) has been strongly associated with visceral fat in postmenopausal women, even after adjusting for insulin resistance. The FAI and SHBG level are interchangeable in their strength of association with visceral fat whereas total testosterone is not related to visceral fat. Thus, the SHBG level is the determinant of this association. Similarly, in young to middle-aged women, SHBG levels, but not total or free testosterone, have been inversely associated with subclinical CVD and coronary artery calcium. Thus SHBG, not testosterone, appears to account for the relationship between the FAI and CVD risk factors in women.

Whereas neither estradiol nor testosterone makes an independent contribution to the variation in total cholesterol, HDL cholesterol, LDL cholesterol, non-HDL cholesterol or triglycerides in postmenopausal women, SHBG makes an independent contribution to HDL cholesterol, non-HDL cholesterol and triglycerides. In essence, there is no evidence that testosterone independently contributes to the metabolic syndrome in women. Instead, the apparent relationship between free testosterone and the metabolic syndrome is a reflection of the relationship between low SHBG level and visceral obesity, hyperinsulinemia and dyslipidemia. There is also evidence that the SHBG level is a sensitive biomarker of the metabolic disturbances associated with increased fructose consumption.

TESTOSTERONE AND COGNITION

Levels of testosterone in the human female brain during the reproductive years are several-fold greater than those of estradiol. Testosterone exhibits neuroprotective effects within the brain, including protection against oxidative stress, serum deprivation-induced apoptosis and soluble β-amyloid toxicity. The protection against β-amyloid toxicity appears to be AR-mediated and has positive effects on endothelial function; it may increase cerebral blood flow.

Oral testosterone undecanoate has been associated with negative cognitive performance. Oral methyltestosterone plus estradiol was associated with no change in Building Memory task, whereas oral estradiol alone showed a decrease in performance.

Recent studies, however, show a consistent beneficial effect of transdermal testosterone on verbal learning and memory, using both conventional and computer-based testing. In an RCT, transdermal testosterone therapy was associated with significant improvements in immediate and delayed verbal memory using the California Verbal Learning Test in postmenopausal women on transdermal estrogen therapy. Similarly, significant improvements in verbal learning and memory, including delayed recall, measured by computer-based cognitive testing, were seen in postmenopausal women not using estrogen, after 26 weeks of transdermal testosterone treatment. The scores for these test outcomes remained unchanged in the control group.

Considering the evidence that testosterone has neuroprotective effects, the use of testosterone to preserve verbal learning and memory in postmenopausal women merits further study.

TESTOSTERONE AND HORMONE-DEPENDENT CANCER

Available data show no adverse effects of transdermal testosterone therapy on the endometrium or on breast density over 12 months. Some, but not all, observational studies have indicated an increase in breast cancer risk in current, but not past, users of methyltestosterone. The use of testosterone implants and transdermal testosterone has not been associated with increased breast cancer risk in observational studies. No RCT has been of sufficient size or duration to definitively determine the effects of transdermal testosterone on breast cancer risk. Of note, the clinical state of continuous estrogen exposure and elevated endogenous testosterone, as seen in PCOS, is not associated with an increased risk of breast cancer.

REALITY OF CLINICAL PRACTICE

Despite the lack of approved testosterone formulations for women in most countries, testosterone therapy for women is not uncommon. This author does not support the use of compounded formulations of testosterone, as the dosing of such therapies is not much better than a ‘best guess’. Overall, pharmacokinetic data for compounded formulations are lacking, individual compounding processes will vary and, as a result, there are no data for efficacy, safety and inter- and intra-variability of applied doses. Oral testosterone preparations cannot be recommended because of their potential adverse metabolic effects. In line with this, ‘troches’ and ‘lozenges’ of compounded testosterone, which are prescribed to be sucked to achieve buccal absorption, will also have gastrointestinal absorption merely with the swallowing of saliva. Thus, until such time that there is evidence that these oral formulations have no adverse lipid effects, they should be considered as having the same profile as other oral testosterone formulations.

Testosterone preparations for men cannot be recommended, but their frequent use in women cannot be ignored. For all testosterone therapies prescribed, serum testosterone levels must be carefully monitored to ensure women are not overdosing. This monitoring should continue for as long as the therapy continues to be prescribed. It is important that patients are advised that physiological doses for women usually do not impact sexual function for several weeks, such that assessment of benefit should be after 10–12 weeks of treatment. Women who have not clearly benefited by 6 months should stop treatment as they are not going to respond with further duration of therapy.
The only two long-term follow-up studies of transdermal testosterone and implanted testosterone pellets, at doses previously studied in women, have not reported any adverse effects in terms of cancer, and no adverse cardiovascular or metabolic effects have been found in RCTs of parenteral testosterone therapy of up to 2 years’ duration. Thus, available data do not indicate a limit for treatment duration.

CONCLUSIONS

Aging, loss of ovarian and/or adrenal function and some medications will lower testosterone levels in women. This may have health consequences, as testosterone has an important role in multiple aspects of normal physiology. Further research to better understand the consequences of testosterone insufficiency is warranted. This should also extend to research into the role in multiple aspects of normal physiology. Further research to better understand the consequences of testosterone insufficiency is warranted. This should also extend to research into the use of anti-androgens in young women with PCOS. Specifically, the cognitive effects of anti-androgen therapy in women with PCOS require careful investigation.

The use of testosterone as a therapy for women continues to attract controversy. Yet off-label use remains widespread. It has been estimated that, when non-proprietary (compounded) testosterone prescriptions are taken into account, in the order of 2 million prescriptions of testosterone are written for women in the USA annually. There is a stark discrepancy between the data that were required for the approval of treatments for male sexual dysfunction compared to what are being required for the approval of testosterone to treat female sexual dysfunction. The phosphodiesterase (PDE) inhibitors were approved with studies showing no greater efficacy in terms of ‘successful’ sexual events than the published studies of testosterone for the treatment for women with low sexual desire. In essence, the PDE inhibitors achieved international approval with studies involving smaller participant numbers, conducted for a shorter duration and with less rigorous entry criteria than the published studies of testosterone for female sexual dysfunction. These PDE inhibitors remain in widespread use despite their documented adverse effects, some of which can be life-threatening.

Regulators need to be pragmatic and consider approval of transdermal testosterone formulations that deliver appropriate female doses. This will abrogate the need for physicians to resort to prescribing compounded testosterone or testosterone formulated for men.

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References

2. Panjari M, Davis SR. Vaginal DHEA to treat menopause related atrophy: a review of the evidence. Maturitas 2011;70:22–5
5. Engstrom WW, Munson PL. Studies on the metabolism of testosterone in normal women in different phases of the menstrual cycle. J Clin Endocrinol Metab 1951;11:427–33
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53. Chiue SE, Martin LA, Campos H, Sacks FM. Effect of the combination of methyltestosterone and esterified estrogens compared with esterified estrogens alone on apolipoprotein CIII and other apolipoproteins in very low density, low density, and high density lipoproteins in surgically postmenopausal women. J Clin Endocrinol Metab 2004;89:2207–13


61. Worsley R, Robinson PJ, Bell RJ, Moufarage A, Davis SR. Endogenous estrogen and androgen levels are not independent predictors of lipid levels in postmenopausal women. Menopause 2013 March 25. Epub ahead of print


