The Safety of Testosterone Therapy in Women

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Abstract

Hypoactive sexual desire disorder (HSDD), a subset of female sexual dysfunction, causes personal distress for surgically and naturally postmenopausal and premenopausal women. HSDD has a multifactorial etiology, including psychosocial factors such as relationship issues and medical factors such as medications, chronic illnesses, and hormonal effects. Although no androgen therapies for female sexual dysfunction are currently approved for use in Canada, clinical trials support the efficacy and short-term safety of testosterone therapy for HSDD. We review the scientific evidence for the safety of testosterone therapy for HSDD.

Résumé

La baisse du désir sexuel (BDS), soit un sous-ensemble de dysfonctions sexuelles chez la femme, est à l'origine de détresse personnelle chez les femmes postménopausées et préménopausées (que ce soit à la suite d'une chirurgie ou de façon naturelle). La BDS compte une étiologie multifactorielle qui comprend des facteurs psychosociaux (tels que des problèmes relationnels) et médicaux (tels que les médicaments, les maladies chroniques et les effets hormonaux). Bien que l'utilisation d'aucune androgénothérapie visant à contrer le dysfonctionnement sexuel féminin n'ait été à l'heure actuelle approuvée au Canada, des essais cliniques soutiennent l'efficacité et l'innocuité à court terme du traitement à la testostérone pour contrer la BDS. Nous analysons les données scientifiques étayant l'innocuité du traitement à la testostérone pour contrer la BDS.

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INTRODUCTION

Hypoactive sexual desire disorder is the most common form of female sexual disorder. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, defines HSDD as "persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity" that causes "marked distress or interpersonal difficulty."[1,2]

Several randomized controlled trials showed significant improvement in the sexual function of premenopausal and naturally and surgically postmenopausal women with testosterone therapy.[3–9] A 2009 Cochrane review of 35 trials with a total of 4768 participants concluded that the addition of testosterone to hormone therapy improves sexual function in postmenopausal women.[10] There has been one RCT conducted since publication of the Cochrane review (the ADORE study).[8] This study evaluated the efficacy of use of a 300 μg/day transdermal testosterone patch over six months in 272 naturally menopausal women with or without concurrent hormone therapy. The women in the testosterone-treated group demonstrated significantly more improvement in satisfying sexual episodes, sexual desire, arousal, orgasms, sexual pleasure, self-image, personal distress, and sexual concerns than the placebo group. Evidence-based recommendations on the efficacy and safety of testosterone therapy are extrapolated on the basis of these trials that are limited to 24 months or less.

The safety concerns of testosterone therapy include the potential for developing hirsutism, acne, behavioural and personality changes, breast cancer, endometrial cancer, hepatotoxicity, and potentially detrimental effects on cardiovascular health and bone health. We review these issues below.

METHODS

We performed a search of articles included in PubMed using key words and citation snowballing to identify articles published in English between January 1, 1970, and March 31, 2012, on the subjects of testosterone therapy and hypoactive sexual desire disorder. Key words used in the search were "hypoactive sexual desire disorder," "female sexual dysfunction," and "testosterone therapy." Our review was restricted to systematic reviews and randomized control trials and controlled clinical trials.

RESULTS

Androgenic Side Effects

Exogenous androgen given to women in sufficient quantities or for a sufficient duration can promote androgenic side effects such as acne, hirsutism, and, in extreme cases, virilization.[11] Virilization includes deepening of the voice, clitoromegaly, masculinization of body habitus, and androgenic alopecia.[12]

The APHRODITE trial investigated the effects of transdermal testosterone patches in postmenopausal women not using concomitant estrogen.[13] Eight hundred fourteen surgically and naturally menopausal women were randomly assigned to receive either 150 μg or 300 μg of transdermal testosterone daily or placebo over a period of 52 weeks.[13] At week 52 of the APHRODITE study, mildly increased hair growth was significantly more common in the 300 μg transdermal testosterone group (19.9%) than in the 150 μg transdermal testosterone group (11.6%) or the placebo group (10.5%). In contrast, the frequency and severity of acne and voice deepening were not significantly different between the groups.

The available data suggest that androgenic side effects tend to be mild with low doses of oral or transdermal testosterone.[11] Compared with oral testosterone, transdermal testosterone has little effect in causing acne or hirsutism.[14] However, moderate acne, moderate hirsutism, and androgenic alopecia are relative contraindications to androgen therapy, and severe acne is an absolute contraindication.[12]

ABBREVIATIONS

BMD	bone mineral density
HSDD	hypoactive sexual desire disorder
IM	intramuscular

Mental Changes

The behavioural changes of anger and hostility are associated with high serum levels of androgens in both men and women.[11] The effect of androgen on mood and behaviour was investigated in a prospective double-blind cross over study of 43 surgically menopausal women.[15] The women received either 1.0 mL IM of Climacteron (containing 150 mg of testosterone enanthate benzilic acid hydrozone and 7.5 mg of estradiol dienanthate) at 28-day intervals, 1.0 mL IM of Delestrogen (containing 10.0 mg of estradiol valerate), 1.0 mL IM of Delatestryl (containing 200 mg of testosterone enanthate), or placebo. Women receiving placebo had higher depression scores than those receiving Delatestryl ($P < 0.01$), Delestrogen ($P < 0.05$), or Climacteron ($P < 0.05$), as measured by the Multiple Adjective Affect Checklist. Women receiving androgen had higher hostility scores than women receiving estrogen alone or placebo ($P < 0.01$).

Women who were given androgen had significantly higher levels of total and free testosterone than women given placebo. In fact, Health Canada and Sandoz Canada announced the discontinuation of Climacteron in 2005. Safety concerns were raised because 1.0 mL IM of Climacteron every four to eight weeks induced serum testosterone levels that were higher than the physiologic levels in premenopausal women.[16]

Anger and hostility are not observed in women with serum testosterone within physiologic limits.[17] Significant improvement in mood and well-being, as measured by the Psychological General Well-Being Index, was found in a study of 49 premenopausal women receiving 10 mg of transdermal testosterone daily (in two 12-week treatment periods separated by a 4-week washout period).[18] Improvement in the scores on the Psychological General Well-Being Index was also found in a randomized placebo controlled trial of 75 surgically menopausal women aged 31 to 56 years.[9] Transdermal testosterone (300 μg/day for 12 weeks) was associated with positive well-being ($P = 0.04$) and improvement in depressed mood ($P = 0.03$).

Anger and hostility, adverse effects of supra-physiologic levels of testosterone, can be averted by transdermal delivery, which provides predictable physiologic doses.[19] Transdermal testosterone, particularly the dose of 300 μg per day, can be used safely from a behavioural standpoint, and can also result in improved mood and well-being.

Breast Cancer

Because there are androgen receptors in the breast, and breast stromal tissues contain aromatase (potentially converting testosterone into estrogen), there is a concern

that testosterone may directly or indirectly stimulate the development of breast cancer.[20] Androgens antagonize estrogen-mediated proliferative effects on breast tissue, and they stimulate apoptosis of breast cancer cells in animals.[21] The available studies of breast cancer and androgen therapy for HSDD used surrogate markers such as mammographic breast density and fine needle aspiration biopsy.[22–24] There are also observational studies on breast cancer incidence.[25] In order to understand the effect of testosterone on breast density in postmenopausal women not on concomitant estrogen-progestogen therapy, 250 postmenopausal women (mean age 54.6 years) were assigned randomly to treatment with either a 150 μg per day transdermal testosterone patch, a 300 μg per day patch, or placebo, for 52 weeks.[22] There were no significant differences between the groups in the area of mammographic density, either the digitally quantified absolute area, the proportion of mammographic density, or in mean change in each group from baseline.

Mammography was used in a retrospective observational study in South Australia to determine breast cancer status.[23] Five hundred eight postmenopausal women (average age 56.4 years) with estrogen and testosterone implants had mammograms at baseline and biannually thereafter, with a mean follow-up duration of 5.8 ± 2.5 years.[23] The incidence of invasive breast cancer in the testosterone group was 238 per 100 000 woman-years, whereas the rate for estrogen-progestogen and testosterone users was 293 per 100 000 woman-years. The age-standardized and age-specific rates of breast cancer in testosterone users were similar to the general population (using South Australia's breast cancer statistics for 1989 to 1996).

Breast cancer incidence in relation to hormone therapy was also determined using fine needle aspiration biopsy. Ninety-nine postmenopausal women (average age 55 years) on combined oral estradiol (2 mg daily) and norethisterone acetate (1 mg daily) were randomly assigned to a 300 μg per day transdermal testosterone patch or placebo for six months.[24] The placebo group had a more than five-fold increase ($P < 0.001$) in total breast cell proliferation from baseline (median 1.1%) to six months (median 6.2%), whereas the transdermal testosterone group had no significant increase in the proliferation of epithelial and stromal breast cells in fine needle aspiration biopsy between baseline and six months (1.6% vs. 2.0%). These results suggest that testosterone may counteract breast cell proliferation induced by estrogen.

The Nurses' Health Study, a prospective cohort study, assessed the risk of breast cancer in 121 700 nurses in the United States (aged 30 to 55 years) from 1978 to 2002. The study showed a 2.5-fold greater risk of breast cancer in women on 1.25 mg daily of esterified estrogen and 2.5 mg daily of methyltestosterone compared with never users (relative risk, 2.48; 95% CI 1.53 to 4.04).[25] Current users of estrogen and methyltestosterone had a significantly greater risk of breast cancer than users of estrogen alone ($P < 0.007$) but not greater than estrogen plus progestogen ($P < 0.11$). Women using postmenopausal hormones containing testosterone had a 17.2% increase in the risk of breast cancer per year of use (95% CI 6.7% to 28.7%).[25]

There are important limitations to this analysis. The authors of the analysis point out that the majority of women in the cohort were past users of other types of hormone therapy, which could confound the results. There are also other potential confounders, as the current users of estrogen and testosterone were younger and leaner, were more likely to have had a benign breast disease, and consumed more alcohol than women who had never used postmenopausal hormone therapy. A recent analysis of the Women's Health Initiative observational study data found that estrogen and methyltestosterone therapy had a non-significant effect on invasive breast cancer risk (adjusted hazard ratio 1.42; 95% CI 0.95 to 2.11), but that the use of Estratest specifically (esterified estrogens with methyltestosterone) was associated with a significant increase in the incidence of invasive breast cancer (adjusted hazard ratio 1.78; 95% CI 1.05 to 3.01).[26] Furthermore, rates of breast cancer were lower in longer-term estrogen and methyltestosterone users than in shorter-term users. The most recent analysis of the Nurses' Health Study data in 2010 examined a subset (646 women; average age 62 years) of Nurses' Health Study participants who provided data from 1989 and 1990.[27] The analysis reported no significant association between breast cancer risk and androgen therapy.

The relationship between testosterone and breast cancer remains unclear.[28,29] Despite this, a history of breast cancer remains a contraindication to testosterone therapy in women.[30]

Endometrial Cancer

There is concern that the aromatization of exogenous testosterone to estrogen increases the risk of developing endometrial cancer in women using testosterone.[10] Testosterone is involved in the regulation of the expression of estrogen, progesterone, and androgen receptors in the endometrium of postmenopausal women and may therefore influence endometrial proliferation.[31] In a three-month study of 63 postmenopausal women (mean age 55 years) who were randomly assigned to treatment with oral testosterone undecanoate (40 mg every second day), estradiol valerate (2 mg daily), or both, endometrial

thickness and histopathology indicative of proliferation were significantly increased in the estrogen-only group ($P < 0.05$), but were not altered in the testosterone-only group.[32] Furthermore, levels of the nuclear antigen Ki-67, which is expressed only by proliferating cells in endometrial stroma and glands, were significantly higher after estrogen therapy than after combined estrogen and testosterone ($P < 0.05$).[32]

Studies of the effects of danazol, a derivative of 17α-ethinyltestosterone used in the treatment of endometriosis, menorrhagia, and endometrial hyperplasia, can contribute to the discussion of the effect of androgens on endometrial growth. In one study, 79 women (mean age 54.5 years) with endometrial hyperplasia received danazol at 400 mg per day for three consecutive months.[33] After this treatment, 82.8% showed a reversal of hyperplasia as assessed by clinical and histological examination. Furthermore, endometrial atrophy was detected in 65.8%, and amenorrhea in 90%. These findings support the biological capacity of danazol, a testosterone derivative, to reverse endometrial growth.

The 52-week APHRODITE trial of 814 women found no cases of endometrial hyperplasia or carcinoma.[13] More women using a 300 µg transdermal testosterone patch reported vaginal bleeding (10.6%) than women using a 150 µg patch (2.7%) or placebo (2.6%). However, all women underwent endometrial biopsy, transvaginal ultrasonography, or both, and only two women who were using a 300 µg patch had proliferative endometrium on biopsy.

Although limited, the available evidence does not suggest an increased risk of endometrial cancer with use of testosterone.[20,29,34] More long-term studies are needed. Known endometrial cancer and unexplained vaginal bleeding remain contraindications to androgen therapy.[34]

Hepatotoxicity

Liver toxicity primarily occurs with high doses of oral 17-α-alkylated steroids that have first-pass effects on the liver.[17] In a study of 60 patients (42 female transsexuals and 18 impotent males), 50 mg of methyltestosterone three times daily was implicated in abnormal liver functions and the development of cholestatic jaundice, peliosis hepatis, and liver tumours, particularly in those treated for more than one year.[35] The transdermal routes of testosterone administration (at a recommended dose of 300 µg/day using the patch) avoid the hepatic first-pass effect and have not been demonstrated to cause hepatotoxic side effects.[11]

Cardiovascular Health

Cardiovascular concerns with androgen therapy include the effects on lipids, plasma viscosity, coagulation, hemoglobin, blood pressure, vascular reactivity, and insulin sensitivity.[10,20]

There appears to be an optimal range of serum testosterone in postmenopausal women for cardiovascular health. The Rancho Bernardo Study of 639 postmenopausal women (mean age 73.8 years; range 50 to 91) measured serum testosterone at baseline and followed cardiovascular events for an average duration of 12.3 years.[36] In age-adjusted analyses, the lowest quintile of serum testosterone was associated with a 1.62-fold increased risk of cardiovascular events (95% CI 1.10 to 2.39) compared with higher levels. Bioavailable testosterone showed a U-shaped association with events, as the age-adjusted relative risks for the lowest and highest quintiles of bioavailable testosterone were 1.79 (95% CI 1.03 to 3.16) and 1.96 (95% CI 1.13 to 3.41), respectively.

A phase III RCT is currently assessing the long-term cardiovascular safety of testosterone gel (300 µg/day) in 2200 postmenopausal women of mean age 57.7 years.[37] The latest update of this ongoing trial found that the rate of cardiovascular events was 0.55%, including one myocardial infarction and no deaths.

Effect on lipids

The effect of exogenous testosterone on lipids in women depends on the dose, route of administration, and concomitant estrogen-progestogen therapy.[10,20] Oral testosterone preparations result in a reduction of high-density lipoprotein cholesterol levels, and a reduction in total cholesterol and triglyceride levels due to the hepatic first-pass effect.[38,39] This reduction in HDL cholesterol does not occur with transdermal therapy.[14] The effect of oral testosterone on low-density lipoprotein cholesterol levels is generally neutral in women.[34]

Supraphysiologic testosterone levels may promote atherogenicity. Significantly higher levels of triglycerides, total cholesterol, LDL cholesterol, and apolipoprotein B, and significantly lower levels of HDL cholesterol were found in a sample of 39 female-to-male transsexuals receiving testosterone esters (250 mg monthly) than in a sample of 29 normally menstruating female-to-male transsexuals prior to starting their androgen treatment.[40]

The 52-week APHRODITE trial of 814 women found no significant differences between the 150 µg transdermal testosterone patch, the 300 µg patch, and placebo with respect to their effects on serum lipid or lipoprotein profiles.[13]

While the evidence supports the safety of the 300 µg transdermal testosterone patch, monitoring the lipid profile of all women receiving testosterone therapy is recommended. Hyperlipidemia remains a relative contraindication to testosterone therapy.[12]

Effect on plasma viscosity

Increased plasma viscosity increases the risk of cardiovascular disease.[20] Oral methyltestosterone appears to decrease plasma viscosity, but transdermal testosterone appears to have no effect.[20]

Effect on coagulation

A hypercoaguble state is one of the risk factors that may lead to cardiovascular disease.[11] No change in clotting factors was observed in response to testosterone implants (100 mg every six months) over a period of two years in premenopausal women.[41]

Effect on hemoglobin

Testosterone increases erythropoietin levels by increasing its production.[42] Polycythemia is one of the risk factors that may lead to cardiovascular disease.[11] Although polycythemia has been observed in hypogonadal men taking high doses of androgens, it has not been found in women receiving physiologic doses of oral, transdermal, injected, or subcutaneously implanted androgens.[20] While these findings are reassuring, polycythemia remains a contraindication to testosterone therapy.[10,12]

Effect on blood pressure

Hypertension is one of the risk factors that may lead to cardiovascular disease.[11] No increase in systolic or diastolic blood pressure has been observed with use of methyltestosterone, testosterone undecanoate, transdermal patches, or subcutaneous testosterone pellets in women.[20]

Effect on vascular reactivity

Physiologic doses of testosterone appear to have beneficial effects on vascular reactivity.[20] Testosterone implants improved brachial artery vasodilation over a period of six months in postmenopausal women on concomitant estrogen.[43]

Effect on insulin resistance

Insulin resistance is associated with the metabolic syndrome and is a risk factor for cardiovascular disease.[17] There is an association between insulin resistance and the hyperandrogenism of polycystic ovary syndrome.[20]

In a randomized clinical study, three months of treatment with testosterone undecanoate (40 mg on alternate days) induced insulin resistance in naturally postmenopausal women.[39] In contrast, use of a 300 µg transdermal testosterone patch twice weekly for 24 weeks did not adversely affect insulin sensitivity in HIV-infected menstruating women.[44] The 12-month APHRODITE study found no effect of testosterone therapy on levels of fasting glucose or fasting insulin, or on insulin resistance as determined by the homeostasis assessment model, HOMA-IR.[13] These findings suggest that transdermal testosterone in physiologic doses does not adversely influence glucose and insulin homeostasis.

Bone Health

Bone mineral density is significantly related to testosterone levels in postmenopausal women.[10,45] The addition of oral testosterone to oral estrogen in surgically menopausal women has positive effects on bone.[46] Total body BMD and BMD of the lumbar vertebrae and hip increased more rapidly in women with testosterone implants (50 mg) plus estradiol implants (50 mg) than in women with estradiol implants (50 mg) alone.[47]

A prospective cohort study of 61 postmenopausal women found that the combination of estradiol and testosterone implants in one year improved BMD.[48] In a study of 232 women aged 67 to 94 years, serum total testosterone was directly associated with BMD at the lumbar spine and hip.[49] Furthermore, free testosterone levels were positively correlated with hip BMD, even after adjusting for estradiol levels.

Supra-physiologic testosterone increases BMD in female-to-male transsexuals. In a study of 15 transsexuals (mean age 37 years) receiving a weekly intramuscular dose of 70mg of testosterone esters, a significant increase in BMD of 7.8% at the femoral neck and a non-significant increase in mean BMD of 3.1% at the spine was observed over a period of two years, as assessed by DEXA.[50]

Although limited, the existing evidence indicates that testosterone therapy has positive protective effects on bone health.

DISCUSSION

The longest available comprehensive data on the effects of testosterone use in women comes from a cohort study of 8412 women from two general practice research databases in the United Kingdom.[51] The mean age of participants was 47 (range 18 to 65). Participants received oral testosterone undecanoate, intramuscular testosterone injections, testosterone implants, mesterolone, or placebo. The average duration of follow-up was 4.4 years. No statistically significant differences between those on active treatment and those on placebo were found in the rates

of breast cancer, acute hepatitis, cardiovascular disease, ischemic heart disease, diabetes mellitus, cerebrovascular disease, or deep venous thrombosis/pulmonary embolism. The rates of androgenic events, although mild, were higher in women on testosterone. This study supports the safety of testosterone therapy over four years in women with a mean age of 47.3 years.

Long-term data on supra-physiologic doses of testosterone in female-to-male transsexuals are reassuring with respect to the use of low-dose testosterone. A recent review of articles on transsexuals published between 1980 and 2010 reported minimal adverse effects and no increase in mortality, breast cancer, or vascular disease.[52]

The 2010 Cochrane review of 35 trials with a total of 4768 women on testosterone therapy found that the significant adverse effects of testosterone therapy were decreased serum HDL cholesterol levels and an increased incidence of hair growth and acne.[10] However, these adverse effects vary with the dose and the route of administration, and do not occur with the transdermal modality.

CONCLUSION

Although no androgen therapies for HSDD are available in Canada, the reviewed clinical evidence supports the safety of short-term testosterone therapy for postmenopausal women with HSDD. The evidence we have reviewed here suggests that transdermal testosterone, at a dose of 150 µg or 300 µg per day, appears to be the safest method of administration. More long-term studies investigating the safety of testosterone therapy in women are needed.

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