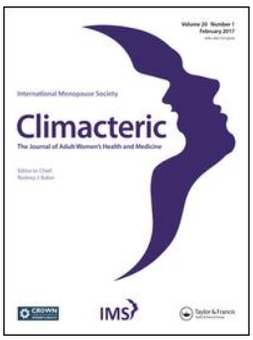

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REVIEW

Testosterone use in postmenopausal women

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ABSTRACT

The physiological, clinical and therapeutic aspects of testosterone in women's health are still a matter of controversy and debate. Quality evidence data of clinical trials favors the use of transdermal testosterone in postmenopausal women with female sexual dysfunction causing distress. Doses of testosterone should approximate physiological testosterone levels found in premenopausal women, avoiding supraphysiological concentrations that expose women to adverse events. Short-term treatment periods have been shown to be effective and safe in postmenopausal women with hypoactive sexual desire disorder/dysfunction. However, long-term safety of testosterone use must be determined.

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Introduction

For more than 70 years, clinicians have been treating women with androgen supplementation for low sexual desire[1–3]. The first clinical trial of androgen therapy for postmenopausal women was published in the early 1950s[4]. However, despite the passage of time, androgen therapy for women remains a controversial topic, in part due to the sparse longer-term safety data[5]. Moreover, in most countries only formulations designed for men are available, potentially exposing women to supraphysiological blood levels, leading to an increased risk of adverse events in this setting[6].

Presently, the only evidence-based indication for testosterone therapy is the treatment of low sexual desire with associated personal distress in postmenopausal women (hypoactive sexual desire disorder/dysfunction; HSDD)[7]. In this article, we have reviewed the physiology of testosterone in women, indications for testosterone use and where we are now in relation to this topic.

Androgen physiology in women – from reproductive years through aging

In premenopausal women, circulating testosterone is directly from ovarian production, as well as being derived from precursor hormones secreted by the ovaries and adrenal glands. These precursors include dehydroepiandrosterone (DHEA) and DHEA sulfate, with the latter almost entirely of adrenal origin, and androstenedione which is secreted by both the adrenals and ovaries. It has been estimated that the ovaries and adrenals each contribute 50% to the circulating testosterone pool during the premenopausal period[8,9]. The testosterone precursors exhibit little biological activity. After their secretion into the circulation, they are activated in peripheral target tissues, mainly adipose tissue and skin, by local intracellular steroidogenic enzymes. Androstenedione, which is also produced peripherally from DHEA, is further metabolized in target tissues to testosterone or estrone[10]. In turn, testosterone may be converted to dihydrotestosterone, the most potent androgen, or to estradiol within the cells. These biosynthetic pathways in peripheral target tissues are the main source of estrogen and testosterone production in postmenopausal women[11].

In premenopausal women, it has been estimated that one-third of circulating testosterone is produced by the ovaries and the remainder comes from peripheral conversion in target tissues[12,13]. However, including the conversion of the androgen precursors released by the ovaries to testosterone into the circulation, almost half of premenopausal woman's daily testosterone production comes from the ovaries[14,15].

During the reproductive years, circulating androgen concentrations steadily decline with age in women with spontaneous regular menstrual cycles[16] and appear to reach the lowest circulating concentrations in postmenopausal women at approximately 62–63 years[17]. A small increase in blood testosterone concentrations has been observed from the age of 70 years, such that testosterone concentrations in older women appear to approximate those of premenopausal women[18,19]. In contrast, circulating DHEA concentrations continue to decrease with age in older women[17,18,20]. It is noteworthy that testosterone concentrations in healthy premenopausal women are of the same order of magnitude as estradiol and estrone concentrations, when measured by liquid chromatography tandem mass spectrometry[16].

Understanding how testosterone circulates is essential to recognize how other factors may affect testosterone physiology. The greatest portion of circulating testosterone (66%) is highly bound to sex hormone binding globulin (SHBG) and

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one-third is bound weakly to albumin and other plasma proteins, allowing 1–2% of testosterone to circulate unbound to plasma proteins (free testosterone)[21]. Free testosterone has generally been considered to be the biologically active testosterone fraction. More recently, this has been questioned. It has been proposed that free testosterone could be the fraction readily available for rapid degradation instead of the bioactive component[22], creating uncertainty as to what fractions of circulating testosterone actually matter. Several mathematical formulae have been used to estimate and report free testosterone concentrations, but these equations generate inconsistent results[23]. Additionally, they all rely on the assumption that the binding of testosterone to SHBG is linear, such that there is lack of validity of the estimations of free testosterone[23]. Because of the above limitations, the recent Global Position Consensus Statement on testosterone for women recommended that research should presently focus on total testosterone levels and not free testosterone[7].

Testosterone therapy for women

Sexual function

A variety of biopsychosocial factors determine sexual function in women[24]. Being partnered is associated with an increased probability of HSDD at all life stages[25–27]. Although associations have been reported between androgen levels and sexual function in premenopausal[17,28,29] and postmenopausal women[17,30], the amount of variation in sexual function explained by variations in the blood concentrations of testosterone and its precursors is small[28].

An international expert panel convened in 2019 concluded that the only evidence-based indication for testosterone therapy is the treatment of HSDD, the most common female sexual dysfunction[7]. The Process of Care algorithm for the diagnosis of HSDD was developed by the International Society for the Study of Women's Sexual Health (ISSWSH), and provides a comprehensive, accessible and practical tool for practitioners to diagnose this condition[24].

There are scant data regarding the estimated prevalence of HSDD. Published estimates ranges for US midlife and older women are 12.4% and 7.4%, respectively and for Australian midlife and older women 32.4% and 13.7%, respectively[26,27,31]. The difference between the two countries may be due not only to differences in the sociocultural backgrounds, but also related to differences in the methodology used in the studies. In addition, over a decade has elapsed between the US PRESIDE study and the Australian studies, which might have influenced women's confidence in talking about their sexual function.

Testosterone's positive therapeutic effect on sexual well-being appears to be related to effects in the central nervous system and on the genital response. A pilot study of testosterone supplementation in surgically postmenopausal women treated with estrogen therapy found that testosterone amplified the activation of brain areas involved with sexual arousal, such as the limbic system[32]. With respect to the genital response, testosterone therapy increases vaginal androgen receptor gene expression and vaginal blood flow, and modulates vaginal smooth muscle activity[33–35]. Thus, intravaginal testosterone has emerged as a promising alternative for treatment of vulvovaginal atrophy, not only for women in general, but also for women with breast cancer taking an aromatase inhibitor[33]. Limited data suggest that intravaginal testosterone could improve sexual function and reduce personal distress in women taking aromatase inhibitor for breast cancer[36]. Larger, double-blind, placebo-controlled clinical trials are still needed to establish efficacy and safety of intravaginal testosterone therapy[33].

Testosterone use: efficacy and safety

A recently published, comprehensive systematic review and meta-analysis of clinical trials of testosterone therapy for women has shown clear beneficial effects of testosterone over placebo in postmenopausal women with HSDD, with or without concurrent estrogen treatment[6]. Benefits were seen in the frequency of satisfying sexual events, sexual desire, arousal, orgasm, responsiveness, self-image, and reduction of personal sexually-related distress. The dearth of well-powered, published studies reporting other effects of testosterone therapy for women meant no conclusions could be made for any of these outcomes[6]. Hence, high-quality randomized controlled trials (RCTs) with standardized endpoints are needed to clarify the effects of testosterone on outcomes such as musculoskeletal health and cognitive performance. There is also a paucity of data available for premenopausal women such that the use of testosterone for HSDD for any purpose in premenopausal women was not recommended[6,7]. An important reassuring finding was the robust evidence supporting a trial of testosterone therapy in postmenopausal women with HSDD. It was recommended that prescribed doses not exceed physiological blood concentrations of testosterone seen in premenopausal women, to avoid supraphysiological concentrations that could cause adverse effects[6,7,37].

Oral testosterone induces an increase in low density lipoprotein cholesterol and decreases in high density lipoprotein cholesterol[6]. As transdermal testosterone does not result in adverse lipid effects, it is the recommended option. Formulations such as subcutaneous pellets, injectable testosterone and compounded 'bioidentical' testosterone lack evidence of efficacy and safety, and may expose women to supraphysiological levels with the risk of virilization. Therefore, there was a strong recommendation against these formulations by the Global Consensus expert panel[7].

With respect to side effects associated with testosterone therapy use, only mild androgenic effects, including hair growth and acne, have been described in clinical trials[6]. No serious adverse events have been demonstrated when testosterone therapy has been used in doses achieving physiological levels found in premenopausal women[6,7]. Endometrial thickness[38] and mammographic breast density[39,40] have been reported as unchanged during testosterone therapy[6].

Cardiometabolic safety has been one of the major concerns about testosterone therapy for women. In relation to this, all women at high risk of cardiovascular disease were

excluded from RCTs; therefore, study results and analyses cannot be generalized to this group of women. This is also true for women with breast cancer, who were not included in the studies. Testosterone is not recommended for women with hormone-sensitive breast cancer, as testosterone can be converted to estradiol in the breast. Testosterone implants have been suggested, by low-quality evidence, to reduce breast cancer risk alone or combined with aromatase inhibitor pellets in an open-label study[41]. However, there are no adequate RCT data to support these claims. Accordingly, testosterone therapy, as implants or injections, should not be used for breast cancer prevention/treatment[7].

The safety of testosterone therapy has not been established for long-term use[7]. However, short-term use of testosterone therapy (< 24 months) for the management of HSDD has not been associated with adverse cardiovascular disease events, cancer or any other serious adverse events[6].

Prescribing testosterone

Testosterone treatment should be considered in postmenopausal women with HSDD, including women with premature ovarian insufficiency of spontaneous or iatrogenic etiology[42]. Testosterone should only be prescribed after a full clinical and biopsychosocial assessment, including medical, sexual and social history in order to identify and manage potentially modifiable factors. As mention above, an expert panel convened by the ISSWSH developed a practical Process of Care to aid clinicians in the diagnosis of HSDD and its management and this is openly accessible[24]. As highlighted in the Process of Care, it is essential to establish whether the patient has experienced psychological, physical or sexual abuse, relationship issues, and to determine their sexual experiences, including whether they are experiencing adequate sexual stimulation, and their knowledge and beliefs about sexuality. A pivotal component of appraisal is to establish whether the low sexual desire has been lifelong or acquired, generalized or situational. A detailed medical history should include all prescribed and non-prescribed medications, which may impact sexual function, and any drug abuse. Physical examination may identify other factors contributing to low sexual desire, for example galactorrhea due to hyperprolactinemia, pale mucosa due to anemia, signs of hypo- or hyperthyroidism, and a gynecological inspection and examination to detect causes of dyspareunia such as vulvovaginal atrophy, which can be alleviated with appropriate therapy[24]. It is important to acknowledge that no cut-off blood level of any androgen can be used to discriminate women with sexual dysfunction from those without[7].

A first management step is often sexual and/or relationship counselling. Consistently, women presenting with lifelong and/or situational dysfunction should be referred for sexual counselling as these indicate strong underlying psychosocial and relationship issues.

When a testosterone trial of therapy is indicated, a transdermal testosterone formulation should be used[7]. This usually presents a challenge given that in most countries there are no testosterone products for women approved or licensed. The only exception is Australia, where a 1% transdermal testosterone cream (0.5 ml dose = 5 mg testosterone) is available and approved specifically for women. This product has been shown to be pharmacokinetically stable and effective in small studies[43,44]. The Global Consensus expert panel recommended that, where an approved therapy for women is not available, a fractionated dose of an approved male formulation should be used with an estimated dose that approximates physiological testosterone levels in premenopausal women[7]. Women must be counselled not to apply more than the prescribed dose, in order to avoid supraphysiological levels. It should be explained that achieving an initial improvement in symptoms of HSDD with transdermal testosterone can take around 4–6 weeks; the peak improvement in sexual desire has been seen at 12–16 weeks. This will ensure their continuing with their trial of testosterone for a sufficient time. Therapy must be discontinued if no improvement is achieved after 6 months, as no benefit will be experienced beyond that time[45–47].

Baseline total testosterone and SHBG levels should be measured before starting treatment. This will exclude women who unexpectedly have high levels from receiving inappropriate therapy. It will also identify women with low SHBG levels who should have a lower initiating dose of testosterone due to more rapid clearance of testosterone from the circulation. Postmenopausal women with SHBG levels above the normal range, such as women taking oral estrogen, have been found to be less responsive to transdermal testosterone therapy[47]. Women with higher SHBG concentrations will also have higher serum total testosterone concentrations for any given transdermal testosterone dose than women with lower SHBG[45,48,49]. Therefore, switching women with elevated SHBG to transdermal estrogen to reduce SHBG levels is recommended before starting testosterone therapy. Total testosterone and SHBG measurements should be repeated within 6 weeks of starting treatment to identify application of an unintentionally excessive dose of testosterone by the patient[7].

Evaluation of therapy response should be monitored clinically in terms of improvement of low sexual desire/well-being after 12 weeks of therapy, and signs of androgen excess with the measurement of total testosterone and SHBG every 6 months to avoid excessive dosing[7].

A final consideration: a variety of testosterone formulations have been available for men for decades, whereas no national regulator has officially approved a testosterone therapy for women. This needs to be corrected to remove the necessity in some countries of prescribing of male formulations for women and expose them to side effects from supraphysiological dosing and to ensure gender equity in the treatment of sexual dysfunction.

In conclusion, transdermal testosterone therapy has been demonstrated to be effective and safe in well-powered clinical trials for the treatment of HSDD in postmenopausal women, when doses used approximate physiological testosterone levels in premenopausal women. However, further research is needed to deepen our knowledge of the effects of testosterone therapy on cognitive performance,

musculoskeletal and cardiovascular health, as well as long-term safety use.

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