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Review

Androgens in postmenopausal women

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Key content:
- Androgen therapy can improve sexual wellbeing, libido and sexual arousal in postmenopausal women through its effect on the central nervous system.
- Testosterone levels gradually decline throughout a woman's lifespan and testosterone therapy may be useful for menopausal women with sexual dysfunction, in whom estrogen therapy alone has been ineffective.

Learning objectives:
- To understand the physiology and the potential impact of changes in testosterone levels in postmenopausal women.
- To be aware of the potential role of androgen therapy in postmenopausal women with low sexual desire causing distress.
- To review the available evidence behind the use of androgen therapy for female sexual dysfunction in the menopause.

Ethical issues:
- More women are spending a greater proportion of their lives in the postmenopausal period, so it is important to gain a greater understanding of the role of testosterone replacement after the menopause in improving sexual dysfunction.
- Off-label use of testosterone gels and creams is common; when prescribing these, clinicians must inform women of the potential benefits and risks as well as the fact that long-term safety data is still lacking.

Keywords: androgens / HSDD / menopause / testosterone

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Introduction

Androgen therapy can improve sexual wellbeing, libido and sexual arousal in postmenopausal women through its effect on the central nervous system. In this review, we examine androgen physiology in women, the factors influencing circulating concentrations of androgens and the potential effects of changes in androgens beyond the menopause. Clinical data pertaining to the use of androgens to treat hypoactive sexual desire disorder (HSDD) or female sexual interest and arousal disorder (FSIAD), are examined, as well as discussing the potential adverse effects.

Androgen physiology

Traditionally, androgens have been classified as compounds that induce and maintain male sexual characteristics by binding to the androgen receptor. The first androgen was identified in 1931 by extraction from approximately 15 000 litres of urine provided by German policemen.[1] Ernst Laquer subsequently isolated and named the compound 'testosterone'.[2]

Although commonly thought of as a male hormone, testosterone is quantitatively the most prevalent active sex steroid in women. It can exert its action via the androgen receptor, as well as being an obligatory precursor for estrogen biosynthesis in female physiology.[3] Testosterone circulates in women at around 5% of the levels found in men.[4] As there is no established feedback loop for testosterone production, the control of its production is poorly understood. Women produce around 3–4 times more testosterone daily than estrogen, which equates to approximately 100–400 micrograms.[5]

In premenopausal women, ovarian theca cells produce testosterone and androstenedione, which are either secreted directly into the circulation, or alternatively converted within the ovarian granulosa cells into estrogens via the aromatase enzyme. During the reproductive years, ovarian production of testosterone has some cyclical features, with peak levels noted mid-cycle.[6] Levels remain high during the luteal phase. Diurnal variation has also been noted, with concentrations highest in the morning.

The adrenal glands produce the relatively weaker androgen, dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S), which act as precursor hormones to testosterone, with conversion taking place within the peripheral circulation. DHEA-S, which is almost only produced by the adrenals, is thought to be the most abundant sex steroid in women. DHEA-S can be converted first to DHEA and then to androstenedione, which is the precursor for both testosterone and estrone (Figure 1).[7]

In premenopausal women, ovarian and adrenal production each contribute an estimated 25% to total

circulating testosterone, with the remaining 50% being the result of peripheral conversion from androgen precursors. Circulating testosterone is highly bound to plasma proteins, with approximately 66% being bound to sex hormone binding globulin (SHBG) and the remaining 33% to albumin. Unbound testosterone, which accounts for the remaining 1–2%, can bind to androgen receptors and is likely to exert most of the biological effect noted with testosterone. However, as testosterone only binds weakly to albumin, bioavailable testosterone is provided by the free testosterone plus a fraction of the albumin–bound testosterone. Factors affecting SHBG concentrations can therefore affect bioavailable testosterone.

Oral estrogen, tamoxifen and oral thyroxine can all increase SHBG levels, thus reducing free androgen levels. The opposite finding, that is, low SHBG and increased free testosterone, can be observed in women receiving oral testosterone and glucocorticosteroid therapy, as well as in women with a high fructose diet, increased visceral adiposity and insulin resistance.[8]

In women, androgen receptors can be found in almost all tissue types throughout the body, including the brain, skin, adipose, bone and vessels. Activation of these receptors induces a direct genomic effect within these target cells; however, the mechanism is unclear. Testosterone can exert its effect directly via the androgen receptor, or be 5-alpha-reduced to the non-aromatisable androgen, dihydrotestosterone, or aromatised to estradiol. Testosterone and dihydrotestosterone are the most potent androgens in terms of receptor binding potential.

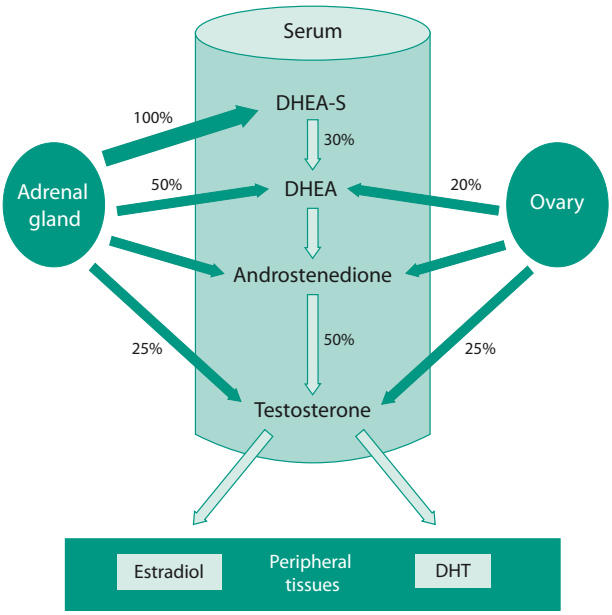

Figure 1. Andrology physiology demonstrating premenopause sources of circulating androgens. DHEA = dehydroepiandrosterone; DHEA-S = dehydroepiandrosterone sulfate; DHT = dihydrotestosterone. Adapted with permission from K. Maclaran.

Effect of ageing on testosterone levels

Testosterone is first noted in girls at the age of 6–8 years old. As maturation of the adrenal zona reticularis commences, production of both DHEA and DHEA-S increases, signalling the onset of adrenarche.[9]

During the reproductive years, the pool of circulating androgens derives from both the ovaries and the adrenal glands. Testosterone levels gradually decline throughout a woman's lifespan. Testosterone levels peak between the ages of 18 and 24 years. Between the ages of 20 and 40 years, there is an estimated 50% decline in total and calculated free testosterone, DHEA-S and androstenedione.[10,11] This fall in circulating androgens is primarily attributed to a reduction in adrenal production of androgen precursors. Age-related atrophy of the adrenal cortex causes its contribution to circulating androgens to drop to just 10% by the time menopause is reached, with 50% originating from the ovaries and the remaining 40% being from peripheral conversion.[12]

Although testosterone concentrations appear to be maintained in women beyond the age of 65, the clinical significance of this has yet to be determined. Data have also shown that naturally occurring menopause does not appear to affect circulating androgens, in contrast to the sharp decline in estradiol that occurs at this time.

However, in women aged 55 years or older who had undergone bilateral oophorectomy and not received exogenous steroids, significantly lower testosterone and free testosterone levels were seen than in women aged 55 years or older in the reference group.[13] Women diagnosed with premature ovarian insufficiency (POI) have also demonstrated lower circulating androgen levels than age-matched controls.[14]

Testosterone assays: measurement and interpretation

While assays allow the calculation of testosterone levels, serum levels are not necessarily the best measure of tissue exposure because much of the biological action of testosterone results from intracellular metabolism. Circulating testosterone is also highly bound to plasma proteins, so any factors affecting SHBG concentrations may also influence serum testosterone levels.

Total testosterone levels can be measured with high accuracy and reproducibility using liquid/gas chromatography and tandem mass spectrometry assays. When spectrometry is not available, direct assays for measuring total and free testosterone can be considered. It is important to note, however, that these direct assays are unreliable, particularly when considering female range levels. Reference ranges should be standardised and, although direct assays are potentially appropriate to exclude high-baseline concentrations as well as supraphysiological responses to exogenous therapy, the

results should be interpreted with the aforementioned points in mind.

To determine the free fraction of testosterone, the rate of testosterone production, metabolic clearance rate and SHBG levels can be considered. Free testosterone is typically calculated using the Södergård equation, which incorporates circulating concentrations of SHBG to accurately measure bioavailable levels.[15] Total testosterone is measured, then SHBG levels are incorporated using the following calculation:

$$\text{Free androgen index (FAI)} = \frac{\text{Total testosterone} \times 100}{\text{SHBG}}$$

Guidance produced by the British Menopause Society in 2022[16] suggests that total testosterone levels are assessed before treatment to ensure that levels are not in the upper range before treatment is started. The guidance also concluded that the correlation between free testosterone levels and biological activity of testosterone assays has not been confirmed, and therefore the assessment of free testosterone levels is not recommended in this context. The guidance also recommended that the effectiveness of testosterone treatment is primarily determined by symptom alleviation. Monitoring should include assessment of total testosterone levels within 2–3 months to ensure that levels remain within the female physiological range.

Role of testosterone in women

Sexual function

Androgens are important in healthy female sexual function, especially in stimulating libido and sexual interest as well as maintaining desire. Testosterone contributes to libido, sexual arousal and orgasm by acting upon the central nervous system to increase dopamine levels. Testosterone might also be involved in maintaining normal metabolic function, muscle and bone strength, urogenital health, mood and cognitive function.

Several studies have examined the association of circulating androgens with sexual function and suggest a positive correlation. There is, however, a degree of heterogeneity within the results, probably owing to difficulties in measuring low androgen levels in women, as well as differences in study design, with patient selection and sexual function endpoints varying significantly. One such study by Wahlin-Jacobsen et al.[17] utilised tandem liquid chromatography–mass spectrometry to establish that free testosterone and androstenedione levels were positively associated with sexual desire in women aged 19–65.

When considering the menopausal population alone, other studies have looked at whether the lower androgen levels noted in this group resulted in sexual dysfunction. A large prospective study conducted as part of the Study of Women's Health Across the Nation (SWAN)[18] noted that, in middle-aged women, total testosterone and DHEA-S levels were positively associated with sexual desire as well as masturbation frequency, a partner-independent behaviour reflecting intrinsic sexual urge.

Findings from observational studies of women with surgical menopause for benign reasons suggest a lack of correlation between postoperative sexual desire and androgen levels despite bilateral salpingoophorectomy resulting in a 50% decline in circulating androgens.

Defining female sexual dysfunction

The term female sexual dysfunction (FSD) can be used to characterise chronic sexual conditions in the domains of desire, arousal, orgasm and pain. FSD pertains particularly to the fact that these symptoms result in sexually related personal distress, as well as being associated with interpersonal difficulties.

Sexual dysfunction can be subgrouped into several categories, namely lifelong or acquired after a period of normal function, generalised or situational (only present with certain situations, or with a specific partner, for example). It can also be divided into mild, moderate or severe. FSD is often multifactorial with biological, psychological, interpersonal and sociocultural factors all at play. Expert opinion groups recommend that a diagnosis of FSD requires persistent symptoms for more than 6 months occurring during at least 75% of all sexual experiences.[19]

In the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V),[20] four categories of FSD are defined, with female sexual interest and arousal disorders being grouped together. In earlier versions of the DSM, female sexual interest and arousal disorder were divided into separate categories; however, they were merged because desire and arousal problems often occur together, and distinguishing desire from other parameters is particularly complex. Some experts have recommended to restore the distinction between hypoactive sexual desire disorder/dysfunction (HSDD) and arousal disorder/dysfunction (FSAD), citing a lack of empirical evidence to combine them.[19]

The fourth edition of DSM (DSM-IV)[21] specifically defines HSDD as the absence of sexual fantasies and desire for sexual activity that causes a woman distress. To date, the largest randomised controlled trials (RCTs) to assess effectiveness of pharmacological interventions for FSD, as well as observational and registry data, have all used the standardised criteria for HSDD. Therefore, application of the findings in clinical practice may benefit from a distinction between HSDD and FSAD.

Loss of sexual desire is perhaps the commonest symptom and there has been a well-reported decline in sexual desire with both age and menopausal status. This can be as high as 52% of naturally menopausal women versus 39% of premenopausal women.[22]

Prevalence of female sexual dysfunction after menopause

Large cohort studies have aimed to determine the prevalence of female sexual problems among the general population. The PRESIDE study,[23] conducted in the USA, found that 8.9% of women aged 18–44 years (95% confidence interval [CI] 8.4–9.4%) experienced decreased sexual desire resulting in distress, with rates of 12.3% of 45 to 64-year-olds (95% CI 11.7–12.9%) and 7.4% in the 65 and older category (95% CI 6.7–8.2%).

A recent population-based study in Australia,[24] using validated questionnaires, found the prevalence of low sexual desire associated with distress among women aged 40–64 years to be as high as 32.2% (95% CI 30.1–34.2%).

The combination of declining estrogen levels associated with the menopause and age-related decline in androgens, low desire, poor arousal, dyspareunia and impaired orgasm are all thought to contribute to overall reduced sexual satisfaction.

Diagnosing female sexual dysfunction

Although validated questionnaires are available for research purposes, diagnosis of HSDD in the clinical setting should be a pragmatic one based primarily on symptoms. Clinical assessment should be guided by available diagnostic criteria outlined by the International Society for the Study of Women's Sexual Health or the International Classification of Diseases, 11th edition.[16]

Sexual dysfunction causing distress should be identified through history taking, which should also distinguish between generalised or situational and acquired versus lifelong dysfunction. It is important to identify and correct modifiable contributing factors, such as endocrine or genitourinary disorders, as well as addressing co-morbidities such as depression.

Although testosterone levels have been correlated with sexual desire, evidence for its usefulness in the diagnosis of sexual dysfunction is lacking.

To arrive at the diagnosis of HSDD, symptoms should result in clinically significant distress and have persisted for a minimum of 6 months. The disorder can further be specified by severity level as well as being subtyped into lifelong versus acquired, generalised versus situational.

Treatment of female sexual dysfunction in the menopause

In the presence of HSDD, women may seek treatment for various reasons. The clinician should tailor this treatment according to the subcategory within which the woman's symptoms fall.

For lifelong or situational low sexual desire, counselling can be useful. In menopausal women with generalised, acquired HSDD, all potential modifiable biopsychological factors should be identified and addressed. If HSDD persists in the absence of modifiable biopsychosocial factors, androgen therapy can be considered as a potential treatment modality. Transdermal testosterone has demonstrated efficacy in the treatment of low desire with associated distress. The remainder of this review will focus on this form of treatment.

By increasing the frequency of satisfying sexual encounters, even from never or occasional to at least once or twice a month, evidence has shown that androgen therapy can significantly improve the personal wellbeing and self-esteem of affected women, their partners and their relationships.

Systemic benefits of testosterone therapy

Wellbeing and quality of life

HSDD remains the main indication for postmenopausal testosterone use. To date, RCTs of testosterone have not demonstrated beneficial effects of testosterone therapy for cognition, mood, energy and musculoskeletal health, despite individual reports of improvement of these symptoms. Adequately powered randomised studies are needed to further assess this. British Menopause Society guidance recommends that until such data becomes available, the primary indication for testosterone should therefore be for HSDD following a biopsychosocial approach.[16]

Davis et al.[25] conducted a 24-week randomised placebo-controlled trial with the testosterone patch to be used with concurrent transdermal estrogen for surgically menopausal women with HSDD. The Psychological General Wellbeing (PGWB) index, which is a 22-item questionnaire to measure wellbeing, was used alongside sexual desire questionnaires. The 61 women who completed the trial showed a significant increase in composite score for the PGWB index with testosterone therapy versus placebo (2.57 versus -2.82; $p = 0.04$).

Another observational study by Glaser et al.[26] assessed the benefits of continuous testosterone therapy, delivered via subcutaneous implant, for both premenopausal and postmenopausal women. The self-administered, validated HRQOL Menopause Rating Scale (MRS) was completed by 300 women at baseline and 3 months after treatment. Although limited by the lack of a placebo arm, improved psychological metrics were seen as part of the MRS.

Cognitive function

In vitro studies suggest that endogenous testosterone may influence amyloid deposition, although this has not been demonstrated in adequately powered studies.[27] Several studies have investigated this effect with varying results, according to age of the women studied, duration and dose of testosterone used.

In 2011, a pilot study by Davison et al.[28] involving nine naturally or surgically postmenopausal women assessed the use of transdermal estrogen with transdermal testosterone for 26 weeks in the treatment arm compared with a control group of 30 women receiving estrogen only. Results suggested improved verbal learning and memory in the treatment arm. The study however, included a small number of women and further research is needed to assess this.

Subsequently, in 2014, a double-blind randomised placebo-controlled trial[29] investigated the effects of daily testosterone gel in 89 naturally menopausal women aged between 55 and 65 years old, not receiving concurrent estrogen. The participants were not cognitively impaired at baseline, and although statistically significant improvements were noted in verbal learning and memory over the observed 6-month period, these improvements remained within the age-adjusted normal range of cognitive function.

Despite differences being observed in small verbal memory studies for postmenopausal women receiving testosterone therapy, pooled meta-analysis data from a total of three RCTs involving a total of 159 women,[30] showed no effect of testosterone on any of the reported cognitive measures being assessed. Until well-conducted RCTs are undertaken and demonstrate benefit of exogenous therapy, the use of testosterone for potentially enhancing cognitive performance or delaying cognitive decline, is not justifiable.

The recent Global Consensus Position Statement on the Use of Testosterone Therapy for Women[31] concurred there is insufficient evidence to support the use of testosterone to enhance cognitive performance, or to delay cognitive decline in postmenopausal women.

Musculoskeletal function and bone density

The androgen receptor is present within both osteoblasts and osteocytes. In men, the skeletal effects of androgens are seen directly via its effect on these receptors; however, in women, the skeletal effects of androgens seem to be mediated indirectly by aromatisation to estrogen. Androgen levels correlate with trabecular and cortical bone mineral density (BMD), particularly approaching the late postmenopausal period, with a decline being more than 1% per year.[32] Findings from the Women's Health Initiative observational studies[33] demonstrated a correlation between higher endogenous bioavailable testosterone levels with a lower incidence of hip fractures, regardless of concentrations of endogenous estradiol and SHBG.

There is a dearth of studies conducted to observe the effects of exogenous testosterone on musculoskeletal and bone health. Studies that have reported musculoskeletal outcomes have been limited by small participant numbers, the issue of concurrent estrogen therapy and the lack of inclusion of women with osteoporosis in the study groups.

In 1999, a 2-year RCT of 311 surgically postmenopausal women on oral conjugated equine estrogen with or without the addition of methyltestosterone was conducted.[34] The women receiving combined estrogen–androgen therapy demonstrated increased BMD at the hip and the spine. Subsequent studies have failed to replicate any sustained benefit for additional exogenous androgen therapy on bone density or musculoskeletal health. Furthermore, we have yet to see an RCT reporting the effect of treatment with testosterone on fracture risk in women.

Endogenous free testosterone is positively associated with lean body mass in women aged 67–94 years.[35] Some RCT data are available showing a greater reduction of fat percentage in women given combined estrogen and testosterone compared with estrogen therapy alone, as well as increased lean body mass.[36]

To date, data have shown testosterone to have an important anabolic role in muscle and bone health. However, there is a lack of data demonstrating significant effects of testosterone administered at physiological doses for postmenopausal women on bone mineral density, lean body mass or muscle strength.

Androgen preparations

Female testosterone replacement following menopause

Testosterone has been used in gynaecology for over 70 years, with initial indications being for symptoms such as menorrhagia, dysmenorrhea, mastalgia, and pelvic inflammatory disease.[37] The first clinical trials using testosterone therapy to treat sexual dysfunction in surgically menopausal women involved the administration of high doses of intramuscular testosterone with or without concurrent estrogen treatment. Although significantly higher scores of sexual desire, arousal and fantasies were observed in the testosterone group compared with estrogen alone and placebo, the doses resulted in supraphysiological testosterone levels. The results were also hampered by the fact that investigators knew which treatments the women received.[38]

Oral formulations of testosterone were considered; however, these were limited by both poor absorption and first-pass hepatic metabolism adverse effects on lipoprotein (HDL)-cholesterol and liver function.[39] A transdermal route of delivery appeared to lack these issues and now remains the preferred route of administration in current clinical practice.

In 2005, Nathorst-Böös et al.[40] produced data from a double-blind randomised crossover study, which compared outcomes important to sexuality and overall wellbeing. In postmenopausal women already on hormone replacement therapy (HRT), application of 10 mg testosterone gel per day to the outer thigh improved sexual function calculated using the Psychological General Well-Being Questionnaire. This 10 mg daily dose was also sufficient to achieve testosterone levels in the premenopausal female range. The group did not uncover any safety concerns with regards to this therapy.

A greater understanding of the effect of transdermal testosterone on sexual function came following a large series of multicentre, double-blind, randomised, placebo-controlled trials published from 2005 onwards.[41–46] These studies are included in Table 1 below. Initial studies were performed in surgically menopausal women taking concomitant estrogen therapy. Following on from this, naturally menopausal women on estrogen therapy were randomised to receiving transdermal testosterone. Finally, both naturally and surgically menopausal women not on estrogen therapy received transdermal testosterone.

The APHRODITE study

In 2008, the APHRODITE study by Davis et al.[45] looked at the efficacy of transdermal testosterone for low libido in postmenopausal women not taking estrogen. In the trial, 814 women were randomised to receive either 150 or 300 micrograms of transdermal testosterone or a placebo patch. After 24 weeks, women receiving 300 micrograms of testosterone per day experienced significantly more satisfying sexual episodes than the placebo group (an increase of 2.1 episodes per month versus 0.7 in the placebo group, $p < 0.001$). No significant difference was seen between the group receiving 150 micrograms per day and the placebo group (an increase of 1.2 episodes per months versus 0.7, $p = 0.11$). There was, however, an overall increase in desire and decrease in distress in both treatment groups than the placebo group. The results confirmed meaningful improvements in patient reported outcomes with androgen replacement therapy without the need for concurrent estrogen.

The effects noted in all domains of the Profile of Female Sexual Function assessment were sustained at week 24 and were independent of baseline levels of free testosterone. Androgenic adverse events, predominantly unwanted hair growth, were higher in the group receiving 300 micrograms of testosterone per day than the placebo group (30.0% versus 23.1%).

The ADORE study

Panay et al.[46] published the results of the ADORE study in 2010. This study aimed to establish the efficacy of transdermal testosterone in the treatment of HSDD, solely when occurring in naturally menopausal women. The data confirmed the efficacy of administration of 300 micrograms transdermal testosterone with or without estrogen replacement, with a statistically significant difference in total satisfying sexual episodes with treatment compared with placebo. Women receiving 300 micrograms per day experienced a mean increase of 1.69 total satisfying sexual episodes per month compared with a mean increase of 0.53 total satisfying sexual episodes per month for those receiving placebo at week 24 ($p = 0.0089$).

Table 1. Studies of transdermal androgen therapy in the treatment of women with sexual dysfunction

Year	Authors	No. of patients	Duration (weeks)	Treatment	Indication	Results
2005	Buster et al.[41] (RCT)	533	24	Testosterone patch, 300 μg	BSO on E with HSDD	↑ SD + SSA
2005	Braunstein et al.[42] (RCT)	447	24	Testosterone patch, 150, 300, 450 μg	BSO with HSDD	↑ SD + SSA
2005	Simon et al.[43] (RCT)	562	24	Testosterone patch, 300 μg	BSO on E with HSDD	↑ SD + SSA
2006	Shifren et al.[44] (INTIMATE)	483	24	Testosterone patch, 300 μg	HSDD on E	↑ SD + SSA
2008	Davis et al.[45] (APHRODITE)	814	24	Testosterone patch, 150 or 300 μg	HSDD without E	↑ SD + SSA
2010	Panay et al.[46] (ADORE)	272	24	Testosterone patch, 300 μg	Natural menopause with HSDD	↑ SD + SSA

Abbreviations: BSO = bilateral salpingo-oophorectomy; E = estrogen; HSDD = hypoactive sexual desire disorder; RCT = randomised controlled trial; SD = sexual desire; SSA = satisfying sexual activity

The study also reaffirmed that, provided mean free testosterone levels remained within physiological ranges, the incidence of adverse androgenic events remained low. Overall, 76% of patients completed the study and total mean exposure to the study drug was 147 days. Overall adverse events were reported in a higher percentage of the placebo patients (71.1%) versus the 300-microgram testosterone patch group (62.3%). Only three serious adverse events (2.1%) were noted in the placebo group. Although most adverse events were mild in severity and did not result in discontinuation, 14.1% of patients in the placebo group withdrew from the study and 6.9% withdrew from the treatment group. No myocardial infarctions or breast cancers were reported in the study.

Meta-analysis and systematic review findings

In 2017, Achilli et al.[47] conducted a systematic review and meta-analysis to assess the efficacy and safety of transdermal testosterone, specifically in the treatment of hypoactive sexual desire in postmenopausal women. The analysis concluded there was evidence that testosterone did increase the number of satisfying sexual events compared with placebo. There was also, however an increase in androgenic adverse events, acne and hair growth in the pooled treatment groups compared with placebo. Overall, the review found no significant increases in total adverse events and serious adverse events, but the group still recommended close surveillance for any androgenic side effects.

In July 2019, a comprehensive systematic review and meta-analysis conducted by Islam et al.[30] presented data for all modes of administration (oral and non-oral) from completed RCTs, concerning both the efficacy and safety of testosterone in women. The meta-analysis showed that testosterone supplementation improves sexual function in both naturally and surgically postmenopausal women, with or without concurrent estrogen (Figure 2).

Importantly, this study also reaffirmed that only non-oral testosterone should be prescribed owing to the adverse lipoprotein effects of oral testosterone. This recommendation stemmed from the finding that testosterone given orally increased low-density lipoprotein (LDL) cholesterol (mean difference 0.29, 95% CI 0.04–0.53; $p < 0.0001$) and reduced total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides. Non-oral testosterone was not associated

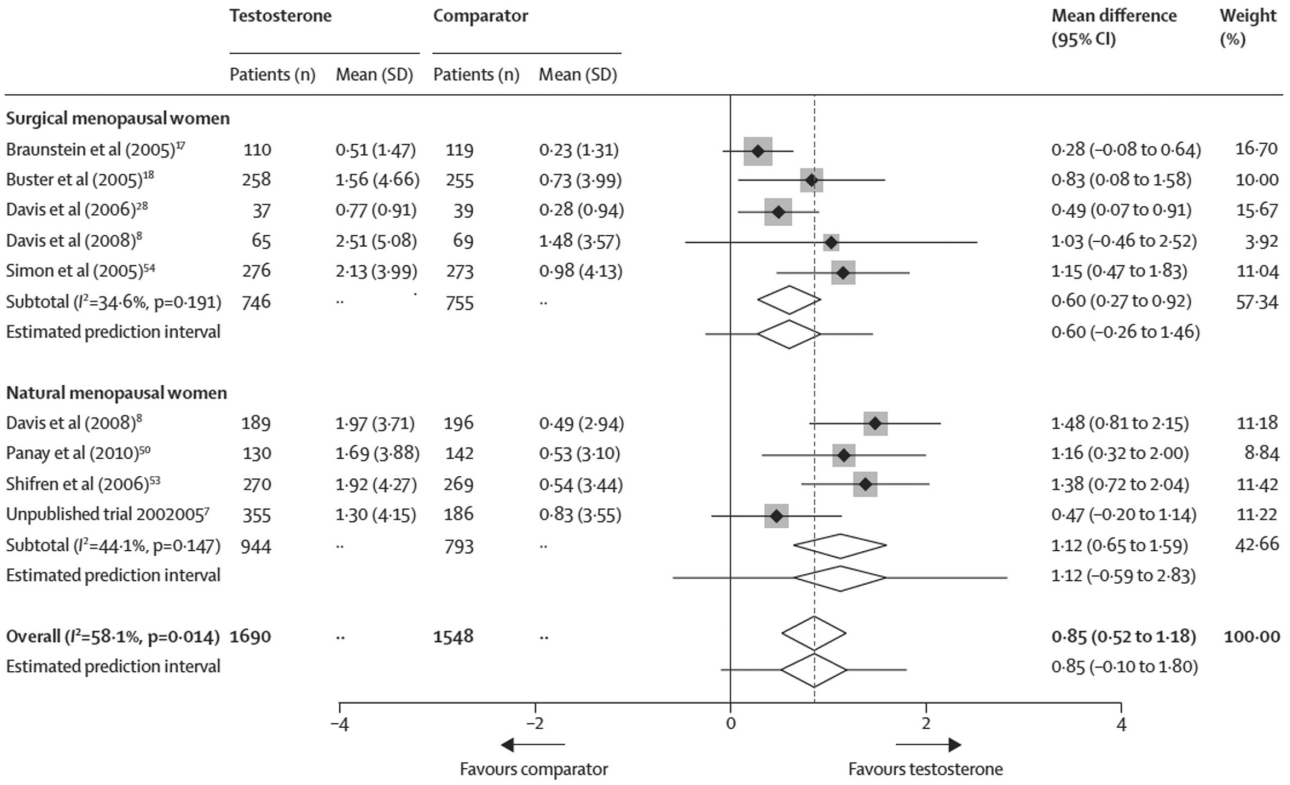

Figure 2. Effect of testosterone versus comparator on satisfying sexual events, by menopausal status. Reproduced with permission from a systematic review by Islam et al., 2019.[30] Shown is change in the number of satisfactory sexual events per month. Vertical dotted line represents overall mean difference.

with any significant lipid effects. A further pertinent outcome from the review included a small but significant increase in weight with testosterone treatment.

Available meta-analysis data to date do not support the use of testosterone in premenopausal women or to prevent depression, bone loss or prevention of cognitive decline as a consequence of the menopause.

Summary of NICE recommendation on androgens

Guideline NG23, updated and published by the National Institute for Health and Care Excellence (NICE) in 2015,[48] advised that testosterone supplementation could be considered for menopausal women with low sexual desire if estrogen therapy alone is not effective. However, although the guideline recommends prescription of systemic HRT before a trial of testosterone, trial data in women with HSDD indicate that testosterone alone used without systemic estrogen can be equally effective and safe. However, the incidence of adverse androgenic side effects such as acne and excess hair growth is higher, and in view of this, such an approach is not usually recommended in routine clinical practice.[16] In addition, vaginal estrogen should be offered to women with urogenital atrophy (including those on systemic HRT) and continued for as long as needed to relieve symptoms related to vaginal dryness and dyspareunia.

Current availability

Various testosterone products are available for the treatment of male hypogonadism, including intramuscular injections, subcutaneous implants, transdermal patches and gels. By extrapolation of efficacy and safety data from testosterone patch trials, it has been deemed acceptable for products licensed in men (mainly gels) to be prescribed off label in female doses for the treatment of HSDD given the lack of availability of preparations for female use due to commercial reasons. As testosterone levels in women are approximately 5% of male levels, these products must be used in women with caution, since there is a potential risk of administering supraphysiological dosing.

Although the off-label use of testosterone gels and creams for women is common, there are currently no preparations specifically designed for use in women that are recognised by the UK or European regulatory authorities, or by the Food and Drug Administration (FDA) in the USA. It is possible to use medicines without their product license, as long as certain criteria proposed by the General Medical Council (GMC) and Medicines and Healthcare Products Regulatory Authority (MHRA) on prescribing an unlicensed medicine or using a medicine off-label are met (see Box 1).

Box 1. Criteria for prescribing an unlicensed medicine or using a medicine off-label

Unlicensed medicines, or licensed medicines for an off-label use, may be used if:

- No other suitably licensed products are available
- There is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy
- A clear record is made of the reasons for prescribing an unlicensed/off-label medicine
- Patients, or those authorising treatment on their behalf, have sufficient information about the proposed treatment.

Testosterone treatment should not be used in women with acute liver disease, competitive athletes for whom levels must be maintained within physiological levels, or in women with upper-normal or high baseline testosterone levels.

Box 2 lists the testosterone preparations currently available in the UK.

Alternatives to testosterone

Oral DHEA is available as a dietary supplement and, as such, product quality, purity and doses are highly variable. A 2014 systematic review and meta-analysis[49] looked at the benefits and potential harms of DHEA use in postmenopausal women with normal adrenal function. The review included 23 randomised trials, which – in general – were considered to have moderate-to-high risk of bias. Data from a total of 1188 women enrolled in the review suggested that DHEA use was not associated with significant improvement in libido or sexual function. As such, current consensus is to recommend against the use of DHEA in this setting.

The synthetic orally active steroid tibolone is weakly androgenic and lowers SHBG, resulting in an increase in

Box 2. Testosterone preparations currently available within the UK

- **Testogel (Besins Healthcare UK):** A 1% testosterone gel in 5.0 g sachets containing 50 mg testosterone, with a starting dose of 1/10 of a sachet/day (5 mg/day; i.e., each sachet should last 10 days). A new preparation of Testogel has now been released in the UK. This contains 40.5mg of testosterone per sachet. This could be administered as 1/8 of a sachet/day to deliver the recommended dose of 5 mg/day; i.e., each sachet should last 8 days.
- **Testim (Endo Pharmaceuticals):** A 1% testosterone gel in 5.0 g tube containing 50 mg testosterone, with a starting dose of 1/10 of a tube/day (5 mg/day; i.e., each sachet should last 10 days).
- **Tostran (Kyowa Kirin Ltd):** A 2% testosterone gel in a canister containing 60 g, with a starting dose of one metered pump of 0.5 g (10 mg) on alternate days or three times a week.
- **AndroFeme (Lawley Pharma):** A 1% testosterone cream in 50-ml screw-capped tubes, with a starting dose of 0.5 ml/day (5 mg /day). AndroFeme is designed for female use but not currently available on the UK National Health Service. It can, however, be imported from Australia via special license from the MHRA.

endogenous free testosterone. However, meta-analysis data[50] failed to confirm the benefit of tibolone on sexual desire in postmenopausal women.

Compounded testosterone therapy is not recommended for the treatment of HSDD owing to the lack of evidence for its safety and efficacy.

Monitoring and surveillance

Testosterone gel or cream should be used on clean, dry skin on the lower abdomen and upper thighs. Skin contact with others should be avoided until the skin is dry and hands should be washed immediately after application.

Response to therapy usually requires at least 8 weeks to manifest, so treatment should be trialled for a minimum of 3 months. If there has been no improvement after 6 months, then testosterone should be discontinued. To assess whether a satisfactory response is maintained, and to identify adverse androgenic events, regular reviews should be undertaken, at least on an annual basis.

The optimal duration of treatment has yet to be ascertained. Research studies predominantly involved 6–12 months of use, so efficacy and safety beyond this period is unclear.

Side effects and safety of testosterone therapy

The primary concern of licensing authorities is lack of long-term safety, particularly in relation to cardiovascular health, and the risk of breast and endometrial cancers.

Clinical trials have centred around the assessment of androgenic events and basic blood parameters. Several reviews have emphasised the importance of long-term safety data.

Androgenic side-effects

The use of testosterone, particularly in supraphysiological doses, can be associated with androgenic side effects. These include hirsutism, acne, alopecia and – in some extreme circumstances – virilisation. When testosterone is used to attain physiological levels, side effects take several months to develop and remain dose dependent. Cessation of treatment usually results in prompt resolution.

Transdermal patch RCTs reported incidence of hirsutism between approximately 3 and 20%. One study that observed side effects over 52 weeks,[38] did note a statistically significant increase in hirsutism when a transdermal testosterone patch was used. Pooled data from 4178 participants in 11 studies[29] showed a greater likelihood of hair growth (RR 1.69, 95% CI 1.33–2.14).

Acne has been shown to increase with androgen use compared with controls, according to a meta-analysis of pooled data from 11 studies involving 3264 participants (RR 1.46, 95% CI 1.11–1.92).[31] The incidence across all participants appears to be 4.6–7.5%.[39]

To study long term outcomes, Nachtigall et al.[51] analysed data from open-label extensions of two RCTs using the transdermal testosterone patch for up to 4 years. Of the 1094 participants, the rate of androgenic events was 28.4% after the first year, 14.3% in the second year, 10.5% in the third year and 3.5% in the fourth year. All reported events were mild and were not deemed severe enough to discontinue treatment.

The more severe androgenic side effects of virilisation (for example, voice deepening, male pattern hair loss and clitoromegaly) are very rare and only associated with supraphysiological levels of testosterone administered via parenteral routes for a prolonged period. There have been no reported incidences of virilisation in the studies examining transdermal androgens to date.

A recent comprehensive systematic review concluded that, provided testosterone treatment is administered at doses aimed to achieve premenopausal physiological levels, there is a greater likelihood of acne and hair growth but not alopecia, voice deepening or clitoromegaly compared with placebo.[30] This reiterates the need to inform women who are initiating testosterone treatment of these side effects and the importance of adhering to the prescribed doses.

Breast safety

Breast carcinomas differ in histopathology, expression and bioactivity of hormone receptors, and pathophysiology. Evidence demonstrates that the risk of breast cancer is associated with age, age at menarche, family history, gene mutations, parity, obesity and smoking. Lifetime exposure to progestogen and estrogen has therefore been proposed as central to the mechanism of breast cancer pathophysiology, but a similar association with androgens has yet to be determined.

Women with polycystic ovarian syndrome or women receiving high-dose androgen therapy for female to male gender transition, do not appear to be at a greater risk of breast cancer.[52]

Androgens can be aromatised to estrogens, so concerns have been raised that risk associated with the use of postmenopausal estrogen therapy may well be applicable to androgen therapy, including breast cancer. The effect of these androgens may be mediated either directly via the androgen receptor, which has been demonstrated in breast tissue, or from conversion to estradiol by the aromatase enzyme, which is also found in breast tissue. Indirect effect on the breast may also be induced by altering SHBG levels and, as a consequence, the bioavailability of estradiol.[53]

Early case-control studies had previously reported an increased risk of breast cancer in women using intramuscular testosterone in addition to estrogen or estrogen plus progestogen therapy. On examining 4610 cases of breast cancer in the Nurses' Health Study,[54] the combined estrogen and testosterone group had an increased risk of breast cancer compared with never-users of HRT (RR 2.48, 95% CI 1.53–4.0).

In contrast, a study assessing postmenopausal women taking conjugated equine estrogen methyltestosterone in the Women's Health Initiative did not report increased hazard risk ratios of breast cancer.[55] Several other observational studies since have yet to show a causative correlation with androgen therapy and breast cancer.

Randomised data examining breast cell proliferation and mammographic density did not note an adverse effect of transdermal testosterone on these parameters compared with placebo.[56]

To date, the most comprehensive safety data on testosterone from a single study comes from the APHRODITE trial of 814 postmenopausal women with HSDD randomised to a testosterone patch (150 or 300 micrograms/day) versus placebo without concurrent estrogen use. Safety was assessed over a 52-week period and an additional year of follow-up was conducted in a subgroup of the initial cohort (40% of the initial participants). Breast cancer was diagnosed in four women in the testosterone group compared with no cases in the placebo group. However, two of these women were likely to have had the cancer before randomisation. The group concluded that this excess of cases may have been down to chance, but the possibility of a causal relationship must be considered.[45]

Although the study was not powered to assess solely for breast cancer risk as a primary outcome, the data, along with other RCTs, suggest that breast cancer incidence does not increase with short-term use of transdermal testosterone at doses resulting in circulating blood levels within the premenopausal range. The absolute number of breast cancer cases in these studies is small, however, and there is insufficient published evidence to guide on the risk of breast cancer with testosterone therapy. Furthermore, available RCT data cannot be generalised to support the safety of either long-term or high-dose testosterone therapy.

A 2018 systematic review concluded that the use of transdermal testosterone to treat HSDD in postmenopausal women did not appear to increase breast cancer incidence, although the numbers of cases included was small.

In conclusion, both experimental and observational data suggest that testosterone therapy does not increase the risk of breast cancer, although robust evidence on this is lacking. Further research from adequately powered RCTs with breast cancer incidence being the primary endpoint is required.[57]

Endometrial safety

Androgen receptors have been reported in the stromal compartment of postmenopausal endometrium, as well as in the atypical glandular compartment of endometrial cancers. The atrophic effect of androgens on the endometrium has been shown in vitro; however, the conversion of testosterone to estradiol by aromatase activity resulting in an abnormal endometrium must be considered.[58,59]

The APRHODITE study[45] investigated endometrial safety. The 814 women were followed up over 52 weeks and, although vaginal bleeding was more common in the testosterone group (10.6%) compared with placebo (2.6%), no subjects developed endometrial hyperplasia or carcinoma.

In conclusion, current data do not suggest any increased risk of endometrial cancer in association with testosterone therapy. However, adequately powered long-term studies are needed.

Cardiovascular disease

Cardiovascular disease (CVD) affects approximately one in three women during their lifetime and remains the leading cause of death (22.3% of all deaths in women). Clinical presentation, pathophysiology and response to treatment of CVD differs between men and women.

Prior to the onset of menopause, circulating estrogen levels are thought to confer a protective effect on women. After the menopause, this effect reverses and by the age of 70, cardiovascular risk is identical in men and women. The cardioprotective effect of estrogen has been well studied; however, whether co-treatment with testosterone neutralises this benefit or in fact induces a deleterious effect has yet to be established.

Spoletini et al.[60] conducted a systematic review examining the association between androgens and CVD in postmenopausal women. The authors concluded that studies to date suggest a chronic hyperandrogenic state; that is, high testosterone and low SHBG levels may have a harmful effect on the cardiovascular system.

On the other hand, several observational studies have also demonstrated that women with low endogenous total and free testosterone levels may be at greater risk for coronary heart disease events. A population-based study prospectively followed 639 women for a mean of 12.3 years to investigate cardiovascular events in relation to baseline testosterone levels.[61] A total of 134 cardiovascular events were noted during the follow-up, with women in both the highest and lowest quintile found to be most at risk. This U-shaped risk curve indicates the importance of maintaining testosterone levels at physiological levels to optimise cardiovascular health.

At physiological concentrations, testosterone has been shown to have favourable effects on aspects of the blood

Strong evidence

Diagnosis of HSDD in clinical practice should be based on thorough clinical assessment guided by available diagnostic criteria.

Treatment of HSDD should follow a biopsychosocial model.

Testosterone therapy exerts a beneficial effect on sexual function:

- Number of satisfying sexual events per month
- Increased sexual desire, arousal, orgasmic function and responsiveness
- Reduction in sexual concerns, including sexual distress

Systemic testosterone therapy in physiological doses, i.e. that of premenopausal women, is associated with mild increases in acne and hair grown but no other androgenic side effects.

Oral testosterone therapy is associated with adverse lipid profiles, an effect that is not seen with transdermal testosterone over the short term.

Limited evidence

A baseline total testosterone concentration should be measured before starting treatment and repeated 6 weeks after commencement. Signs of androgen excess can be screened for with 6-monthly levels.

Treatment should be stopped if no benefit after 6 months.

Testosterone may improve wellbeing but data are inconclusive.

Available data to date show that short-term transdermal testosterone therapy does not appear to impact breask cancer risk, but RCT data for long-term breast cancer risk is insufficient.

Weak/no evidence

The association between endogenous androgen concentrations and sexual function in women is uncertain, and there is no cut-off level that can be used to differentiate women with or without sexual dysfunction.

Insufficient evidence that testosterone enhances cognitive performance or improves depressed mood.

Insufficient evidence that testosterone improves musculoskeletal outcomes, including bone mineral density.

A nonsignificant trend for increased deep vein thrombosis has been seen with transdermal testosterone; however, this could be associated with estrogen therapy.

Safety data for testosterone therapy beyond 24 months is not available.

Figure 3. Summary of practice points based on the evidence available for testosterone therapy for postmenopausal women. HSDD = hypoactive sexual desire disorder; RCT = randomised controlled trial

vessel wall, namely vasomotor tone, endothelial function and peripheral vascular resistance. Studies in men and animal models have demonstrated that this improvement in arterial function is mediated by both flow-mediated changes (endothelium dependent effects) and endothelium independent vasodilatation.[62] Flow-mediated vasodilation has been correlated with coronary endothelial function and deterioration has been noted following menopause with improvement following estrogen therapy.[63]

In 2022, Islam et al.[64] published a study that reported on the correlation between endogenous testosterone and DHEA levels and the risk of cardiovascular events in women over the age of 70. The study included 9180 Australian women with no prior history of cardiovascular disease events, of which 5535 were included in the analysis, with a median age of 74 years. The study suggested that women over the age of 70 with higher background serum testosterone levels (median 0.79 nmol/l) and DHEA levels (median 5.58 nmol/l) had a lower risk of major adverse cardiovascular events compared with women with lower testosterone (median 0.17 nmol/l) and DHEA (median 1.11 nmol/l). The authors concluded that the study findings cannot ascertain conclusively whether the associations between blood testosterone and DHEA concentrations and risk of major adverse cardiovascular events were causative effects. Further research is needed to better understand testosterone action in blood vessels and the heart, including whether treating postmenopausal women with low testosterone protects against cardiovascular disease.[64]

Worboys et al.[65] reported that exogenous parenteral testosterone improved both endothelium-dependent and endothelium-independent vasodilatation in postmenopausal women who were already on long-term estrogen therapy. The authors concluded that their data suggested a potential mechanism by which parenteral testosterone could exert a positive effect on cardiovascular parameters; however, this requires further investigation. Although testosterone is a potential vasodilator when given to postmenopausal women, data on the overall effect on blood pressure appears to be neutral.

Oral testosterone has been shown to adversely alter lipid profiles, negatively affecting both HDL and LDL-cholesterol levels, and therefore should be avoided. Data from studies of non-oral testosterone (both percutaneous and injectable), did not show this adverse lipid effect, provided doses achieved premenopausal physiological concentrations.

In summary, although RCTs have not shown an increase in coronary artery disease, stroke or thrombosis with testosterone therapy, none of the studies were sufficiently powered to investigate the effect of testosterone on major cardiovascular events. Currently available data indicate that transdermal testosterone therapy given in physiological doses has no significant adverse effects on lipid profile and no increase in blood pressure, blood glucose or HbA1c levels.

Conclusion

There is an age-related decline in androgen levels in postmenopausal women. The effects of this decreased concentration of bioavailable androgens on sexual function is not yet fully understood. Clinical data does support the use of low-dose transdermal testosterone to alleviate the symptoms of HSDD, with improved sexual function noted in heterosexual women with both naturally occurring and surgically induced menopause.

Clinicians, whether in primary or secondary care, who are trained in the biopsychosocial assessment of sexual dysfunction, should establish the diagnosis of HSDD and exclude modifiable factors prior to considering testosterone therapy for symptomatic menopausal women.

Off-label use of testosterone gels and creams is common. When prescribing these, clinicians must inform women of the potential benefits and risks, as well as the fact that long-term safety data is still lacking. After commencing therapy, serum testosterone levels should be performed after 6–8 weeks to exclude androgen excess. Women should be seen regularly to assess continued response in sexual function as well as identification of adverse effects. The above aspects should be documented within the medical record to maintain appropriate clinical governance and for audit purposes. A national surveillance system to act as a database of adverse event reporting would potentially help to further determine likelihood of risk and guide in developing future standards of practice.

Further research is needed to assess the long-term safety of testosterone therapy on cardiovascular disease, breast cancer risk, cognitive performance, musculoskeletal health and fragility fracture risk. Figure 3 provides a summary of practice points based on the evidence available for testosterone therapy for postmenopausal women.

Disclosure of interests

There are no conflicts of interest.

Contribution to authorship

KV and HH instigated, researched and wrote the article and approved the final version.

Supporting Information

Additional supporting information may be found in the online version of this article at http://wileyonlinelibrary.com/journal/tog

Infographic S1. Androgens in postmenopausal women.

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