

## COMMENTARY

# The role of testosterone in menopausal hormone treatment. What is the evidence?

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## Abstract

About 40% of postmenopausal women have decreased sexual desire, causing distress. Estrogen therapy attenuates vaginal complaints but has no effect on sexual desire. Although sexual function has been linked to testosterone, there is no clear relation between sexual desire and circulating levels of testosterone. Nevertheless, treatment with transdermal (patch) testosterone improved sexual function in several randomized controlled trials. Women with hypoactive sexual desire disorder who were treated with testosterone reported more satisfying sexual episodes and sexual desire compared with the placebo group. Adverse effects were mild. However, there is no testosterone drug designed for women available on the European market. Consequently, women who opt for testosterone treatment have to use preparations made for men with a high drug concentration. Adequate dosage for women is therefore challenging. A trial of 5 mg transdermal testosterone (gel or cream) daily or less has been suggested, followed by close monitoring of side effects and hormone level.

## KEYWORDS

drug treatment, menopause, practice guidelines as topic, sexual dysfunction, testosterone

## 1 | SEXUAL FUNCTION AFTER MENOPAUSE

After menopause, serum estradiol levels are reduced by 90%, whereas testosterone steadily declines by age from 25 years of age.<sup>1</sup> Most women experience menopausal symptoms, and it is well known that estrogen largely relieves hot flashes, sweating, sleep disturbance and vaginal dryness. In addition, difficulties with sexual desire, arousal and orgasm increase with age, and these problems may cause distress in menopausal women.<sup>2</sup> In a Norwegian population-based survey on sexual habits, 41% of the women between 50 and 59 years of age reported lack of sexual desire as a manifest problem.<sup>3</sup> Young women after premenopausal bilateral salpingo-oophorectomy experience even more severe sexual problems compared with older women with a natural menopause.<sup>4</sup> Women with surgical menopause were more likely to have low sexual desire compared

with premenopausal or naturally menopausal women (odds ratio 1.4, confidence interval 1.1-1.9). Furthermore, the women with low sexual desire had less sexual activity and were more dissatisfied with their sexual life and partner relationship than women with normal sexual desire.<sup>4</sup>

## 2 | TESTOSTERONE LEVELS AND FEMALE SEXUAL FUNCTION

Androgens comprise testosterone, dihydrotestosterone, and substances that can be converted to testosterone.

Circulating testosterone is produced by the ovaries (25%) and the adrenal cortex (25%), and from peripheral conversion of adrenal androgens (50%). In addition, a significant contribution to the female androgen action is due to intracellular production of testosterone in

target tissues.<sup>5</sup> Sexual problems after menopause have been linked to the decline in testosterone production. Although studies have shown a modest positive relation between dehydroepiandrosterone (DHEA, a testosterone precursor) levels and female sexual function, there is no evidence of a causal relation between a woman's testosterone level and her sexual function.<sup>6,7</sup> Despite this, factors that alter the amount of free proportion of total testosterone are thought to have an impact on female sexual function. Androgen receptors are present in several tissues, and androgen action in the skin, internal and external genitalia, and the brain is related to female sexual function. Yet, only 1%-2% of the total circulating testosterone is free and able to bind to the androgen receptor; more than 70% is firmly bound to sex hormone-binding globulin and 25% is loosely attached to albumin. Oral estrogen, thyroxin supplement, low body mass index, and older age increase the amount of sex hormone-binding globulin, and thereby reduce the level of free testosterone. On the other hand, androgens, high body mass index and increased insulin levels decrease the sex hormone-binding globulin level.

### 3 | TESTOSTERONE TREATMENT FOR WOMEN WITH SEXUAL DYSFUNCTION

Testosterone treatment is defined as a testosterone supplement given as a drug. There are no established indications for testosterone therapy in women. However, most studies have been performed in postmenopausal women with hypoactive sexual desire disorder.

Older studies have shown an effect of testosterone treatment in women with hypoactive sexual desire disorder given either testosterone orally or as an intramuscular injection. Many of the women in these trials obtained supra-physiological testosterone levels, and oral testosterone was associated with an impaired lipid profile.<sup>8,9</sup> In later trials, testosterone was given as a patch.<sup>10-16</sup> By transdermal administration, the first pass metabolism in the liver is avoided, and thereby the negative effect on lipids. Additionally, transdermal administration continuously releases the drug and provides a stable serum level of testosterone comparable to premenopausal production.

Seven randomized controlled trials of testosterone patch given to postmenopausal women with hypoactive sexual desire disorder have been conducted.<sup>10-16</sup> The main outcome in all these studies was the frequency of satisfying sexual episodes. Furthermore, sexual desire, distress related to sexual life, adverse effects, as well as hormone levels were measured. The results were consistent, women given 300 µg testosterone patches reporting a significantly greater increase in the number of satisfying sexual episodes, a greater increase in sexual desire, and less distress related to their sexual life compared with placebo. The effect in naturally menopausal women<sup>11,12</sup> was similar to that in women after surgical menopause,<sup>10,13,16</sup> and was unrelated to estrogen therapy. In one study, dosages of 150, 300 or 450 µg testosterone/d were compared with placebo.<sup>16</sup> Only women who received 300 µg testosterone/d reported a significantly greater increase in the number of satisfying sexual episodes

#### Key message

Reduced sexual desire is common among postmenopausal women. A positive effect of testosterone is well-documented, but there are no female preparations available in Europe. Therefore, a maximum of 5 mg testosterone/d from a product for men is suggested, with close follow up.

and a greater increase in sexual desire compared with placebo. One explanation for the lack of effect of the highest dose, may be that 300 µg/d (equivalent to premenopausal endogenous production) represents the top of the dose-response curve, and that a higher dose of testosterone therefore does not increase the response further.<sup>16</sup> The testosterone treatment groups in these seven studies showed an increase in satisfying sexual episodes between 0.7 and 2.5 during a 4-week trial (compared with 0.5-1 in the placebo groups). A subgroup of women were asked whether the effect of testosterone treatment was meaningful, and they confirmed that an increase of 0.8-1 satisfying sexual episode during a period of 4 weeks was meaningful.<sup>17</sup>

### 4 | OTHER EFFECTS OF TESTOSTERONE TREATMENT

Some studies have shown a positive effect of testosterone treatment on bone health and cognitive function, but in a recent systematic review of the effects of testosterone therapy to postmenopausal women, these results were heterogeneous.<sup>18</sup> In a 2019 meta-analysis of 36 randomized controlled studies of testosterone therapy, Islam et al<sup>19</sup> found no effect on body composition, musculoskeletal variables or cognitive measures; however, the number of women who contributed to these outcomes was small. Prior studies have found that testosterone treatment increases well-being in postmenopausal women. However, Islam et al<sup>19</sup> concluded that this effect warrants further investigation.

### 5 | CONCERNS ABOUT TESTOSTERONE TREATMENT IN POSTMENOPAUSAL WOMEN

There may be some concerns about testosterone treatment in postmenopausal women. Adverse effects in the testosterone groups were acne and increased hair growth, but the differences were significant in only a few of the studies and the effect was modest. The testosterone levels were increased in the groups who received testosterone, but mostly they remained below the upper limit for premenopausal women.<sup>10-16</sup>

Long-term safety data is limited to 2 years of treatment.

Furthermore, most studies have included healthy women only. Nevertheless, transdermal testosterone resulting in physiological concentrations has not increased cardiovascular risk factors, including blood lipids,<sup>19</sup> blood pressure and insulin resistance in healthy postmenopausal women.<sup>18</sup> Regarding breast safety, testosterone treatment does not increase mammographic breast density and there is no indication of enhanced breast cancer risk from short-term data.<sup>18</sup> Furthermore, testosterone addition to menopausal hormone therapy seems to counteract breast cell proliferation.<sup>20</sup> In addition, Glaser and Dimitrakakis<sup>21</sup> studied the effect of testosterone in combination with aromatase inhibitor on postmenopausal symptoms in 72 women with previous breast cancer. They found a significant improvement of nearly all postmenopausal complaints after treatment with this combination after up to 9.4 years of follow up. None of the women had recurrence of their breast cancer during the follow up. There are no studies on testosterone therapy in women with *BRCA* mutations (and hence inherited increased risk of breast cancer) but there is currently no evidence suggesting that *BRCA* mutation carriers with no prior breast cancer are not eligible for testosterone treatment. However, long-term breast safety data are lacking. The same goes for endometrial safety. Testosterone treatment does not stimulate endometrial proliferation but may counteract such a proliferation induced by estrogen.<sup>22</sup> In a 2019 meta-analysis of 36 randomized controlled trials of testosterone therapy, there were no increased risks of serious events.<sup>19</sup> Indications and cautions regarding testosterone therapy are summarized in Table 1.

## 6 | GUIDELINES OF TESTOSTERONE TREATMENT IN POSTMENOPAUSAL WOMEN

Recently, Davis et al<sup>23</sup> published a global consensus position statement on the use of testosterone treatment for women. None of the Nordic countries participated in this collaboration. Although less detailed, the Norwegian guidelines<sup>24</sup> are broadly in line with the global consensus. British<sup>25</sup> and Australasian<sup>26</sup> guidelines include a more detailed assessment before considering testosterone treatment. They state that if a postmenopausal woman has sexual desire problems, estrogen treatment should be optimized, and transdermal application should be preferred to minimize the increase of sex

hormone-binding globulin. If no improvement of sexual function occurs, testosterone treatment should be the next choice. Although not mentioned in the guidelines, women who suffer from androgen deficiency due to premature ovarian insufficiency, pituitary failure or adrenal deficiency might also benefit from testosterone therapy in the case of reduced sexual function. However, at present, there are no transdermal testosterone preparations for women in the Nordic countries. Hence, most testosterone prescriptions given to women are preparations made for men (gel, cream or spray) having a high drug concentration, which makes it difficult to obtain an effective dose for women. Another problem is that there are no studies of the efficacy and safety with this type of testosterone administration in women. The effective dose of 300 µg testosterone patch/d is not transferable to gel, cream and spray. The British Menopause Society considered this;<sup>25</sup> they suggest that an equivalent dose of male gel or cream is 5 mg/d. Based on clinical experience, in some women this dose can be too high and needs to be reduced, for instance by application every other day. In 2018, more than 2000 Norwegian women received a testosterone prescription<sup>27</sup> and this elucidates the need for a testosterone drug customized for women.

In the global consensus, Davis et al<sup>23</sup> suggested a procedure for testosterone treatment in women. Before treatment, baseline testosterone level should be measured. After a trial of testosterone treatment for 3–6 weeks, one should control for the testosterone level and adverse effects including increased hair growth and acne. If serum testosterone is kept within normal reference values for premenopausal women, there is no risk of deepening of the voice, alopecia, enlargement of clitoris or other virilizing symptoms. Treatment effect can be expected within 3 months. Patients should be monitored for response to treatment and for overuse every 6 months. If there is no effect on sexual function after 6 months, discontinuation of treatment is recommended.<sup>23</sup> Management of testosterone therapy is described in Table 2.

With today's knowledge, there is no evidence supporting different testosterone doses with regard to age. The general recommendation is to treat women with surgical or natural menopause in doses resulting in physiological testosterone concentrations for premenopausal women.

**TABLE 1** Indication and cautions regarding testosterone therapy

Indication	Cautions
Hypoactive sexual desire disorder	Previous diagnosis of hormone-sensitive breast cancer
With or without concurrent estrogen therapy	Women at risk of cardiometabolic disease
Surgically or naturally postmenopausal women	No safety data beyond 24 mo of treatment
	Testosterone treatment that causes supra-physiological concentrations of testosterone

**TABLE 2** Management of testosterone treatment

Measurement of serum testosterone level before treatment
A trial of up to 5 mg of transdermal testosterone gel or cream daily
Follow up for effect on sexual function, adverse effects (body hair growth, hair loss, voice changes, acne, clitoral enlargement) and hormone levels after 6 wk of treatment
Monitoring of efficacy and safety (adverse effects and testosterone level) every 6 mo during treatment
If no effect on sexual function within 3–6 mo, discontinue the therapy
Information to the woman regarding limitation of long-term safety data

## CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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