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THE ROLE OF TESTOSTERONE IN HYPOACTIVE SEXUAL DESIRE IN POSTMENOPAUSAL WOMEN – AN INTERGRATIVE REVIEW

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Abstract: This literature review explores the role of testosterone therapy in postmenopausal women with Hypoactive Sexual Desire Disorder (HSDD). Menopause, a natural physiological process, leads to a decline in reproductive hormones, causing symptoms like vaginal dryness, decreased libido, and sexual dysfunction. Androgens, particularly testosterone, play a vital role in maintaining sexual functions and overall health. This review discusses the use of testosterone therapy in alleviating symptoms of HSDD, emphasizing its effectiveness in improving sexual function and desire. The research was conducted through a bibliographic search in PubMed, Google Scholar, and Cochrane databases, focusing on studies published between 2005 and 2024, in English and Portuguese. The review highlights the importance of considering physical, psychological, and relational factors affecting sexual health in menopausal women and recognizes testosterone's significant role in female sexual function. While testosterone therapy shows promise, the review notes the need for caution due to mixed findings on long-term safety and the potential for adverse effects.

INTRODUCTION

Sexual well-being is integral to a woman's overall health, particularly during menopause. This natural phase marks a key shift in a woman's life, characterized by a decline in reproductive hormones and the end of menstrual cycles. The decrease in estrogen during menopause commonly results in symptoms such as vaginal dryness, reduced elasticity, and thinning of vaginal tissues. These physical changes often lead to discomfort during sexual activities, a decrease in libido, and potential sexual dysfunction (1).

Fluctuating hormone levels during menopause can also contribute to changes of mood, anxiety, and depression. These psychological changes, along with societal attitudes towards aging, can affect a woman's sexual self-esteem and desire. Sexual health is not just about physical symptoms; it's also intertwined with relationship dynamics. Changes in sexual desire or function can affect intimacy and partner relationships, leading to additional stress and emotional challenges (2-5).

It is known that the role of androgens in women extends beyond merely supporting estrogen production. These hormones are crucial in regulating and maintaining several physiological aspects, including the vulvovaginal complex, pelvic floor, bladder, as well as essential sexual functions (6). In women, testosterone is produced by the ovaries and the adrenal glands. During menopause, there is a general reduction in androgen production, attributed to the age-related decrease in ovarian and adrenal function. Androgens are known to contribute significantly to sexual motivation in women, encompassing aspects such as showing sexual interest, initiating sexual activity, and responding to sexual stimuli. Consequently, a reduction in testosterone levels is believed to be a significant and potentially reversible factor in the development of Hypoactive Sexual Desire Disorder (HSDD) (6-9).

In summary, sexual health in menopausal women is a complex interplay of physical, psychological, and relational factors. Testosterone plays a noteworthy role in female sexual function, and its therapeutic use in menopause is a promising yet cautiously approached area in women's health. Understanding and addressing these aspects can significantly improve the quality of life for menopausal women. The primary aim of this review is to explore and elucidate the role of testosterone therapy in addressing Hypoactive Sexual Desire Disorder (HSDD) among

postmenopausal women. Specifically, it seeks to unravel the complexities of HSDD in the context of menopause, examine the impact of testosterone on women's sexual health, and assess the challenges and considerations in the therapeutic use of testosterone. Through an examination of studies and clinical trials, this review aims to provide a nuanced understanding of testosterone's role in enhancing sexual function and overall quality of life for postmenopausal women

METHODS

This review is based on an extensive literature survey using PubMed, Google Scholar, and Cochrane databases. It was included original articles and bibliographic reviews published from 2014 to 2024. However, to ensure a comprehensive understanding, the scope was expanded to include earlier publications in cases where more recent literature on specific topics was scarce. The research was conducted in two languages: English and Portuguese and the search terms encompassed 'testosterone', 'woman', 'women', 'hypoactive sexual desire', 'HSDD', and 'menopause' or 'postmenopausal women'. These terms were used individually and in various combinations to ensure a comprehensive collection of relevant literature. This methodological approach was aimed at providing a thorough and up-to-date analysis of the role of testosterone in addressing hypoactive sexual desire disorder in postmenopausal women.

HSDD: ADDRESSING SEXUAL DESIRE CHALLENGES IN MENOPAUSE

Hypoactive Sexual Desire Disorder (HSDD) is a multifaceted issue deeply affecting women's sexual well-being and overall quality of life. This disorder is marked by a consistent and troubling disinterest in sexual activities, which results in both personal challenges and complications in interpersonal relationships (10). An HSDD may be primary or secondary, lifelong or acquired, or generalized or situational. The broadened definition of HSDD may include lack of motivation for sexual activity, reduced or absent spontaneous desire, loss of desire to initiate or participate in sexual activity. Each of these factors can individually or in combination influence a woman's sexual function during menopause, requiring a holistic approach to management and treatment (10, 11).

HSDD is associated with profound negative effects on mood, self-esteem, and partner relationships and can cause significant decrease in quality of life. Nearly half of menopausal or postmenopausal women (ages 57–85) in the United States have some element of sexual dysfunction with HSDD being the most reported form. This number is likely to increase in the upcoming years due to the progressively aging population (6, 12). Research demonstrates a significant connection between distressing low sexual desire and a diminished health-related quality of life, highlighting numerous psychosocial factors. These include discontent with sex life, partnership dissatisfaction, and negative emotional states such as frustration, hopelessness, anger, low self-esteem, and feelings of diminished femininity. Additionally, there's a notable correlation between depression, anxiety, and low sexual desire, underscoring the integral relationship between mental health and sexual well-being. These findings emphasize the importance of addressing both psychological and relational aspects when dealing with low sexual desire (13).

The prevalence of Hypoactive Sexual Desire Disorder (HSDD), widely studied but varied in findings, is recognized as the most common sexual dysfunction among

women, especially during menopause. Research indicates that around 10% of adult women experience HSDD, with higher rates observed in postmenopausal women. A study by Simon et al. (2022) highlighted that HSDD's impact on mental health is more pronounced in premenopausal women than in their postmenopausal counterparts (14). In a comprehensive survey of 3,350 women aged 40 to 80 across several Asian countries, 27% reported a reduced interest in sex, with reported rates ranging from 17% to 50% (15). Low sexual desire increases with age, from 11% in the 20-29 age group to 53% in the 60-70 age group, though associated distress decreased over time. This trend results in a relatively stable prevalence of HSDD, between 6% to 13%, across these age groups. In the United States, the condition affects about 12% of women aged 45-64, showcasing the varied impacts of HSDD across different demographics and stages of life (16). The prevalence was 32% in Australian women aged 40-64 and 14% in those aged 65-79 (17, 18). All these data show the importance of accurately assessing patients presenting with HSDD to detect any possible concomitant conditions and treatments.

A cross-sectional survey involving 530 pre and postmenopausal women revealed that 75% had discussed low sexual desire with a doctor or therapist. Notably, 82% of these women had to initiate the conversation themselves. The study also identified reasons for not speaking to a doctor: 30% of women felt embarrassed, and 35% believed their low sexual desire was a normal aspect of aging (14). For effective diagnosis and treatment of HSDD, a biopsychosocial approach is advised, involving collaboration between mental health providers, sexual health experts, and physical therapists. A recent study highlighted challenges faced by healthcare professionals in addressing HSDD. It found that 40% of the women reported that were incorrectly diagnosed with depression or anxiety instead of HSDD. Furthermore, 18% experienced a delayed diagnosis because their doctors or therapists were unaware that HSDD is a recognized medical condition (14). The key objective is to conduct a thorough patient history to accurately diagnose HSDD subtypes and exclude reversible causes like depression, medication side effects, relationship problems, neurological disorders, and dyspareunia. Utilizing validated questionnaires is also beneficial in diagnosing HSDD (6). Brazilian cross-sectional study found a notable correlation between HSDD in postmenopausal women and the presence of metabolic syndrome. The study revealed that postmenopausal women with metabolic syndrome (N = 153) had significantly lower FSFI scores (desire, lubrification, orgasm, satisfaction), indicating a higher incidence of sexual dysfunction, compared to those without metabolic syndrome (N = 138) (19). Even with all studies that have been conducted on the theme a definitive pathophysiology of HSDD has yet to be discovered.

In the management and treatment of Hypoactive Sexual Desire Disorder (HSDD), nonpharmacological approaches are frequently recommended. These include the use of lubricants and moisturizers, psychotherapy, adjustments in diet or exercise, and the use of herbal or homeopathic products. Additionally, testosterone therapy has been found to be effective in treating postmenopausal women with HSDD. This approach addresses the hormonal aspect of HSDD, particularly in the postmenopausal phase where hormonal changes are a key factor (14, 20).

THE ANDROGEN FACTOR: UNDERSTANDING HORMONAL DECLINES IN MENOPAUSE

Androgens, a group of essential steroid hormones, play a significant role in human sexual development and reproductive functions, as well as influencing growth, body shape, and behavior. Produced primarily in the ovaries in women, androgens are released into the bloodstream, affecting target organs. Androgens are transported in the bloodstream mostly bound with sex hormone-binding globulin (SHBG) (66%) or albumins (33%), being not able to show any biological activity (21). They produce their biological effects primarily by activating androgen receptors (AR) and indirectly through their conversion to estrogen via the process of aromatization. These androgen receptors are found in various organs, such as the breasts, brain, ovaries, bones, muscles, fat tissue, liver, and skin. This wide distribution of receptors underscores the extensive role androgens play in several functions. They undergo metabolism in the liver and are eventually excreted through urine (22, 23).

According to Elzenaty et al. (2022), while testosterone is a major circulating androgen in men, women predominantly have classic androgens or pre-androgens like DHEA-S (dehydroepiandrosterone sulfate), DHEA (dehydroepiandrosterone), and androstenedione (24-26). Androgens like DHEAS, DHEA, and androstenedione, despite their abundance in circulation, act as pro-hormones. They require conversion into testosterone or DHT (dihydrotestosterone) to manifest their androgenic effects. Similarly, testosterone itself, needing conversion into estradiol (E2) or DHT to exert its biological effects, can also be considered a pro-hormone in both males and females (reviewed by Jayasena (2019)) (20). In women, the concentration of testosterone is significantly lower than estradiol, yet it plays a vital role in estrogen biosynthesis, particularly after menopause. Postmenopausal, as the ovaries cease estrogen production, the body converts testosterone and adrenal pre-androgens into estrogens in tissues outside the gonads, highlighting the connection of these hormonal pathways (9, 27).

The reduced levels of sex steroids have been shown to play an important role in deterioration of sexual response leading to a worse sexual function as menopause level increases (21). The production of androgens and their precursors in women is highest between the ages of 20 and 30. After that, their levels decrease by about 50% by the age of 40 and continue to drop by another 25% up to the age of 50. Beyond 50, the reduction in androgen levels continues but at a slower pace (28). Moreover, this hormonal decline leads to structural and functional changes in the genitourinary tract. Anatomical changes can be observed in the vulva, clitoris, vestibule, urethra, vagina, and bladder tissues (29).

HSDD, characterized by a persistent lack of sexual desire, is not attributable to any other medical issue, physiological change, or side effect of medication. In this population, HSDD can coexist with other conditions like hyperprolactinemia, hypopituitarism, adrenal insufficiency, and chemical ovarian suppression. These conditions might either exacerbate the effects of low androgen levels or directly contribute to the development of HSDD (21, 30). However, recent research has brought androgens back into focus as key regulators of women sexual health. Both preclinical and clinical studies consistently demonstrate that estrogens and androgens synergistically stimulate the female sexual response by interacting within a complex network of neurotransmitters that balance excitatory and inhibitory signals. Thus, the reduction of androgens can be taken as

risk for HSDD in postmenopausal women (11, 31). Sexual health issues are often not properly diagnosed or treated. There's a need for better education for both healthcare professionals and patients. Treatments should be personalized, taking into account symptom severity, impact on life quality, possible side effects, and individual preferences (11, 30).

TESTOSTERONE THERAPY: EVIDENCE FOR ITS ROLE IN ENHANCING SEXUAL HEALTH IN POSTMENOPAUSAL WOMEN

Testosterone plays a pivotal role in sexual differentiation of genitalia and the brain, and in the development of secondary sexual characteristics during puberty and adult life. It also influences sexual behavior and maintains the functional state of these characteristics in adulthood. Therapeutically, androgen therapy for women, which includes testosterone and DHEA, is often prescribed. Testosterone is administered in various forms like oral transdermal or implanted formulations, while DHEA is commonly used orally. Such therapies are significant in addressing hormonal imbalances, particularly in postmenopausal women (13, 25). The use of testosterone therapy for HSDD women is still controversial.

Among the various forms of testosterone administration (oral, gel, creams, intramuscular, sprays, and subdermal implants) oral and intramuscular formulations are not recommended due to potential side effects (9, 26). Consequently, these forms are not covered in this review. Instead, transdermal formulations like patches, gels, creams, and sprays are preferred and most widely used in women. Their popularity is due to the ease of administration and the ability to adjust dosages to match physiological hormone levels effectively (reviewed by Uloko et al. (2022))(6).

In a systematic review and meta-analysis encompassing seven studies on testosterone therapy in postmenopausal women with HSDD, it was found that those receiving testosterone patches had significantly more satisfying sexual episodes (SSE) than those on placebo, particularly in naturally postmenopausal women (MD, 1.30; 95% CI, 0.73, 1.87; P<.00001). Subgroup analysis showed similar improvements in SSE in women using testosterone patches, whether they were on estrogen plus progestogen hormone therapy (HT) or not. Additionally, pooling data from two studies revealed that the testosterone group experienced a significant increase in overall sexual activity compared to placebo (MD, 0.96; 95% CI, 0.51, 1.41; P<.0001). For those results the author included data only from one regimen in the analysis (300 mg of T, twice weekly). There was also homogeneity in the length of the treatment in all seven studies (24 weeks) (32). These findings support the efficacy of testosterone therapy in enhancing sexual function in postmenopausal women with HSDD.

Another systematic review pointed out several randomized, placebo-controlled clinical trials indicate that testosterone therapy notably enhances sexual function in postmenopausal women who have sexual dysfunction or HSDD. This improvement is consistently observed in assessments using validated questionnaires, underscoring the therapy's effectiveness in addressing sexual health issues in this population (20). Among the results reported by Jayasena et al. (2019) we can highlight some considering the use of testosterone patches (20). In menopausal women, two studies involved randomizing participants to either a placebo or a 300 μg/d testosterone patch for 24 weeks. Both studies observed a significant increase in satisfying sexual events (SSEs) in the group

receiving the testosterone patch compared to the placebo group (16, 33). Additionally, a placebo controlled trial study by Braunstein et al. (2005), which randomized 447 women to varying doses of testosterone (150, 300, or 450 μg) or a placebo, found that the group receiving the 300 μg dose experienced a significant increase in libido compared to those on the placebo (34). These findings collectively suggest that testosterone therapy can effectively improve sexual desire and overall sexual life in menopausal women. Another placebo-controlled, double-blind study involving 207 participants, compared the effects of a 300 μg testosterone patch against a placebo over 24 weeks. They found a notable increase in total satisfying sexual episodes – an average of 1.15 more per 4-week period in the group receiving the testosterone compared to placebo (48.7% vs. 27.3%, p= 0.0006) and sexual desire (55.1% vs. 32.8%, p= 0.0004) (35). The effectiveness of testosterone therapy in enhancing sexual function in menopausal women is further supported by various studies and positively impacts sexual desire; however, its long-term safety remains unproven (6, 20).

Hormone pellet implants function by forming a capillary network around them, allowing hormone absorption to be dependent on cardiac output (36). There are only two studies, reviewed by Parish et al. in 2021, that investigate the use of testosterone implants in treating sexual dysfunction(9). These studies compared the effects of combined estrogen and testosterone implants against estrogen-only implants. The findings demonstrated a positive impact on libido and overall sexual quality when testosterone was added (37, 38). Specifically, the addition of testosterone led to significantly greater improvements in sexual activity ($P < 0.03$), satisfaction ($P < 0.03$), pleasure ($P < 0.01$), orgasm ($P < 0.035$), and relevancy ($P < 0.05$) compared to estrogen alone (38). While testosterone implants have seen widespread use, they have limitations due to their potential to cause supraphysiological (higher than normal) hormone levels in the body. Additionally, these implants do not allow for adjusting or titrating the dosage. Due to these factors, testosterone implants are generally not recommended as a primary option for hormone treatment (9).

A double blind, randomized, crossover design study checked testosterone gel of 10mg in postmenopausal women as a complement to their ongoing hormonal replacement therapy. The results were positive effects on frequency of sexual activity, orgasm, arousal, fantasies and sexual interest. The authors highlighted an important increase in serum levels but no differences concerning adverse effects between groups and 10mg was considered a safe dose for percutaneous gel in this population (39, 40). In a controlled study, postmenopausal women experiencing low sexual function were divided into two groups. One group received a combination treatment of 50 mg transdermal testosterone gel weekly and 1 mg daily oral estradiol valerate, while the other group received only estrogen therapy for 8 weeks. Results showed that the group receiving the testosterone and estrogen combination had a significantly higher Female Sexual Function Index (FSFI) score, averaging 7.2 ± 5.5, compared to 4.6 ± 3.9 in the estrogen-only group ($p = 0.02$). Additionally, an increase in serum total testosterone levels was observed in the testosterone group, but no adverse effects were reported (41). Other studies were published reporting the effectiveness of testosterone cream formulations appear to be safe for use in postmenopausal women (42-45). Importantly, these formulations have been found to effectively enhance sexual function in postmenopausal women, addressing key aspects of sexual health during this phase of life.

TESTOSTERONE THERAPY IN HSDD: SAFETY AND MANAGEMENT

In 2019, The Global Consensus Position Statement on the Use of Testosterone Therapy for Women, a significant document in women's health, was published in four different journals. This statement was authored by representatives from ten different societies, including International Society for the Study of Women's Sexual Health (ISSWSH). The statement suggests that testosterone therapy, when administered in doses mirroring physiological levels found in premenopausal women, has been shown to positively impact sexual function. Also, endorses that testosterone therapy is allowed only for HSDD treatment and cannot be generalized for other sexual disfunctions and they pointed out that acne and body/facial hair growth in some women, clitoromegaly, or voice change can be some of the side effects of this therapy (46). It's crucial to note that there are no standardized methods for measuring testosterone levels in laboratories. The measurement of total and free testosterone is particularly unreliable within the female range (9, 46). This lack of reliable measurement poses limitations for the use of testosterone therapy, as it interferes in the accurate assessment of a patient's baseline hormone levels. Given the absence of standardized methods for measuring testosterone levels in the bloodstream, involves adopting an individualized dosing algorithm. This strategy focuses on tailoring the dosage to reduce clinical symptoms specific to the patient while ensuring that serum levels are maintained at a threshold low enough to minimize any potential androgenic side effects (36).

Recent studies on the safety of testosterone therapy in postmenopausal women have yielded mixed but insightful findings. Renke and Tostes (2023) emphasize the controversial nature of the cardiovascular safety of testosterone therapy, indicating a need for further research (47). Jayasena et al. (2019) reported improvements in sexual function and bone mineral density but caution against the unclear long-term safety profile (20). Similarly, Osborne (2013) and Abedi et al. (2023) highlight the uncertain safety landscape due to limited efficacy and safety data for testosterone treatment on HSDD condition(48, 49). Jiang et al. (2021) point out the higher incidence of side effects and elevated hormone levels compared to FDA-approved therapies (50). Somboonporn (2006) notes the benefits of improved sexual function and reduced triglyceride levels but warns of possible reductions in HDL cholesterol and other side effects(51). Davis and Braunstein (2012) provide a more reassuring view, citing low rates of cardiovascular events and breast cancer in clinical trials, though they stress the need for more long-term safety data (52). Lastly, Zeihen et al. (2019) remark on the limited evidence regarding the overall safety of this therapy (53). These diverse viewpoints underscore the complexity and need for caution in considering testosterone therapy for postmenopausal women, balancing potential benefits with acknowledged risks. Testosterone has proven to be effective for postmenopausal women experiencing low sexual desire that leads to distress. Non-oral routes of administration, such as transdermal application, are preferred due to their neutral impact on lipid profiles. However, the broader implications of testosterone therapy on aspects like individual wellbeing, musculoskeletal health, cognitive function, and its long-term safety remain areas that need further exploration. This gap in understanding calls for additional research to fully comprehend the comprehensive effects of testosterone therapy in postmenopausal women (54).

Testosterone preparations designed for

men are generally not recommended for women due to the high risk of adverse effects (16, 36). When administering testosterone therapy to women, it's essential to monitor serum testosterone levels closely to avoid overdosing. The Global consensus specifically recommends testosterone for treating HSDD in postmenopausal women. In cases where there are no approved female-specific formulations, off-label prescribing of male formulations may be acceptable, provided they maintain physiological female hormone levels. The need for testosterone treatments specifically formulated for women, including those targeting premenopausal physiological levels, is recognized. However, compounded "bioidentical" testosterone therapies are not recommended for HSDD due to insufficient evidence of efficacy and safety (46, 55). Parish et al. (2021) also suggests that if a suitable female formulation isn't available, using one-tenth of a standard male dose of 1% transdermal testosterone, approximately 300 mcg/day, can usually achieve the normal premenopausal physiological range (9).

LIMITATIONS: ACKNOWLEDGE THE LIMITATIONS OF YOUR REVIEW AND THE STUDIES INCLUDED

The review acknowledges several limitations. Firstly, the efficacy and long-term safety of testosterone therapy in postmenopausal women with HSDD are still under investigation, with mixed results from different studies. Secondly, the lack of standardized methods for measuring testosterone levels poses challenges in ensuring appropriate dosing and current analysis methods were not considered here. Thirdly, there is limited evidence on the safety of compounded "bioidentical" testosterone therapies. Lastly, the review is constrained by the availability and scope of the studies included, primarily from 2005 to 2024, which may not encompass the entire spectrum of research on the subject.

CONCLUSION

Testosterone therapy demonstrates potential in treating HSDD in postmenopausal women, improving sexual function and desire. However, long-term safety remains a concern, with studies showing varied results regarding cardiovascular health, cancer risks, and other side effects. The review underlines the need for individualized treatment approaches and careful monitoring of testosterone levels. Further research is essential to establish comprehensive safety profiles and to develop female-specific testosterone formulations for optimal therapeutic outcomes.

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