Review Article

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Review of the Literature on Different Aspects of Testosterone Therapy for Women

Amir Reza Abedi[1], Farzad Allameh[2]*, Sedighe Hosseini[3], Seyed Mohammad Ghahestani[4] and Niki Tadayon[5]

1. Department of Urology, Shohada-e-Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. Urology and Nephrology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
3. Department of Infertility and IVF, Taleghani Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
4. Pediatric Urology Ward, Children Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran
5. Department of Surgery, Shohada-e-Tajrish Hospital, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

*** Corresponding author**

Farzad Allameh, MD, MPH
Urology and Nephrology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Tel: +98 912 3885545
Email: farzadallame@gmail.com

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Abstract

Background: Testosterone is necessary for general well- being, mental and physical health. Testosterone level decreases with age. Women also benefit from testosterone therapy. Testosterone therapy improves mood, mental and physical health. Testosterone therapy mitigates risk of cardiovascular event and improves measures of body habitus and can be considered as an adjuvant therapy for weigh loss. Pre-treatment with testosterone seems promising to improve the success of In-vitro Fertilization (IVF) in patients with ovarian failure. Transdermal testosterone use by postmenopausal woman does not influence mammographic density leading to probable misdiagnoses. The only evidence-based indication for testosterone therapy for women is for the treatment of Hypoactive Sexual Desire Disorder (HSDD). No female testosterone product has been approved by national regulatory authority due to the lack of data concerning efficacy and safety of these preparations in women.

Keywords: Androgens, Health, Hormones, Testosterone, Women

Introduction

Testosterone is a crucial active hormone in the female (1,2). Nevertheless, testosterone level declines since the third decade of life (3). This decline of testosterone in the midlife leads to weight gain, bone density loss, depression and feeling tired and reduction of libido (4,5). Testosterone is necessary for maintaining energy and sense of wellbeing in the female gender (6). Androgens help women maintain a healthy body habitus (7). Women who take oral contraceptive pills for birth control in their twenties experience low testosterone and its earlier effects (8).

The effect of testosterone on blood vessel and blood flow can decrease risk of cardiovascular events in women (9). Low testosterone in women increases risk of cardiovascular events (10). Therefore, increasing testosterone level leads to improvement in general well-being, mood and sexual function (4,6). Testosterone is a vital part of every woman's healthcare plan, and it is important to maintain testosterone level as women age and hormones decline.

Materials and Methods

Review team searched the PUBMED, SCOPUS, MEDLINE, COCHRANE, and Google SCHOLAR databases from 2005 to 2020 using the following keywords in the title: female or women AND testosterone. 1761 articles were found. The initial search resulted in 68 articles reporting the role of testosterone therapy for women of which 52 articles were written in English and were published between 2005 to present. English papers were included exclusively. References from the included studies were manually retrieved to identify additional studies of interest.

Evidences

Testosterone physiology in women

In either sex, testosterone is important for general well-being and normal sexual function (7). Adrenal gland and ovaries in female produce one third of circulating testosterone, the remaining two-thirds arise from the peripheral metabolism of pre-hormones, including androstenedione and DHEA (Dehydroepiandrosterone) (11). Testosterone has a circadian rhythm in the female with higher level in the morning (12). Moreover, testosterone level surge was observed in the mid-cycle coincident with the LH surge in the ovulatory cycle (13). Apart from this mid-cycle testosterone peak, testosterone level is steady during luteal and follicular phase (14). During late reproductive age and the initial phase of anovulatory cycle, testosterone production was progressively decreased by the ovaries and adrenal glands (15). At this stage, peripheral production of testosterone is of paramount importance (15). During the menopause transition, the balance between estrogen and testosterone is negatively impacted which may engender a relative hyperandrogenic state (16).

Facts about testosterone in women

1. The circulating levels of Testosterone is higher in men than women, but testosterone is an important and active sex hormone throughout the female lifespan (1).
2. Androgen receptors are distributed all throughout the body in both genders, so testosterone is crucial for general wellbeing, sexual function and mental and physical health in both sexes (17,19).
3. Testosterone stimulates ovulation and increases fertility (20).
4. There is no compelling evidence that therapeutic dose of testosterone causes hoarseness in women. Developing hoarseness on testosterone therapy warrants standard workup (21).
5. There is no evidence showing that testosterone therapy causes hair loss in women. Some studies showed that women on testosterone therapy have scalp hair re-growth (22).
6. Testosterone has a protective effect on heart. In addition, it has a good effect on lean body mass, glucose and lipid metabolism in both sexes. Therefore, the adequate level of testosterone mitigates the risk of cardiovascular events (23,24).
7. Non-oral testosterone bypasses the liver so that it does not have adverse influence on liver or liver enzymes or clotting factors (1,25). Unlike oral contraceptive pills, it does not increase the risk of deep vein thrombosis or pulmonary emboli (1).
8. Although anabolic steroid causes aggressive behavior, it does not occur with testosterone therapy. Some studies showed that testosterone therapy decreases aggressive behavior and anxiety in women (26).
9. Testosterone is protective against breast cancer

Table 1. Testosterone preparation

Rout	Dose	Formulation
Transdermal gel	40-120 *mg* every day	Androgel Testim axiron
Nasal	11 *mg* 3 times a day	Natesto 5.5 *mg/pump*
Oral buccal	30 *mg* 2 times a day	Striant 30 *mg tablet*
Topical patches	2-6 *mg* every day	Androderm 2,4 *mg/patch*
Short acting injection	100 *mg* IM every week or 200 *mg* IM every two week	Enanthate 200 *mg/mL* Cypionate 100 or 200 *mg/mL*
Long acting injection	750 *mg* every 10 weeks	Aveed 750 *mg/mL*
Subcutaneous pellets	150-450 *mg* every 4 to 6 months	Testopel 75 *mg pellet*

(27,28). Moreover, transdermal testosterone use by postmenopausal woman does not influence mammographic density over 52 weeks (29).

The effect of testosterone on sexual function in women

There is compelling evidence that testosterone therapy is an effective treatment for Hypoactive Sexual Desire Disorder (HSDD) in women (30,31). The sexual satisfaction depends on many factors such as age, premenopausal status, body mass index, sexual activity, depression, testosterone level, pregnancy, relationship problems, medication, and others (32). In women, circulating testosterone level decreases with age which causes decreased sexual function during the menopause (15). The diagnosis of HSDD hinged on the symptom of reduced or loss of sexual desire for sexual activity, which caused clinically significant distress (33,34). Testosterone therapy has a good influence on sexual desire but the long-term safety of testosterone therapy has not been proven (35). Total testosterone level should not be considered as a marker to diagnose HSDD (5). The guideline recommends considering testosterone therapy for women with low sexual desire if Hormone Replacement Therapy (HRT) has been ineffective (5).

Testosterone therapy for women with Poor Ovarian Response (POR) undergoing In-vitro Fertilization (IVF)

Both men and women have a role in fertility (36). The rate of oocyte retrieval in the case of poor ovarian response will be low, thus the probability of IVF failure will be high. Testosterone therapy seems to improve the number of pre-antral and antral follicles (37,38), as well as boosting the expression of FSH receptors in granulosa cells and enhances the ovarian responsiveness to gonadotropins (39,41). Therefore, testosterone therapy can improve IVF results in POR patients.

Testosterone therapy and cardiovascular event

Low serum level of testosterone exposes patients to cardiovascular events and negatively influences vascular mortality and all-cause mortality (42,46). However, in some studies there is no relationship between testosterone level and coronary artery disease (47). On the other hand, there are reports that testosterone therapy may increase the risk of cardiovascular events in men (46). Testosterone therapy slightly decreases HDL and LDL cholesterol and improved insulin sensitivity but does not change fasting blood glucose or HBA1C (48,49). In summary, health care providers should share the risks and benefits of testosterone therapy before recommending testosterone therapy.

Testosterone and obesity

Testosterone and obesity are closely related (50). Low testosterone levels are correlated with central obesity and reduced lean body mass (51). Weight loss

can improve testosterone levels (50). Testosterone deficiency is correlated with impaired glucose control, reduced insulin sensitivity and dyslipidemia (52). Testosterone therapy has specific metabolic effect on muscle, fat and liver. Furthermore, patients' motivation is strongly influenced by testosterone therapy which allows them to participate in active life style programs (50). These effects benefit obese patients. The degree of these beneficial effects may be dependent on how long these patients are under treatment (51). Testosterone replacement can be considered as an effective adjunct treatment for weight management in obese women.

Testosterone and anxiety

The beneficial effects of testosterone therapy on anxiety disorders in male hypogonadism was shown (53), however, there are a few studies in women which demonstrated testosterone therapy significantly improved mood and psychological well-being (54). Moreover, it can improve symptoms of anxiety and major depressive disorder in women (53).

Available testosterone preparations

Table 1 shows characteristics of available testosterone preparation. Subcutaneous pellets (Testopel) are an FDA-approved form of testosterone replacement therapy for men (55). The pellets are implanted under the skin typically near hip area through a small incision in the office which slowly releases testosterone and provides the steady dose of testosterone. They are to be replaced every 3 to 6 months (56). The pellets are metabolized by body and do not need to be removed (55). It is important to note that testosterone preparations are formulated for men. Unfortunately, no female testosterone product has been approved by national regulatory authority due to lack of data concerning efficacy and safety of these preparations in women (1,5). Male formulations can be used in women carefully (5).

Conclusion

There are compelling evidences in favor of testosterone therapy in female but there is a pressing need for more research into testosterone therapy for women and development and licensing of products indicated specifically for women.

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Conflict of Interest

None.

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