Review

TRANSLATIONAL&PRACTICAL MEDICINE

DOI: 10.51271/JTPM-0002

J Transl Pract Med 2022; 1(2): 61-64

Effect of mesterolone on genitourinary system symptoms

Harun Düğeroğlu

Ordu University, Medical Faculty, Department of Internal Diseases, Ordu, Turkey

Cite this article as: Düğeroğlu H. Effect of mesterolone on genitourinary system symptoms. J Transl Pract Med 2022; 1(2): 61-64.

ABSTRACT

Androgen replacement therapy may bring varying impacts on genitourinary system symptoms. Despite being a popular molecule used in this therapy, mesterolone is an androgen preparation whose biological effects are not well elucidated. It also has significant advantages over other androgens; for example, it has no liver toxicity, does not aromatize with estrogen and suppress gonadotropins, and has an undetectable toxic dose. It binds to sex hormone binding globulin (SHBG) with high affinity, increasing free testosterone fractions and suppressing SHBG levels. It also exerts anti-estrogenic effects. It has been utilized for infertility as it increases the sperm count, revealing partial benefits. Yet, its impacts on the prostate, lipid profile, and metabolic parameters have not markedly been explored. It is expected to have a neutral effect on the prostate as it has a dihydrotestosterone (DHT)-like effect.

Keywords: Androgen replacement therapy, hypogonadism therapy, testosterone, prostate/drug effects

INTRODUCTION

Androgen replacement therapy may bring varying impacts on genitourinary system symptoms. Mesterolone in this therapy is a testosterone derivative that exerts an androgenic effect but does not inhibit the secretion of gonadotropins. It is taken orally at 50-100 mg per day. Despite being a popular molecule used in this therapy, mesterolone is an androgen preparation whose biological effects are not well elucidated. It also has significant advantages over other androgens; for example, it has no liver toxicity, does not aromatize with estrogen and suppress gonadotropins, and has an undetectable toxic dose. It binds to sex hormone binding globulin (SHBG) with high affinity, increasing free testosterone fractions and suppressing SHBG levels. It also exerts anti-estrogenic effects. It has been utilized for infertility as it increases the sperm count, revealing partial benefits. Yet, its impacts on the prostate, lipid profile, and metabolic parameters have not markedly been explored. It is expected to have a neutral effect on the prostate as it has a dihydrotestosterone (DHT)-like effect.

Biological Effects of Androgens

At different stages of life, androgenic hormones bring different impacts on the determination, formation, and preservation of the characteristics of the male sex. Appropriate differentiation of external genitalia and internal genital organs during fetal development and development of scrotum, epididymis, vas deferens, seminal vesicles, prostate, and penis, skeletal-muscle development, voice thickening, pubic-axillary hair growth, beard and mustache formation, body and extremity hair distribution, skin lubrication, increased acne, erythropoiesis, and bone mass, and behavioral changes in the puberty are biological and behavioral features that occur thanks to the impacts of androgenic hormones, particularly testosterone (1).

Testosterone Metabolism in an Aging Male

The knowledge of gonadal dysfunction and the subsequent decrease in androgen levels among males with aging is well-established today. Aging brings decreased testicular blood supply and the impaired response of Leydig cells to luteinizing hormone (LHRH). Hypothalamo-hypophyseal axis dysfunction leads to a loss in the oscillation frequencies and amplitudes of gonadotropins, and SHBG levels increase. The consequence is decreased total and bioavailable testosterone levels (2). This condition, called androgen deficiency in the aging male (ADAM), andropause, late-onset hypogonadism in aging men (LOH) and characterized by a tendency to a reduced total testosterone level particularly between the ages of 45-50, has recently become a popular subject. The

Corresponding Author: Harun Düğeroğlu, harun.dugeroglu@hotmail.com

Received: 21.03.2022 **Accepted:** 07.07.2022

International Society for the Study of the Aging Male (ISSAM) describes LOH as "a clinical and biochemical syndrome, characterized by a decrease in serum androgen levels with age, accompanied by decreased genomic susceptibility to androgens, leading to serious changes in quality of life and affecting more than one organ" (2).

Androgen Deficiency Symptoms

1. Decreased sexual desire and quality of erections, especially nocturnal erections
2. Behavioral changes, decreased intellectual capacity, fatigue, depression, and irritability
3. Decreased body mass, particularly muscle density and strength
4. Body hair reduction and skin changes
5. Decreased bone mineral density causing osteoporosis
6. Increase in visceral adipose tissue, obesity

Other Conditions Accompanying Hypogonadism with Aging

Endocrinal causes lie at the root of many health problems in older males. The incidence of hypogonadism, obesity, metabolic syndrome, and type 2 diabetes mellitus (DM) increases with aging. While obesity causes hypogonadism due to both increasing 5-α reductase activity and leading to dysregulation in the hypothalamic-pituitary axis, hyperinsulinemia due to insulin resistance adversely affects SHBG production. Previous research documented that low SHBG and free and total testosterone levels are associated with type 2 DM, abdominal obesity, insulin resistance, dyslipidemia, and metabolic syndrome among males (2). Psychiatric symptoms due to hypogonadism overlap depression symptoms; examples include reduced libido, fatigue, poor self-confidence, and irritability. Mood disorders, depression, and cognitive disorders are rather prevalent in older males with hypogonadism and metabolic syndrome. Various studies previously associated these disorders with testosterone deficiency (3). A prospective study found an increase in the frequency of depression among hypogonadal men during the 2-year follow-up period. While the 2-year prevalence of depression was 29% in men with a total testosterone level of < 150 ng/dL, it was 13% in those with a total testosterone level of 350 ng/dL and above (4).

Androgen Replacement Therapy in the Aging Male

The dramatic increase in life expectancy is significantly constrained by the intrinsic factors associated with aging and the resulting deterioration in health. Aging triggers some symptoms among males, particularly seen in hypogonadism, such as reduced libido and potency, bone loss, decreased muscle mass and strength, poor appetite, memory disorders, and psychological changes (4). On the other hand, it was clearly shown that there is a decrease in serum androgens in parallel with aging. The testosterone concentration drops by about 100 ng/dL per decade. Between the ages of 25 and 75, serum-free testosterone decreases by 50-60% from 430±100 pmol/l to 220±80 pmol/l (4).

It was suggested that bone fractures, a prominent cause of morbidity among older men, may also be associated with a decrease in testosterone. The incidence of hip fractures is 4-5/1000 in males over 65 years, while hypogonadism is reported in 20% of males with vertebral fractures (4). A plethora of reviews extensively discussed the clinical manifestations associated with hypogonadism in older men. The relevant data, thus, suggest that testosterone deficiency may account for the mentioned symptoms and that the symptoms can be delayed or prevented with testosterone replacement therapy. The literature on androgen replacement therapy (ART) in older hypogonadal males is reviewed below.

Optimal Androgen Replacement Therapy

An ideal hormone replacement therapy should i) create a physiological level of testosterone concentration in the blood (400 - 700 ng/dL in blood taken between 08:00 - 12:00); ii) be similar to the physiological rhythm of testosterone release, and iii) maintain normal DHT/testosterone and estradiol/testosterone ratios (5). In addition, its first metallization should occur out of the liver, and it should be cost-effective, not cause local irritation, not lead to environmental pollution, be stopped immediately in case of side effects, and allow confidentiality.

Impacts of Androgen Replacement Therapy on the Genitourinary System

The most significant discussion of ART focuses on its undesirable impacts on the prostate. A man with prostate cancer is not often recommended to undertake ART; thus, it needs to be eliminated before the therapy (5). In addition, PSA values should be continuously monitored during the treatment, and the possible activation of occult prostate cancer should be detected at an early stage.

A substantial body of research reported that testosterone replacement therapy in hypogonadal men does not increase the risk of prostate cancer development (5). Snyder et al. discovered no difference in either prostate cancer or urinary flow rates among older adult men that were followed for a long time using a scrotal testosterone patch (5). On the other hand, both surgery and castration with LHRH agonists or antiandrogens undoubtedly reduce the aggressiveness of metastatic prostate cancer, albeit temporarily. However, it does not mean that testosterone administration will always provoke prostate cancer. A study reported prostate cancer in a man who used high-dose testosterone in addition to other drugs

for bodybuilding but highlighted that it may not be appropriate only to attribute cancer development to testosterone rather than other drugs received for a long time (6).

A definite relationship between serum androgens and prostate cancer has not been demonstrated so far. The association between high testosterone concentration and increased prostate cancer risk is probably mediated by androgen receptors (6). The development of a genetic mutation causing subnormal C-A-G repeats in this receptor boosts transcriptional activity, which results in increased androgenic activity at the cellular level accompanied by an increased prevalence of prostate cancer (6). That is, the molecular structure of the androgen receptor seems more significant than the direct impact of testosterone on prostate cancer development. On the other hand, it should be noted that prolonged exposure of prostate cells to high circulating testosterone may facilitate the emergence of prostate cancer, even if the androgen receptors are genetically typical.

Prostate cancer bears both androgen-dependent and androgen-independent components and may enlarge and metastasize despite aggressive antiandrogen therapy. On the other hand, considering the increased risk of prostate cancer development in parallel with the age-related decrease in testosterone, it was previously suggested that androgens cause prostate cancer, not due to subsequent administration of testosterone but exposure to androgens since early life (6). Consistently, there is no conclusive evidence that testosterone therapy initiates the development of prostate cancer or stimulates existing cancer or that there is a relationship between endogenous testosterone level and benign prostatic hyperplasia (BPH) (7). Indeed, the incidence of prostate cancer increases at the same time in a man's life as when testosterone begins to decline. Accordingly, it was shown that elevated testosterone levels in young adults may be a preventative factor against the risk of prostate cancer (8).

DISCUSSION

An exact cut-off value for testosterone levels has not been reported yet; thus, controversy continues as to under which testosterone levels the symptoms of hypogonadism occur. In fact, this issue becomes even more complicated as not all individuals with low testosterone levels develop the symptoms.

The literature offers varying findings about the changes in age-dependent LHRH levels. Some studies reported that LHRH levels decrease with aging; such a decrease is attributed to the decline in Gonadotrophin releasing hormone (GnRH) with aging and the decreased LHRH response to it. It is argued that this decrease in LHRH response causes a decline in testosterone (9). Some others suggested that aging leads to an increase in LHRH levels, which was attributed to the decrease in the negative feedback effect of testosterone on LHRH due to testicular failure (10).

One may have somatic, psychological, and sexual complaints with aging, and these complaints may be encountered individually or together (11). Then, a standard form is needed to assess these symptoms. Contemporarily, the ISSAM widely recognizes the Aging Male's Symptoms Scale (AMS) to evaluate aging-related symptoms. It is uttered that this form may be helpful not only in assessing symptoms related to androgen deficiency but also in uncovering the impacts of these symptoms on quality of life and the effectiveness of ART (12).

CONCLUSION

Unlike other testosterone preparations, the use of mesterolone in hypogonadal male patients with low serum total testosterone and/or free testosterone levels and androgen deficiency-related complaints improves the symptoms of androgen deficiency on the one hand and reduces the complaints of prostatism and contributes to the quality of life on the other hand..

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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