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The Effect of Transdermal Testosterone Administration on Lower Urinary Tract Symptoms and Erectile Dysfunction: A Prospective, Randomized, Placebo-Controlled Trial

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Key Words
Testosterone • Treatment • Urinary tract

Abstract
Objective: This study aimed to evaluate the effects of transdermal testosterone administration on lower urinary tract symptoms (LUTS) and erectile dysfunction (ED). ***Materials and Method:*** Sixty-two male patients with Ageing Male Symptom Questionnaire (AMS-Q) scores over 27 and a total serum testosterone level below 350 ng/dl (12.1 nmol/l) who presented to our urology clinic with complaints of LUTS and ED, were enrolled in this study. Uroflowmetry and the International Prostate Symptom Scale were used to evaluate the severity of LUTS. The International Index of Erectile Function was used to detect the severity of ED. In addition, the AMS-Q was used to quantify the severity of hypogonadism. We randomly divided patients into 2 groups. Thirty-one patients in the first group had transdermal testosterone administered at a daily dose of 50 mg (a sachet of 5 g) on the skin for 3 months. In the second group, 31 patients had a placebo administered for 3 months. The scales were recompleted based on interviews and uroflowmetry was repeated during checks of the patients performed in the first and third months. ***Results:*** We detected a decrease in AMS-Q scores and an increase in maximum uroflow rate values and the International Index of Erectile Function scores in the first group compared with the placebo group. Although a decrease was detected in post-treatment International Prostate Symptom Scale scores in the first group, it was not regarded as statistically significant. ***Conclusion:*** This study revealed that testosterone replacement therapy is effective in improving LUTS and ED symptoms.

Introduction

Lower urinary tract symptoms (LUTS) are characterized as abnormal voiding sensations that occur with a frequency or severity that affects the quality of life. Common LUTS include urinary frequency, urgency, nocturia, intermittency, incomplete emptying, and weak stream [1, 2]. While the most common cause of LUTS in men aged over 40 is bladder outlet obstruction due to benign prostatic hyperplasia, urethral stricture, bladder dysfunction, psychogenic disorders, and drugs also may cause LUTS [3].

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Erectile dysfunction (ED) is defined as the inability to develop and maintain an erection during sexual activity [4]. Men with ED were shown to have lower testosterone levels compared with men who did not have ED [5]. Testosterone is necessary for the development, growth, and function of penile tissue [6]. Functions such as sexual behavior, libido, ejaculation, and spontaneous erection in adults are testosterone dependent.

Many studies showed a decline in androgen levels in aging men [7]. Different researchers have given different names to the testosterone decline in aging men, however, the generally accepted name is late onset hypogonadism (LOH) [8]. Testosterone decline has become a common problem in today's world where the elderly male population is increasing.

Although testosterone receptors have been shown to be intensely present in epithelial cells in urethra and bladder, and the effect of testosterone on the autonomic nervous system has been identified, revealing the direct effect of testosterone on LUTS, is not easy [9]. There are some causes not completely explained for the correlation between testosterone decline, ED, and LUTS in aging men, beyond being disorders observed in the same patient group [10]. This study aimed to evaluate the effects of transdermal testosterone administration on LUTS and ED in the aging male population, and to present a better understanding of the relationship between testosterone therapy and LUTS in accordance with objective data and clinical findings.

Materials and Methods

The study was designed as a prospective randomized clinical placebo-controlled trial during a period of 3 months at the Department of Urology, Faculty of Medicine, University of Baskent. Sixty-two male patients, aged between 24 and 76 years, with Ageing Male Symptom Questionnaire (AMS-Q) scores over 27 and a total serum testosterone level below 350 ng/dl (12.1 nmol/l) who presented to our urology clinic with complaints of LUTS and ED, were enrolled in this study. Exclusion criteria for this study included patients who had chronic diseases (diabetes, hyperlipidemia, hypertension, or cardiovascular disease), malignancy, psychiatric disorders, an abnormal digital rectal examination, and elevated serum prostate-specific antigen (PSA) levels higher than 4 ng/ml. The study was approved by our institutional ethical committee, and informed consent was sought from all patients. The uroflow rate test (uroflowmetry) and the International Prostate Symptom Scale (IPSS) were used to evaluate the severity of LUTS. The International Index of Erectile Function with 5 questions (IIEF-5) was used to detect the severity of ED. In addition, AMS-Q was used to quantify the severity of hypogonadism in aging men. The patients were randomly divided into 2 groups. Thirty-one patients in the first group had transdermal testosterone administered at a daily dose of 50 mg (a sachet of 5 g) on the skin for 3 months. In the second group 31 patients had a placebo administered for 3 months. During checks of the patients performed in the first and third months, the scales used for the pre-treatment evaluation were recompleted based on interviews, serum total testosterone and PSA values were measured, and maximum flow rates (Qmax) were measured by repeated uroflowmetry.

Univariate and multivariate analyses were applied for the statistics. We compared initial, first, and third month visit scales by using the Kruskal-Wallis test and post-hoc Dunn's test. The Student's *t*-test and chi-square test were used for analyses of continuous variables. Data analysis was performed using the Statistical Package for the Social Science (SPSS Inc, Chicago, Illinois, USA) version 17.0 program and $p < 0.05$ was considered as significant.

Table 1. Mean pretreatment values of patients demographics data

Variable	First group	Second group	p
Age, year	57.6 ± 15.8	61.7 ± 11.7	0.94
BMI, kg/m^2	29.2 ± 4.8	29.1 ± 6.4	0.92
PSA, ng/dl	2.1 ± 0.7	1.9 ± 0.8	0.88
Testosterone			0.54
ng/dl	275.5 ± 59.9	267.3 ± 43.5	
nmol/l	9.6 ± 2.0	9.3 ± 1.5	
AMS-Q	52.1 ± 14.5	60 ± 11.8	0.76
IIEF	15 ± 5	12.7 ± 4.6	0.76
IPSS	16.5 ± 8.5	15.9 ± 7.08	0.86
Qmax, ml/s	16.4 ± 8.8	16.2 ± 8.2	0.96

BMI = Body mass index.

Results

Sixty-two patients with a mean age of 59.6 ± 14 years were included in the study. The average age in the first group was 57.6 ± 15 years, and the average age in the second (placebo) group was 61.7 ± 11 years. The mean total testosterone level of both groups was 271.4 ± 52 ng/dl (9.4 ± 1.8 nmol/l). This value was 275.5 ± 59 ng/dl (9.6 ± 2.0 nmol/l) in the first group and was 267.3 ± 43 ng/dl (9.3 ± 1.5 nmol/l) in the second (placebo) group (table 1). There was a significant negative correlation between the age and testosterone level.

We found that the mean pre-treatment score of IPSS was 16.5 ± 8. The mean post-treatment score was 15.7 ± 7 in the first group, while in the second (placebo) group, the mean pre-treatment score of IPSS was 15.9 ± 7 and the mean post-treatment score was 17.8 ± 8. Although

a decrease was detected in post-treatment IPSS scores in the first group, it was not statistically significant (p = 0.206) (table 2).

A significant positive correlation between age and pre-treatment Ageing Male Symptom (AMS) scores was observed (p < 0.001). The mean pre-treatment score was 52.1 ± 14. The mean post-treatment score was 37.4 ± 11 in the first group, while in the second (placebo) group, the mean pre-treatment score was 60 ± 11 and the mean post-treatment score was 60.09 ± 11 (table 2). There was a statistically significant decrease in AMS levels in the first group compared with the second (placebo) group (p = 0.001).

A significant negative correlation between the age and the pre-treatment IIEF scores was observed (p < 0.001). There was a significant increase in IIEF scores in the first group compared with the second (placebo) group (p < 0.001) (table 2).

Uroflowmetric evaluation was performed by measuring the Qmax. There was a statistically significant increase in the Qmax parameter in the first group compared with the second (placebo) group (p = 0.019) (table 2).

There was no statistically significantly difference on PSA values between the first and second groups in the first and third months control (p = 0.786) (table 2).

Table 2. Data, means, and p values of groups before treatment, and in the first and third months of treatment

Variable	n	Mean ± SD	p
IPSS (0)			0.206
First group	31	16.5 ± 8.5	
Placebo group	31	15.9 ± 7.08	
IPSS (1st)			
First group	31	16.0 ± 7.4	
Placebo group	31	16.8 ± 7.72	
IPSS (3rd)			
First group	31	15.7 ± 7.6	
Placebo group	31	17.8 ± 8.3	
Qmax, ml/s (0)			0.019
First group	31	16.4 ± 8.84	
Placebo group	31	16.2 ± 8.2	
Qmax, ml/s (1st)			
First group	31	17.7 ± 9.25	
Placebo group	31	15.4 ± 7.54	
Qmax, ml/s (3rd)			
First group	31	18.4 ± 9.29	
Placebo group	31	13.7 ± 8.27	
AMS-Q (0)			< 0.001
First group	31	52.1 ± 14.5	
Placebo group	31	60 ± 11.8	
AMS-Q (1st)			
First group	31	42.1 ± 12.7	
Placebo group	31	60 ± 11.9	
AMS-Q (3rd)			
First group	31	37.4 ± 11.2	
Placebo group	31	60 ± 11.7	
IIEF-5 (0)			< 0.001
First group	31	15 ± 5	
Placebo group	31	12.7 ± 4.64	
IIEF-5 (1st)			
First group	31	18.5 ± 4.4	
Placebo group	31	12 ± 4.57	
IIEF-5 (3rd)			
First group	31	19.6±4.18	
Placebo group	31	12 ± 4.71	
PSA, ng/dl (0)			0.786
First group	31	2.1 ± 0.7	
Placebo group	31	1.9 ± 0.8	
PSA, ng/dl (1st)			
First group	31	2.2 ± 0.5	
Placebo group	31	2.1 ± 0.7	
PSA, ng/dl (3rd)			
First group	31	1.9 ± 0.7	
Placebo group	31	2.1 ± 0.9	

Discussion

Androgen deficiency in aging men has been a frequently emphasized issue for a long time. Demographical data show that the human population is getting older. LOH is a clinical and biochemical syndrome associated with advancing age and characterized by symptoms and a deficiency in serum testosterone levels. It may result in significant detriment in the quality of life and adversely affect the function of multiple organ systems. Many studies showed that serum testosterone levels decrease with aging and there is a high rate of men who are aged over 60 years and have testosterone levels below the lower limits [11]. Reduction in testosterone with aging was described for the first time by Hollander et al. [12] during the determination of testosterone levels in spermatic vein blood. Kaufman et al. [13] found that testosterone levels started to decrease after the age of 31 and continued to decrease. In our study, there was a significant negative correlation between age and testosterone values consistent with the literature.

Clinical and biochemical diagnosis of LOH should certainly be made. There are multiple questionnaires developed for clinical diagnosis. The AMS questionnaire was used in our study. T'Sjoen et al. [14] reported that there was not any significant correlation between AMS scores and testosterone levels in a study performed on men aged over 70 years. Contrary to that, a significant

negative correlation was found between testosterone levels and AMS scores in our study. Yoshiji et al. [15] reported that there was not any statistically significant correlation between AMS-Q scores and age. Based on our study, a statistically significant decrease in AMS levels was observed in the testosterone administration group compared with the placebo group. As a result of this correlation, our study also indicated that AMS-Q including questions about somatic, psychological, and sexual complaints in aging men are a critical indicator for clinical diagnosis.

Although a lot of studies that investigated the correlation between benign prostatic hyperplasia and androgens are available, the number of the studies aimed at revealing the interaction between testosterone deficiency and LUTS is limited [16]. A study by Schatzl et al. [17] showed that 1 of every 5 men with LUTS had testosterone deficiency. On the other hand, Litman et al. [18] found a correlation between LUTS and plasma testosterone levels, but that result disappeared after statistical age classification. Holmang et al. [19] reported that there were increases in Qmax parameters of a group of men administered with testosterone in their placebo-controlled study. There are other studies supporting this research in the literature. Consistent with the literature, we found a statistically significant increase in Qmax parameter in the testosterone administration group compared with the placebo group.

Studies investigating the testosterone forms that provide positive changes in LUTS and how much time passes until the changes occur, have contradictory results. It was reported in a study that parenteral testosterone undecanoate provides higher testosterone levels and lower IPSS compared to testosterone gel [20]. We used testosterone gel in our study and detected a decrease in post-treatment IPSS scores in the testosterone administration group, but it was not a statistically significant decrease. The fact that the sensitivity of IPSS used in the LUTS evaluation was below 100% was considered as the reason for this. This result shows that evaluations performed on the basis of objective uroflowmetric parameters are not always supported by subjective scales such as IPSS.

There is ample evidence from many epidemiological studies that LUTS and ED are strongly linked, independently of age and comorbidities such as hypertension, diabetes, dyslipidemia, or coronary heart disease. However, a causal link between both conditions has not yet been established. In the study performed by Shiri et al. [21] 1,683 patients with moderate ED, severe ED, and without ED were followed-up for 5 years. The development of LUTS in patients with severe ED was 2.3 times that of patients without ED and it was stated that the development of ED and LUTS could be dependent on the same pathophysiological mechanism. Our findings confirmed that testosterone administration positively affects ED and LUTS.

Our study has 2 major limitations. First, the treatment period duration was only 3 months and therefore, the long-term outcome is unknown. The second major limitation of this study was the small number of patients enrolled the study and this limitation greatly affected the interpretation of testosterone effectiveness. A larger pool of patients will provide a more accurate picture.

Conclusion

This study revealed that testosterone replacement therapy is effective in improving the LUTS and ED symptoms. This therapy could become a standard treatment for aged patients who have LUTS and ED in the near future. However, further studies with larger study groups are required.

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