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DYNAMICS OF PROSTATE-SPECIFIC ANTIGEN LEVELS DURING TREATMENT WITH TESTOSTERONE UNDECANOATE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Rucsandra Dănciulescu Miulescu [1,2,✉], ***Suzana Dănoiu*** [3], ***Denisa Margină*** [1], ***Sorin Păun*** [1,4], ***Cătălina Poiană*** [1,5]

[1] Carol Davila University of Medicine and Pharmacy, Bucharest
[2] "N.C.Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases Bucharest
[3] University of Medicine and Pharmacy of Craiova
[4] Floreasca Emergency Hospital, Bucharest
[5] "C.I.Parhon" National Institute of Endocrinology, Bucharest

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Abstract

Objectives. *Prostate-specific antigen (PSA) is the most used and validated marker of prostate cancer risk. The aim of this study was to assess PSA levels during treatment with testosteronum undecanoat in patients with type 2 diabetes (T2DM).* ***Material and Methods****. We evaluated 38 T2DM patients aged between 48 and 61 years with confirmed hypogonadism. 1000 mg testosterone undecanoate was injected intramuscular every 10 to 14 weeks. Total testosterone and PSA levels were assessed at baseline and after 6, 12, 24 months of treatment.* ***Results.*** *The average age was 55.03 ± 2.40 years and 3 patients (7.89%) had a family history of prostate cancer. Treatment with testosterone undecanoate generated significant changes in serum total testosterone (482.29±50.78 ng/dl vs. 246.66±51.50 ng/dl, p < 0.001) but not in serum PSA levels (2.11±.0.49 ng/ml vs. 2.09±0.47 ng/ml, p - NS).* ***Conclusion.*** *Testosterone replacement therapy may normalize serum androgen levels but appears to have little effect on PSA levels.*

key words: *prostate-specific antigen, diabetes mellitus, testosterone replacement therapy, risk factors*

Introduction

Prostate-specific antigen (PSA) is a member of the kallikrein-related peptidase family and is secreted by the epithelial cells of the prostate gland. PSA is the most used and validated marker of prostate cancer risk [1].

The normal development of the prostate is dependent on androgens acting through the androgen receptor while androgen receptor is important in the initiation, promotion, and

✉ 5-7 Ion Movila Street, Bucharest, District 2, Postal Code 11420; Tel: 0040748134500; fax: 004021/2105575; *corresponding author e-mail*: rucsandra_m@yahoo.com

progression of prostate cancer [2]. Androgen receptor activity is regulated by its 2 major ligands: testosterone and dihydrotestosterone. Androgen hormones play a role in prostate carcinogenesis by altering the balance between cell proliferation and apoptosis. Within the prostate, androgens are capable of both stimulating proliferation as well as inhibiting the rate of the glandular epithelial cell death [3,4]. Some studies showed that prolonged administration of testosterone generates prostate tumors in rodents [5], and androgens enhance the growth of several human prostate cancer cell lines [6].

Numerous studies found that men with diabetes have lower testosterone levels compared to men without a history of diabetes, and low testosterone is now recognised as an independent risk factor for obesity, metabolic syndrome, and type 2 diabetes (T2DM) [7,8]. Several observations indicated an association between testosterone replacement therapy and the risk of prostate cancer [9,10] but a definite correlation has not been shown between adjusted testosterone levels in hypogonadal men and the initiation and/or acceleration of latent prostate cancer. Androgens have been implicated in prostate tumorigenesis, although circulating testosterone levels have not been found to be consistently associated with prostate cancer incidence [11]. Intra-prostatic androgen status may be more important than circulating levels in determining risk of prostate cancer [12].

The aim of this study was to assess the PSA levels during treatment with testosteronum undecanoate in patients with T2DM.

Materials and Methods

We evaluated 38 T2DM patients aged between 48 and 61 years with confirmed hypogonadism. The diagnosis of hypogonadism was based on the presence of suggestive symptoms and signs of testosterone deficiency (low libido, erectile dysfunction, decreased muscle mass and strength) and hormonal determinations. The most widely accepted parameters to establish the presence of hypogonadism is the measurement of serum total testosterone. Total testosterone levels higher than 500 ng/dl do not require substitution; patients with serum total testosterone levels below 300 ng/dl will usually benefit from testosterone replacement therapy. Low testosterone levels were confirmed by two separate blood testosterone measurements. Prior to testosterone initiation, all patients were screened with a questionnaire detailing their prostatic cancer family history. In addition, detailed examinations were performed in order to exclude a risk of pre-existing prostatic cancer, benign and malignant liver tumours, severe cardiac, hepatic or renal insufficiency or ischemic heart disease. Regular monitoring of the PSA, haemoglobin, haematocrit, and liver function tests was performed. 1000 mg testosterone undecanoate was injected intramuscular every 10 to 14 weeks. Serum testosterone levels have been measured before the start and periodically during the initiation phase of the treatment. Depending on serum testosterone levels and clinical symptoms, the interval between the first testosterone injections has been reduced to a minimum of 6 weeks as compared to the recommended range of 10 to 14 weeks in cases of inadequate response to treatment. In cases of high serum testosterone

levels, an extension of the injection interval was taken into account. Total testosterone and PSA levels were assessed at baseline and after 6, 12 and 24 months of treatment.

Statistical analyses

Data are presented as mean ± SD. Clinical characteristics were compared using the t Student Test. Pearson's moment-product correlation coefficients were calculated to evaluate correlations between variables. Significance was defined at the 0.05 level of confidence. All calculations were performed using the Statistical Package for Social Sciences Software (SPSS) version 15.

Results

The average age of the participants was 55.03 ± 2.40 years. 3 patients (7.89%) had a family history of prostate cancer.

Total testosterone and PSA levels at baseline and after 6, 12 and 24 months of testosterone treatment are given in Table 1. As shown, treatment with testosterone undecanoate generated significant changes in serum total testosterone (482.29±50.78 ng/dl at 24 months *vs* 246.66±51.50 ng/dl at baseline, $p < 0.001$), but not in serum PSA levels (2.11±0.49 ng/ml at 24 months *vs* 2.09±0.47 ng/ml at baseline, p-NS). Changes in serum total testosterone and PSA levels during treatment with testosterone undecanoate are shown in Figure 1 and 2.

Changes in haemoglobin and hematocrit were not significant in terms of dropping or modifying testosterone undecanoate therapy and liver status was maintained. These results are the subject of another article to be published.

Table 1. Characteristics of patients during treatment with testosterone undecanoate.

	Baseline	6 months	p *vs* baseline	12 months	p *vs* baseline	24 months	p *vs* baseline
Total testosterone levels (ng/dl)	246.66±51.50	310.76±54.81	p<0.001	407.29±65.15	p<0.001	482.29±50.78	p<0.001
PSA levels (ng/ml)	2.09±0.47	2.14±0.48	0.074	2.13±0.48	0.422	2.11±0.49	0.264

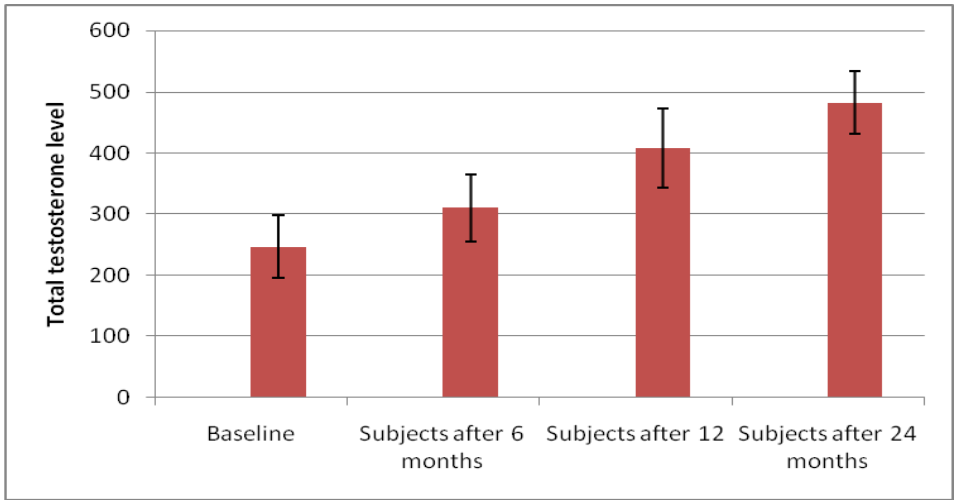

Figure 1. Changes in serum total testosterone levels during treatment with testosterone undecanoate.

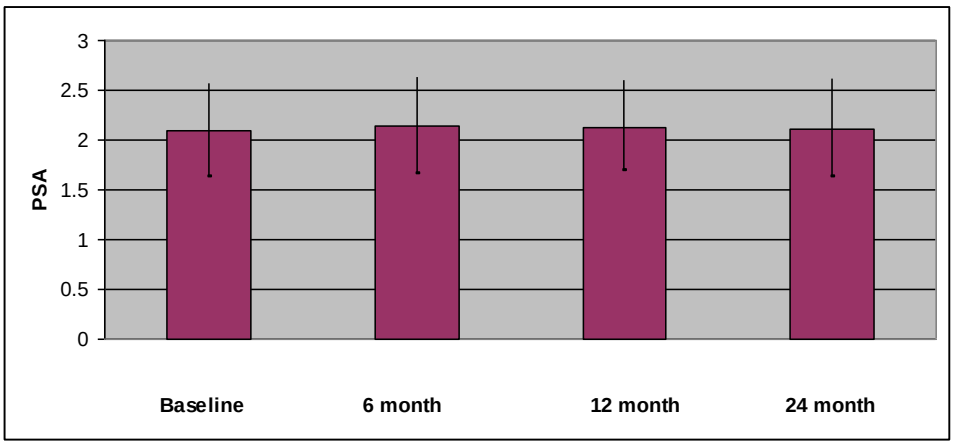

Figure 2. Changes s in serum PSA levels during treatment with testosterone undecanoate.

Discussion

Hypogonadism is a condition in which low levels of serum testosterone are found in association with suggestive signs and symptoms such as low libido, erectile dysfunction, and decreased muscle mass and strength. Type 2 diabetes is associated with lower total testosterone levels in cross-sectional studies. It is not known whether the defect is primary or secondary [13]. In 2011, Paresh Dandona and Sandeep Dhindsa published in the *Journal of Clinical Endocrinology and Metabolism* a clinical review about the Hypogonadotropic Hypogonadism in Type 2 Diabetes and Obesity. In this review, the authors state that: "*Studies over the last few years have clearly established that at least 25% of men with type 2 diabetes have subnormal free testosterone concentrations in association with inappropriately low luteinizing hormone (LH) and follicle-stimulating hormone concentrations (FSH). Another 4% have subnormal testosterone concentrations with elevated LH and FSH concentrations. The Endocrine Society, therefore, now recommends the measurement of testosterone in patients with type 2 diabetes on a routine basis. The subnormal testosterone concentrations are not related to glycosylated hemoglobin or duration of diabetes, but are associated with obesity, very high C-reactive protein concentrations, and mild anemia. In addition, subnormal testosterone concentrations in these men are associated with a two to three times elevated risk of cardiovascular events and death in two early studies. The Endocrine Society recommends that men with low testosterone and symptoms of androgen deficiency be considered for therapy with testosterone. The guidelines do not recommend treatment of asymptomatic men with low testosterone. Trials of a longer duration are clearly required to definitively establish the benefits and risks of testosterone replacement in patients with type 2 diabetes and low testosterone*" [14].

Nazem Bassil *et al* published in 2009 in *Therapeutics and Clinical Risk Management* a clinical review about the benefits and risks of testosterone replacement therapy. In this review the authors recommend: "*Testosterone levels should be monitored 3 months after initiation of testosterone therapy. A mid-morning total serum testosterone level should be obtained. A target range of 400 to 500*

ng/dl (14.0 to 17.5 nmol/) for older men is suggested. However, if there is no symptomatic response, higher levels may be necessary" [15].

In our study, treatment with testosterone undecanoate generated significant changes in serum total testosterone (482.29±50.78 ng/dl *vs* 246.66±51.50 ng/dl, p < 0.001). Restoring serum testosterone levels to the normal range using testosterone replacement therapy was found in 21 patients (55.26%). In comparison, Moisey R *et al* reported that total testosterone increased by 50% after treatment with testosterone undecanoate and 75% of evaluated subjects (51 patients) had a total testosterone within the reference range after 18 weeks of treatment [16]. Testosterone replacement therapy may normalize serum androgen levels but appears to have little effect on prostate tissue. Our data confirm clinical experience that treatment with testosterone undecanoate does not generate significant changes in serum PSA levels. Thus, in the current study PSA levels after 24 weeks of treatment (2.11±0.49 ng/ml) were not significantly different compared to the baseline values (2.09±0.47 ng/ml, p NS). At the present time, there is no conclusive evidence that testosterone therapy increases the risk of prostate cancer [17-20].

Despite the theoretical dangers of treating hypogonadal men with testosterone therapy, there are relatively few studies that evaluate the long-term safety of this treatment. A study performed by Rhoden and Morgentaler analysed 75 hypogonadal men (with and without high grade prostatic intraepithelial neoplasia) during 12 months of testosterone replacement therapy. They found that men with prostatic intraepithelial neoplasia do not have a greater increase in PSA or a significantly increased risk of cancer than men without this affection [21]. Douglas *et al* studied the effect of exogenous testosterone administration on the serum levels of PSA and prostate-specific membrane antigen in 10 hypogonadal men. The study suggested that in hypogonadal men, neither prostate-specific membrane antigen nor PSA expression is testosterone-dependent [22]. In another study Gooren found no cases of prostate cancer in 33 men aged 15-62 years treated with oral testosterone undecanoate for a minimum of 10 years. They also found no significant change in PSA levels during testosterone treatment, and no patient required prostate biopsy [23].

However, for safety reasons, a man receiving testosterone treatment should undergo prostate biopsy if PSA rises above 4.0 ng/ml or if it increases either by more than 1.5 ng/ml/year or by more than 0.75 ng/ml/year over 2 years or if PSA rises by more than 1.0 ng/ml in the first 6 months of treatment or by more than 0.4 ng/ml/year thereafter [24,25].

Conclusion

Treatment with testosterone undecanoate generates significant changes in serum total testosterone. We succeeded in restoring serum testosterone levels to the normal range using testosterone replacement therapy in 21 patients (55.26%).

In our study treatment with testosterone undecanoate has not generated significant changes in serum PSA levels. However, establishing the benefits and risks of prolonged exposure to testosterone in patients with T2DM and low testosterone requires further investigation.

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