Journal of Medical and Biomedical Discoveries

Yassin A, et al. J Med Biomed Discoveries 7: 136.

www.doi.org/10.29011/2688-8718.100036

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Review Article

Testosterone Treatment Outcomes with Topical Gel versus Injectable Testosterone Undecamoate on Metabolic Syndrome and Sexual Function

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Citation: Yassin A, Kamkoum H, Alzubaidi RT, Abdallah H, Albaba B, Al Ansari A. (2025) Testosterone Treatment Outcomes with Topical Gel versus Injectable Testosterone Undecamoate on Metabolic Syndrome and Sexual Function. J Med Biomed Discoveries 7: 136. DOI: https://doi.org/10.29011/2688-8718.100136

Received Date: 21 March, 2025; **Accepted Date:** 01 April, 2025; **Published Date:** 04 April, 2025

Abstract

The objective of this study was to observe the dose response effects of testosterone (T) treatment on symptoms of sexual dysfunction and the metabolic syndrome. Two cohorts of elderly men with late-onset hypogonadism were followed over 9 months.

Group 1, consisting of 28 men (mean age, 61 years; mean T level, 2.07+- 0.50 ng/mL), received long-acting T undecanoate (TU; 1000 mg); Group 2, composed of 27 men (mean age, 60 years; mean T level, 2.24 +- 0.41 ng/mL), received T gel (50 mg/day) for 9 months. In patients treated with T gel, plasma T levels rose from 2.24 +- 0.41 to 2.95 +- 0.52 (statistically significant) at 3 months, 3.49 +- 0.89 (statistically significant) at 6 months, and 3.80 +- 0.73 ng/mL at 9 months (T level at 6 months was compared with T level at 3 months). With TU, plasma T levels rose from 2.08 +- 0.56 to 4.81+- 0.83 (statistically significant) at 3 months, 5.29 +- 0.91 at 6 months, and 5.40 6 0.77 ng/mL at 9 months. With TU, the plasma T levels were statistically higher than with T gel with TU, there was a greater improvement in sexual symptoms and in symptoms of the metabolic syndrome. with both treatments, changes in waist circumference correlated with changes in total, low density, and high-density lipoprotein cholesterol. Parameters of safety were not different between the 2 treatments. T administration had a beneficial effect on sexual dysfunction and symptoms of the metabolic syndrome in elderly men. The higher plasma levels of T generated with TU than with T gel were clearly more effective, indicating that there is a T dose-effect relationship.

Keywords: International index of erectile function, Waist circumference, Lipids, Sex hormone–binding globulin, Prostate safety, Hematocrit

Introduction

The goal of androgen treatment is to replicate the physiologic actions of endogenous testosterone (T), usually for the remainder of the patient's life. This requires rectifying the deficit and maintaining androgenic/ anabolic effects on bone, muscle, blood-forming marrow, other androgen-responsive tissues, and sexual function [1]. The criteria for efficacious androgen treatment require that plasma T levels are in the normal range for the full 24 hours of the day during the interval between 2 administrations [2]. The normal range of plasma T levels in eugonadal men is very wide between 3.0 and 8.6 ng/mL or 10 to 35 nmol/L in most laboratories. It is becoming increasingly clear that the thresholds for androgen actions vary for the various androgen-dependent biologic functions and that these thresholds differ among men [3,4].

In this study, we analyzed the impact of 2 androgen treatment modalities, T gel and long-term parenteral T undecanoate (TU), in androgen-deficient men with "late-onset hypogonadism." The value of these 2 treatment modalities of T has been well documented [5-7]. These 2 treatment modalities, although meeting the requirement to restore plasma T levels to within reference values, generate different patterns and magnitudes of changes in plasma T levels [2]. The men participating in this study complained of sexual dysfunction. There is increasing evidence that sexual dysfunction in elderly men is associated with the metabolic syndrome [8-12] of which the key elements are visceral obesity, hypertension, insulin resistance and dyslipidemia [13-15].

The metabolic syndrome, in turn, is associated with lower than normal plasma T levels [14,16,17], and low plasma T levels predict the metabolic syndrome (Laaksonen et al, 2004 [17-19]. Therefore, the impact that these 2 treatment regimens had on sexual dysfunction, symptoms of the metabolic syndrome, and parameters of safety of T administration were analyzed.

Patients and Methods

The men in this study had sought consultation for sexual dysfunction. They were recruited at a single center. Inclusion were plasma T levels below the lower limit of normal (3.4–8.6 ng/mL) and the ability to come to the center for 3 monthly visits. Exclusion criteria were prostate carcinoma, elevated plasma levels of prostate-specific antigen (PSA 4 mg/L), and comorbid diseases such as terminal cardiac disease, severe diabetes mellitus, and serious renal or hepatic disease which might be aggravated by T administration. All subjects gave their informed consent to the study, which was approved by the institute's ethical review board. This prospective study analyzed the dose-response effects of 2 treatment modalities of T: T gel (Testogel; Bayer Schering, Berlin, Germany) and TU (Nebido; Bayer Schering, Berlin, Germany). Pharmacokinetic profiles of these 2 modalities have been extensively studied. T gel was a daily application [20], and the first 2 injections of 1000 mg each of TU [4,20] were administered with an interval of 6 weeks (loading dose) followed by injections every 12 weeks. The total observation period was 9 months for each treatment modality.

Two cohorts of elderly men with late-onset hypogonadism were studied. Group 1 (n 28; mean age, 61 years; mean T level, 2.07 +- 0.05 ng/mL) was treated for 9 months with long acting TU (1000 mg at weeks 0 and 6 and thereafter every 12 weeks). Group 2 (n 27; mean age, 60 years; mean T level, 2.24 +- 0.41 ng/mL) was treated with T gel (50 mg/day). Throughout this observation period, there were no dose adaptations. Many of these patients were suffering from the metabolic syndrome, cardiovascular disease, and/or type 2 diabetes mellitus, for which most received drug treatment. There were no statistically significant differences in baseline variables between the 2 groups except that weight was higher in the group receiving T gel. Whether patients received treatment with T gel or TU was their own preference. Patients were examined every 3 months.

The follow-up period was 9 months. At baseline and every 3 months, the following variables were assessed (for treatment with TU, measurements were taken before the next injection was due): plasma T levels, sex hormone–binding globulin (SHBG), international index of erectile function (IIEF) score, aging male scale (AMS) score, waist circumference (which is now viewed as a pivotal index of the metabolic syndrome), systolic/diastolic blood pressure, and levels of plasma total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein(HDL), and triglycerides. The following safety parameters were assessed: plasma PSA, international prostate symptoms score (IPSS), blood glucose levels, haemoglobin A1c levels, haemoglobin and haematocrit levels, and tests of liver functions (levels of serum bilirubin, c-glutamyl transpeptidase [cGT], serum glutamic oxaloacetic transaminase [SGOT], and serum glutamic pyruvic transaminase [SGPT]). Plasma T levels were measured with immunoassays (Architect intra-assay; Abbott Diagnostics, Abbott Park, Ill); variation was 3.4% and intraassay variation was 5.1%. Plasma SHBG levels were measured with Immulite 2000 chemilumin essence immunochemical assay (Siemens Medical Solutions Diagnostics, Tarrytown, NY); intra-assay variation was 2.5% and intraassay variation 4.2%.

Statistical Analysis

Data were analysed by descriptive statistical methods using SAS version 6.12 (SAS Institute Inc, Cary, NC). The Wilcoxon rank sum test was used to compare the 2 groups at baseline. Treatment-induced changes in the parameters of interest were analysed for

each group using the Wilcoxon signed rank test. All results are presented as means 6 SD. Changes in waist circumference were correlated to changes in plasma total cholesterol, LDL, HDL, and triglycerides with Pearson's correlation test.

Results

The only significant differences between the 2 groups were higher body weights and better IIEF scores in the group receiving T gel. Other variables were not significantly different. Plasma T levels in both cohorts were measured every 3 months and showed values significantly above baseline levels. However, during treatment plasma T levels were significantly higher with TU than with T gel at each measuring point. Plasma SHBG levels fell significantly over the 9-month study period with T gel, but they rose slightly but significantly with TU. Over the 9-month study period, the IIEF scores rose significantly with both T gel and TU, but the changes were larger with TU than with T gel. Scores of the AMS dropped significantly with both T gel and TU, but the changes were larger with TU than with T gel. Bodyweights did not change significantly over the study period in either cohort. The waist circumferences declined significantly over the first 9 months of the study with both T gel and TU; however, they declined slightly but significantly further with TU.

There were parallel declines in plasma total cholesterol, LDL, and triglycerides, whereas plasma HDL showed a parallel rise. The magnitude of these changes was greater with TU than with T gel. With both T gel and TU, the declines in waist circumference were significantly correlated with the falls in plasma total cholesterol and LDL. The declines were not correlated with the changes in triglycerides and were inversely correlated with the rises in plasma HDL.

After 9 months, there was a modest but significant drop in values of systolic and diastolic blood pressure only with TU. No clear correlations could be established between changes in the variables and the increases in plasma T levels over baseline values.

Safety Parameters

Plasma PSA values remained stable over the study period with both T gel and TU, whereas the scores on the IPSS improved slightly but significantly over 9 months with both T gel and TU, and the changes were not different. Levels of plasma glucose, hemoglobin A1c, SGOT, SGPT, cGT, and bilirubin did not change (data not shown). Hemoglobin and hematocrit levels rose over the 9 months to a similar degree as both T gel and TU. None of the measured single values exceeded the upper limits of normal.

Discussion

This study assessed dose-response effects of 2 treatment modalities of T in men with sexual dysfunction and signs and symptoms of the metabolic syndrome:

T gel (50 mg/ day with no dose adaptations during the study) and TU. Throughout the study period both treatments achieved plasma levels of T within the reference range. Whereas plasma T levels reached the low end of normal in the reference range with T gel treatment, plasma T levels were in the middle of normal with TU treatment, and plasma T levels were significantly higher with TU than with T gel at all time points. TU produced better results for all efficacy parameters of T treatment. The IIEF and AMS scores and all features of the metabolic syndrome improved with both T gel and TU treatments, but they improved significantly more with TU than with T gel.

Plasma dihydrotestosterone (DHT) levels were not measured in this study. It is known that T gel generates high levels of DHT (up to 300% above baseline [21]. However, TU administration also leads to increases in plasma DHT levels of 200% to 300% [20].

Therefore, it is not likely that substantial differences in increases in plasma DHT levels biased the outcome of the study. As the above data indicate, increases in plasma estradiol levels are of similar magnitude with either type of treatment. The difference in patterns of SHBG levels following treatment with T gel and TU was remarkable. SHBG levels fell during the study period with T gel treatment, whereas treatment with TU produced a small but significant increase in spite of a larger increase in plasma T levels with TU than with T gel. This observation could be interpreted as follows. The fall in SHBG levels with T gel could have been a result of the increase in plasma T levels. Then over the course of treatment symptoms of the metabolic syndrome improved to a larger degree with TU than with T gel, and there probably would have been a reduction in hyperinsulinemia [22], leading to a rise in plasma SHBG levels. Plasma SHBG has been proposed to be an indicator of the degree of hyperinsulinism of the metabolic syndrome [19,23].

There were several methodologic shortcomings in this study: there were no control groups, and the subjects were not randomized to receive either T gel or TU.

Therefore, the positive results of this study and the observation that plasma levels of T in the mid-normal range of reference values are more efficacious than levels in low-normal range must be interpreted with caution until more appropriate studies have been performed.

Conclusion

It appears that improvements in a number of androgen-related functions is more favourable when plasma T levels are in the mid-normal range of reference values of plasma T levels than in the low range of reference values. This notion is becoming increasingly clear in the literature. The thresholds for androgen action vary for

the various androgen-dependent biologic functions, and moreover, these thresholds differ among men [3,4,24,25].

This study argues for checking plasma T levels during T treatment to see if they reach a certain threshold. This applies particularly for treatment with T gel. In this study in which all men received a dose of 50 mg/day with no dose adaptations, the efficacy of treatment was significantly less than with TU, generating plasma T levels in the mid-range of reference values. Therefore, patients treated with T, particularly T gel, should receive modifications of the dose administered if the resulting plasma T levels are low and do not reach the mid-normal range of the reference values.

Disclosure

Authors have nothing to disclose to this paper

Acknowledgement

We thank our volunteers Ms. Ayah Alzubaidi and Ms. Dalia Alzubaidi for their precious help in data collection and coordination of tables.

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