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Transdermal or Endogenous Testosterone in Men with Androgen Deficiency Syndrome and Type 2 Diabetes Mellitus?

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Abstract

Objective: To compare the effect of Transdermal Testosterone (TT) or Clomiphene Citrate (CC) administration on metabolic control, erectile function and quality of life in patients with T2DM.

Materials and patients: The study population included 40 men with T2DM up to 60 years old, who were on metformin monotherapy at doses up to 2550 mg daily over the last three months. The patients had total testosterone values between 8 and 12 nmol/L and LH levels within the normal range. Other causes of hypogonadism were excluded. The patients were asked to answer the IIEF and the SF-36 surveys. BMI, WC, lipid profile, HbA1c, testosterone, SHBG, LH, FSH, PSA, and albuminuria were monitored at their initial visits, and on the 12th and the 24th weeks. 19 of the patients were treated with TT and 21 with CC.

Results: Both groups corresponded in age, BMI, and HbA1c. Three-month administration of TT resulted in a significant increase of serum T and SHBG levels, and a reduction in BMI, HbA1c, WC, TC, TG, that extended to the 6th month. In the group treated with CC the monitored parameters showed the same dynamics.

In the group treated with TT we found significant improvement in all indicators of IIEF at the 3rd month. At the 6th month of and the overall satisfaction declined. In patients treated with CC it was found a significant improvement in all domains during the follow-up period, but without reaching statistical significance. We found significant improvement in physical ($p<0.001$) and mental ($p<0.01$) health and in quality of life ($p<0.01$) at the 3rd month, that extended until the 6th month.

Conclusions: The on time initiation of treatment, that increases testosterone levels, is essential for the metabolic disorders, erectile dysfunction and quality of life. Trials of a longer duration are required to establish the benefits and risks of that therapy in patients with T2DM and Androgen Deficiency Syndrome.

Keywords: Transdermal testosterone; Clomiphene citrate; Diabetes mellitus type 2; Androgen deficiency

Introduction

Testosterone (T) is a hormone that plays a critical role in the protein, lipid and carbohydrate metabolism. It is involved in the maintenance of muscle strength and mass and fat distribution in men [1]. Total testosterone concentrations in men peak around their late 20's, and then begin to decline gradually from the age of 30 onward, decreasing about 1-2 % per year [2,3,4]. In approximately 40 % of men over 45 years symptomatic hypogonadism is established. Under physiological conditions the decrease in bioavailable testosterone is expected to be greater than that of total testosterone due to age-associated increase in SHBG. Testosterone deficiency is associated with visceral obesity, insulin resistance, impaired carbohydrate tolerance, elevated triglycerides and total cholesterol, and low HDL-cholesterol. It has been found that total testosterone and SHBG levels were lower in men with metabolic syndrome (MS) and/or Type 2 Diabetes Mellitus (T2DM) compared to healthy controls [5]. According to some authors, the levels of these two hormones can be used as early markers of cardiovascular and/or metabolic disorders. On the other hand, MS and T2DM themselves lead to a decrease in testosterone levels [4].

Overt hypogonadism is presented by clinical symptoms and low testosterone levels - total testosterone less than 8 nmol/l and/or bioavailable testosterone less than 2.5 nmol/l. In those cases the initiation of testosterone replacement therapy (TRT) is needed and in the absence of contraindications, usually lifelong. In cases with total testosterone levels between 8 and 12 mmol/l and/or bioavailable testosterone levels between 2.5 and 4 mmol/l but with clinical symptoms and signs of hypogonadism (the so called Androgen Deficiency Syndrome) [6], testosterone replacement therapy can be considered according to the individual needs of the patient [7].

In the clinical practice guidelines measurement of testosterone is recommended for all of the obese men, those diagnosed with MS and/or T2DM and in patients with clear symptoms and signs of hypogonadism.

Clinical studies have shown that TRT in hypogonadal patients with T2DM and/or MS resulted in a significant improvement in insulin sensitivity [8], glycemic control [9] and lipid disturbances [10], and

reduction of visceral adipose tissue [9]. A benefit from TRT is reported even in patients with low-normal T levels. All the above-mentioned effects of T ultimately improve the quality of life of patients, a fact of undeniable social importance. Many epidemiological studies have shown an association between testosterone deficiency and an increased risk of cardiovascular disease and mortality [11, 12] but there is a little data to support the protective effect of testosterone [13]. While the benefits of TRT in young men with pituitary disease are well established, the potential advantages of this treatment in older men are less studied.

Objective: To compare the effect of 12 week application of transdermal testosterone or clomiphene citrate on the metabolic control, erectile function and quality of life in patients with T2DM.

Methods and Materials

Single-center, randomized, prospective, open-label, comparative study of the effect of 12 weeks administration of transdermal testosterone or clomiphene citrate on the metabolic control, erectile function and quality of life in patients with T2DM and borderline hypogonadism. The study was conducted at Clinic of Endocrinology and metabolic diseases, University Hospital "St. George", Medical University of Plovdiv, Bulgaria. The Ethics Committee of Medical University of Plovdiv approved this study, and signed informed consent was obtained from each of the subjects before recruitment.

Subjects

The study population included 40 men with T2DM up to 60 years old, who were on metformin monotherapy at doses up to 2550 mg per day over the last three months preceding the study. The patients had glycated hemoglobin ≤7.5 % and total testosterone values between 8 and 12 nmol/L and/or bioavailable testosterone between 2.5 and 4 nmol/L and LH levels were within the normal range. 19 of them were treated with transdermal testosterone, and 21 of them with clomiphene citrate.

Other causes of hypogonadism were excluded. The study did not include patients on other hypoglycemic therapy or with uncontrolled dyslipidemia, patients who had micro- or macroangiopathy; with accompanying severe chronic diseases, such as uncontrolled hypertensive heart disease, coronary artery disease and other conditions requiring continuing medication. An important requirement for the patients was the permanent cohabitation with a partner not less than 12 months. Examinations by neurologist or urologist were made a week before the beginning of the study.

At their initial visits, and on the 12^{th} and the 24^{th} week of their monitoring, all subjects underwent medical examination and demographic data was recorded. The patients were asked to answer the validated for Bulgaria questionnaire surveys: International Index of Erectile Dysfunction (IIEF) and the Short Form [36] Health Survey (SF-36). Body weight, Body Mass Index (BMI), Waist Circumference (WC), albumin, lipid profile, glycated hemoglobin (HbA1C); Testosterone (T), Sex-Hormone Binding Globulin (SHBG), Estradiol (E2), Luteinizing Hormone (LH), Follicle-Stimulating Hormone (FSH), Prostate-Specific Antigen (PSA), and micro albuminuria were monitored. Blood was drawn in the morning, between 7:30 and 8:00 AM, after at least 10 hour overnight fast. The collected blood samples were allowed to clot and were centrifuged within 60 minutes after venipuncture. Glucose and hormone levels were determined immediately after centrifugation. Fasting blood glucose levels were measured by commercially available Konelab 60i, Thermo Electron Corporation (Finland) chemistry auto analyzer. Hormonal analysis of serum LH, FSH, T, E2 and SHBG, were done by chemiluminescence methods using Access 2 Immunoassay System, Beckman Coulter, Inc., USA.

After receiving information about hormonal status, determining the degree of diabetes management and long-term complications, patients were divided into two groups. Transdermal testosterone treatment, (Androgel® (Abbott)) 50 mg daily, was immediately started for the first group. The second group performed seven-day Clomiphene Citrate Challenge Test (CCCT) (Clostilbegyt® EGIS 50 mg BID) and after that the patients continued to take the drug in dose of 50 mg QD. The duration of treatment was 12 weeks followed by a 12 week monitoring period. For the period of the study, no serious side effects (including gynecomastia, morphological changes in the prostate, increased PSA, polycythemia, etc.) were registered.

The evaluation of erectile function was carried out using a questionnaire IIEF. It is a validated, multi-dimensional, self-administered investigation that has been found useful in the clinical assessment of erectile dysfunction and treatment outcomes in clinical trials. A score of 0-5 was awarded to each of the 15 questions that examine the 4 main domains of male sexual function: A: Erectile Function (EF); B: Orgasmic Function (OF); C: Sexual Desire (SD); D: Intercourse Satisfaction (IS) [14]. Patients with score <25 in domain A were included in our study.

Quality of life was assessed by the questionnaire SF-36. It is a set of generic, coherent, and easily administered quality-of-life measures. These measures rely upon patient self-reporting and are now widely utilized by managed care organizations and by Medicare for routine monitoring and assessment of care outcomes in adult patients. The SF-36 consists of eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. The lower the score the more disability. The eight sections are: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health [15].

Data analysis was performed by using IBM SPSS Statistics for Windows (IBM Acquires SPSS Inc., Somers, NY, USA), version 17.0. Values are presented as mean ± Standard Error for Mean (SEM). Whether the distributions of metric discrete and continuous variables were normally or not was determined by Kolmogorov–Smirnov test. Nonparametric statistical analysis, single- and multi logistic regression; variance and correlation analysis were performed. The level of statistical significance was set at 5 % ($p \leq 0.05$).

Results

Both groups corresponded in age, BMI, WC, HbA1C, HDL-C, TC, TG and E2, but differed in the starting values of T, SHBG and LH. Of all the patients completed the study 30 people were with different degrees of obesity, 9 (22.5 %) of them were overweight and only 1 (2.5 %) was with normal body weight. 39 people (97.5 %) had WC >94 cm. 3 persons (7.5 %) were with the levels of total cholesterol >5,6 mmol/l, 25 (62.5 %) were with TG >1.7 mmol/l and 16 (40 %) had a level of HDL cholesterol <1 mmol/l.

Results of the laboratory tests of the monitored patients are presented in Table 1 and Table 2.

When we analyzed the results for all 40 patients we found a significant positive correlation between BMI and HbA1C (r=0.452, p=0.001) and negative one with T (r=-0.468, p=0.001), SHBG (r=-0.315, p=0.027). There was also a statistically significant negative correlation between T and HbA1C (r=-0.332, p<0.05) and a positive one with SHBG (r=0.449, p=0.001).

Parameter	Transdermal Testosterone (n = 19)		
	Baseline	3rd month	6th month
Age (y)	51.58 ± 0.92	-	-
Duration of DM (y)	3.54 ± 0.67	-	-
BMI (kg/m2)	32.89 ± 1.39	31.57±1.31**	32.04 ±1.31**††
WC (cm)	116.95 ± 3.03	112.68 ± 2.75**	112.63 ± 2.92**
HbA1C (%)	7.06 ± 0.13	6.70 ± 0.12**	6.86 ±0.13**††
Total Cholesterol (mmol/l)	5.23 ± 0.17	5.03 ± 0.11**	5.01±0.05**
HDL-Cholesterol (mmol/l)	1.11 ± 0.08	1.16 ± 0.06*	1.10±0.07
Triglicerydes (mmol/l)	2.08 ± 0.22	1.92 ± 0.18*	1.94±0.18†
Testosterone (ng/ml)	2.66 ± 0.18	3.03 ± 0.16**	2.87±0.18**††
SHBG (nmol/l)	14.81 ± 1.14	15.64 ± 0.92*	16.17±0.92**†
hLH (IU/L)	3.85 ± 0.16	2.78 ± 0.1	3.15 ± 0.13

*p<0.05; **p<0.01: significant difference with the previous parameters;
†p<0.05; ††p<0.01: significant difference with the baseline parameters.

Table 1: Clinical and laboratory parameters baseline on the 3rd and on the 6th month (Wilcoxon signed-rank test).

Three-month administration of transdermal testosterone resulted in a significant increase of serum T (13.9 %) and SHBG (5.6 %) levels. In the follow-up period, T levels significantly decreased on the 6th month, but remained significantly higher than the baseline (7.89 %). Unlike T, SHBG levels increased significantly on the 3rd month, and the increase extended until the 6th month, though no statistical significance was found. BMI significantly decreased on the 3rd month, after which significantly increased on the 6th month, but remained lower than baseline. WC also significantly decreased at the 3rd month and this reduction was maintained until the 6th month. Similar are changes in the indices of the lipid profile - TC and TG levels decreased on the 3rd month and this reduction was maintained until the 6th month. HDL-C significantly increased on the 3rd month and decreased even under the baseline at the 6th month. HbA1C decreased significantly on the 3rd month, increased significantly on the 6th month, but remained significantly lower than the baseline.

The levels of SHBG and T showed the same dynamics as after administration of transdermal testosterone. T levels increased significantly on the 3rd month, and then decreased, but remained significantly higher than the baseline. SHBG increased not significantly on the 3rd month, the increase became significant between the 3rd and the 6th month of the follow-up period. BMI decreased significantly on the 3rd month. A decrease was registered also on the 6th month, but it was not significant. WC was decreased significantly both, on the 3rd and on the 6th month. TC and TG levels decreased on the 3rd month and this reduction was extended until the 6th month. The changes in HDL-C were not statistically significant. HbA1C decreased significantly on the 3rd month and remained at that level on the 6th month.

Parameter	Clomiphene Citrate (n = 21)		
	Baseline	3rd month	6th month
Age (y)	53.38 ± 0.68		
Duration of DM (y)	4.03 ± 0.4		
BMI (kg/m2)	32.38 ± 0.86	31.72 ± 0.86**	31.49 ± 0,80††
WC (cm)	118.59 ± 2.88	117.10 ± 2.86**	116.2 ± 2.86**††
HbA1C (%)	7.24 ± 0.05	6.90 ± 0.07**	6.92 ± 0.06††
Total Cholesterol (mmol/l)	5.34 ± 0.08	5.04 ± 0.08**	5.02 ± 0.06**
HDL-Cholesterol (mmol/l)	1.02 ± 0.05	1.07 ± 0.04	1.03 ± 0.05
Triglicerydes (mmol/l)	2.11 ± 0.22	1.94 ± 0.18**	1.95 ± 0.18††
Testosterone (ng/ml)	3.23 ± 0.15	4.50 ± 0.21**	4.20 ± 0.18**††
SHBG (nmol/l)	19.86 ± 0.88	20,06 ± 0.77	22.30 ± 0.77**††
hLH (IU/L)	2.62 ± 0.11	3.80 ± 0.24	3.37 ± 0.22

*p<0.05; **p<0.01: significant difference with the previous parameters;
†p<0.05; ††p<0.01: significant difference with the baseline parameters.

Table 2: Clinical and laboratory parameters baseline on the 3rd and on the 6th month (Wilcoxon signed-rank test).

Parameter	Transdermal testosterone (n = 19)			Clomiphene citrate (n = 21)		
	Baseline	3rd month	6th month	Baseline	3rd month	6th month
Erectile function	15.95 ± 0.48	18.21 ± 0.42**	16.79 ± 0.38**†	15.86 ± 0.42	19.05 ± 0.48**	19.24 ± 0.48††
Orgasmic function	7.11 ± 0.23	7.63 ± 0.22*	7.11 ± 0.19*	7.14 ± 0.22	8.19 ± 0.19**	8.29 ± 0.20††
Sexual desire	6.95 ± 0.22	8.84 ± 0.12**	7.42 ± 0.16†	6.86 ± 0.14	7.90 ± 0.15**	8.14 ± 0.16††
Intercourse satisfaction	8.67 ± 0.46	9.56 ± 0.56*	8.74 ± 0.41	9.48 ± 0.40	10.52 ± 0.41**	10.71 ± 0.47††
Overall satisfaction	7.39 ± 0.23	8.00 ± 0.26**	7.26 ± 0.20**	7.14 ± 0.24	8.00 ± 26**	8.10 ± 0.29††

*p<0.05; **p<0.01: significant difference with the previous parameters;
†p<0.05; ††p<0.01: significant difference with the baseline parameters.

Table 3: Results from IIEF before and after treatment.

As already mentioned in the study design, patients treated with clomiphene citrate were further investigated after the 1st week of treatment. Although all of these patients had basal levels of T and LH within the normal range, in some of them those parameters rose substantially after the 7th day. We further divided the patients into two subgroups: responders (when at least one of those parameters

increased more than 1.5 times) 17 (80.95 %) and non-responders (such an increase was not reported) 4 (19.05 %). In the responders subgroup we found same dynamics of the monitored indices, but here we found a better degree of statistical significance. In the non-responders subgroup, there was significant difference only in terms of WC reduction and increasing of the SHBG levels between the 3rd and the 6th month.

During the treatment and the follow-up period no side effects were registered, and the change in the complete blood count, E2 and PSA values did not reach significant importance.

In the group treated with testosterone gel we found significant improvement in all indicators at the 3rd month. At the 6th month there was an inverse dynamics: EF, SD and IS were higher than the basal values but of fell to baseline, and the overall satisfaction was lower than the baseline.

Parameter	Transdermal Testosterone (n = 19)			Clomiphene citrate (n = 21)		
	baseline	3rd month	6th month	baseline	3rd month	6th month
Physical functioning	80.26 ± 2.72	81.58 ± 2.54	79.74 ± 2.14	79.29 ± 2.32	82.14 ± 2.50	82.14 ± 1.88†
Role limitations due to physical healt	39.47 ± 7.72	51.32 ± 7.27**	49.21 ± 6.55†	39.29 ± 7.44	54.76 ± 5.62**	58.33 ± 5.81††
Role limitations due to emotional problem	73.68 ± 6.54	71.93 ± 6.38	71.75 ± 5.49	71.67 ± 6.67	77.62± 5.12**	78.10 ± 4.97††
Vitality	61.58 ± 2,57	62.10 ± 2.54**	60.53 ± 2.56	62.62 ± 2,48	65.71 ± 2.16**	65.95 ± 1.64†
Emotional well being	81.68 ± 2,06	81.47 ± 2.03	80.95 ± 1.96	80.71 ± 1.90	83.57 ± 1.79**	83.57 ± 1.85†
Social functioning	57.24 ± 2.92	57.89 ± 2.9	57.24 ± 2.92	56.67 ± 2.68	58.57 ± 2.82**	59.29 ± 2.56††
Body pain	42.42 ± 2.31	42.11 ± 0.08	40.21 ± 2.71	42.38 ± 1.91	43.57 ± 2.13*	43.29 ± 2.13†
General health	41.68 ± 1.65	42.83 ± 1.52	42.47±1 .39	41.57 ± 1.54	44.29 ± 1.59**	45.29 ± 1.39††
Physical health	43.33 ± 2.00	55.74 ± 2.02**	54.32 ± 1.78**††	52.95 ± 1.98	58.05 ± 1.78**	58.95 ± 1.61††
Mental health	55.24 ± 1.72	63.52 ± 1.73**	62.63 ± 1.56*††	62.57 ± 1.68	65.95 ± 1.30**	66.43 ± 1.36††
Total score	51.32 ± 1.63	61.63 ± 1.37**	60.32 ± 1.22**††	59.38 ± 1.22	63.76 ± 1.04**	64.52 ± 1.06††

*p<0.05; ** p<0.01: significant difference with the previous parameters;
† p<0.05; †† p<0.01: significant difference with the baseline parameters.

Table 4: Results from SF-36 before and after treatment.

The group treated with clomiphene citrate also showed significant improvement in all indicators at the 3rd month. At the 6th month, however, there was an improvement of those parameters, albeit to a lesser degree. The described dynamics was much more demonstrative in the responder's subgroup, while in the non-responders group there were no significant changes in the indicators during the follow-up period.

Quality of life self-assessment in the group treated with transdermal testosterone showed significant improvement at the third month in domains "Emotional role functioning" and "Vitality". We found significant improvement in physical ($p<0.001$) and mental ($p<0.01$) health and therefore a significant improvement in quality of life ($p<0.01$). This improvement continues until the sixth month, despite discontinuation of the therapy.

In patients treated with Clomiphene Citrate it was found significant improvement in all domains, which exist during the follow-up period, but without reaching statistical significance. As expected, the improvement was much better expressed in the group of responders, while in non-responders dynamics is negligible.

Discussion

T2DM is associated with low total testosterone (T) in cross-sectional studies [16, 17]. The testosterone deficiency in men with T2DM is influenced not only by the age but also by many other factors - Body Weight and Waist Circumference, duration and control of the diabetes, comorbidities, therapy, etc. Total T concentrations are also determined to a large extent by circulating SHBG concentrations. And those concentrations are also dependent upon a number of factors. SHBG levels decrease in obesity and increase with aging. Type 2 diabetic patients have even lower SHBG levels compared with age- and BMI-matched non-diabetics [18].

The clinical presentation of hypogonadism in such cases is atypical and it often goes unrecognized. Detailed history, including sexual problems is not often taken in the general clinical practice or in diabetic centers. That is why testing of T and on time treatment are usually delayed and start only after manifestation of clinical symptoms. Our research comprised a small but homogeneous group of men with testosterone levels that do not impose mandatory starting of TRT. Our results show that the on time start of TRT improves metabolic disturbances in T2DM, including erectile dysfunction, and quality of life of the diabetic patients. The overall assessment of the diabetes would help us more accurately to decide whether, in poor metabolic control, to correct the diabetes treatment or to start TRT.

Transdermal testosterone and clomiphene citrate improve metabolic control at the third month of treatment in men with T2DM and low-normal levels of T according to our study. The action of both medications proceeds after discontinuation of their use. Transdermal testosterone has more rapid effect on the above-mentioned indices, but on the other hand the effect of clomiphene citrate is more prolonged. Transdermal testosterone and clomiphene citrate significantly improved EF and quality of life in men with T2DM and T levels. A very good marker for CC sensitivity is the weeklong stimulation test with 100 mg of the medication. According to our results, in men with decreased concentrations of testosterone and T2DM the LH levels should be raised more than 60 % at the first week, while T should be elevated with more than 50 % to expect success of its prolonged application. Hence, the success of this treatment depends on patients' individual sensitivity, and could be predicted after a CC functional test.

According to the recommendations of the American Diabetes Association (ADA), treatment of overweight or obese patients with T2DM should focus on the control of hyperglycemia. The application of anti-diabetic agents must be coupled with a moderate weight loss (~ 5 %), which would lead to improvement of glycemic control and reduction of anti-diabetic medications dose [19]. Weight reduction should be the first goal, but there is potential benefit in normalizing

total and free testosterone levels in those men who fail to achieve good glycemic control by weight reduction.

The results of our study showed that CC or TRT in men with decreased levels of testosterone and T2DM would help the process of weight loss (predominantly visceral fat) and could improve metabolic parameters. Moreover, the improvement of these parameters extends even after treatment discontinuation. This therapeutic memory would allow intermittent administration of CC or TRT, in three months for example, according to the individual needs of the patient.

Conclusions

The on time initiation of treatment, that increases testosterone levels, is essential for the metabolic imbalance, erectile dysfunction and quality of life, in men with decreased levels of testosterone and T2DM. The better the quality of life, as a result of this treatment, the better is the motivation and improvement of patients' compliance.

Trials of a longer duration are required to establish the benefits and risks of testosterone replacement or clomiphene treatment in patients with Type 2 Diabetes and Androgen Deficiency Syndrome.

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