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 included. 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.

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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.

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Introduction

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In the clinical practice guidelines measurement of testosterone is included.
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 12th and the 24th 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 Function (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 microalbuminuria 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≤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).

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Transdermal Testosterone (n = 19)</th>
<th>Clomiphene Citrate (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3rd month</td>
</tr>
<tr>
<td>Age (y)</td>
<td>51.58 ± 0.92</td>
<td>-</td>
</tr>
<tr>
<td>Duration of DM (y)</td>
<td>3.54 ± 0.67</td>
<td>-</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>32.89 ± 1.39</td>
<td>31.57±1.31†</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>116.95 ± 3.03</td>
<td>112.68 ± 2.75‡</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>7.06 ± 0.13</td>
<td>6.70 ± 0.12&quot;</td>
</tr>
<tr>
<td>Total Cholesterol (mmol/l)</td>
<td>5.23 ± 0.17</td>
<td>5.03 ± 0.11&quot;</td>
</tr>
<tr>
<td>HDL-Cholesterol (mmol/l)</td>
<td>1.11 ± 0.05</td>
<td>1.16 ± 0.06&quot;</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>2.08 ± 0.22</td>
<td>1.92 ± 0.18&quot;</td>
</tr>
<tr>
<td>Testosterone (ng/ml)</td>
<td>2.66 ± 0.18</td>
<td>3.03 ± 0.14&quot;</td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td>14.81 ± 1.14</td>
<td>15.64 ± 0.92&quot;</td>
</tr>
<tr>
<td>LH (IU/L)</td>
<td>3.85 ± 0.16</td>
<td>2.78 ± 0.1</td>
</tr>
</tbody>
</table>

*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).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Transdermal testosterone (n = 19)</th>
<th>Clomiphene citrate (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3rd month</td>
</tr>
<tr>
<td>Erectile function</td>
<td>15.95 ± 0.48</td>
<td>16.21 ± 0.42</td>
</tr>
<tr>
<td>Orgasmic function</td>
<td>7.11 ± 0.23</td>
<td>7.63 ± 0.22&quot;</td>
</tr>
<tr>
<td>Sexual desire</td>
<td>6.95 ± 0.22</td>
<td>8.84 ± 0.12&quot;</td>
</tr>
<tr>
<td>Intercourse satisfaction</td>
<td>8.67 ± 0.46</td>
<td>9.56 ± 0.56&quot;</td>
</tr>
<tr>
<td>Overall satisfaction</td>
<td>7.39 ± 0.23</td>
<td>8.00 ± 0.26&quot;</td>
</tr>
</tbody>
</table>

*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.

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

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. 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.  

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Transdermal Testosterone (n = 19)</th>
<th>Clomiphene citrate (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>baseline</td>
<td>3rd month</td>
</tr>
<tr>
<td></td>
<td>80.26 ± 2.72</td>
<td>79.74 ± 2.14</td>
</tr>
<tr>
<td></td>
<td>81.58 ± 2.54</td>
<td>82.14 ± 2.50</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>51.32 ± 9.27</td>
<td>54.76 ± 5.62</td>
</tr>
<tr>
<td></td>
<td>7.27††</td>
<td>5.81††</td>
</tr>
<tr>
<td>Role limitations due to physical</td>
<td>73.68 ± 6.54</td>
<td>71.0 ± 4.97†</td>
</tr>
<tr>
<td>health</td>
<td>71.93 ± 6.38</td>
<td></td>
</tr>
<tr>
<td>Role limitations due to emotional</td>
<td>61.58 ± 2.57</td>
<td>62.62 ± 2.48</td>
</tr>
<tr>
<td>problem</td>
<td>62.10 ± 2.54</td>
<td>61.95 ± 1.64</td>
</tr>
<tr>
<td>vitality</td>
<td>81.68 ± 2.03</td>
<td>81.9 ± 1.79†</td>
</tr>
<tr>
<td>Emotional well being</td>
<td>57.24 ± 2.92</td>
<td>56.7 ± 2.82†</td>
</tr>
<tr>
<td>Social functioning</td>
<td>42.42 ± 2.31</td>
<td>42.9 ± 2.13†</td>
</tr>
<tr>
<td>Body pain</td>
<td>41.68 ± 1.65</td>
<td>41.7 ± 1.54†</td>
</tr>
<tr>
<td>General health</td>
<td>55.24 ± 1.72</td>
<td>62.2 ± 1.68†</td>
</tr>
<tr>
<td>Physical health</td>
<td>51.32 ± 1.63</td>
<td>61.0 ± 1.79†</td>
</tr>
<tr>
<td>Mental health</td>
<td>56.57 ± 2.13</td>
<td>62.75 ± 1.04†</td>
</tr>
<tr>
<td>Total score</td>
<td>58.05 ± 1.54</td>
<td>58.57 ± 1.61</td>
</tr>
</tbody>
</table>

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

References