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Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency

M. A. Boyanov, Z. Boneva* and V. G. Christov

*Endocrinology Clinic, Alexandrovska Hospital, Medical University of Sofia, Sofia; *Endocrinology Unit, Internal Department, Central Police Hospital, Sofia, Bulgaria*

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ABSTRACT

The objective of this study was to assess the effects of oral testosterone supplementation therapy on glucose homeostasis, obesity and sexual function in middle-aged men with type 2 diabetes and mild androgen deficiency. Forty-eight middle-aged men, with type 2 diabetes, (visceral) obesity and symptoms of androgen deficiency, were included in this open-label study. Twenty-four subjects received testosterone undecanoate (TU; 120 mg daily, for 3 months); 24 subjects received no treatment. Body composition was analyzed by bio-impedance. Parameters of metabolic control were determined. Symptoms of androgen deficiency and erectile dysfunction were scored by self-administered questionnaires. TU had a positive effect on (visceral) obesity: statistically significant reduction in body weight (2.66%), waist–hip ratio (–3.96%) and body fat (–5.65%); negligible changes were found in the control group. TU significantly improved metabolic control: decrease in blood glucose values and mean glycated hemoglobin (HbA_{1c}) (from 10.4 to 8.6%). TU treatment significantly improved symptoms of androgen deficiency (including erectile dysfunction), with virtually no change in the control group. There were no adverse effects on blood pressure or hematological, biochemical and lipid parameters, and no adverse events. Oral TU treatment of type 2 diabetic men with androgen deficiency improves glucose homeostasis and body composition (decrease in visceral obesity), and improves symptoms of androgen deficiency (including erectile dysfunction). In these men, the benefit of testosterone supplementation therapy exceeds the correction of symptoms of androgen deficiency and also includes glucose homeostasis and metabolic control.

INTRODUCTION

Diabetes mellitus is a medical condition which is often associated with male sexual dysfunction. Erectile dysfunction is estimated to occur in 28–75% of diabetic males and its prevalence appears to increase with age[1–4]. The etiology of erectile dysfunction in type 2 diabetes is often multifactorial and may include poor metabolic control, diabetes-induced micro- and macrovascular alterations, diabetic neuropathy, and may be induced by certain concomitant non-diabetic medications[2,5–7]. Testosterone levels have been reported to be lower in both diabetic mice and men with type 2 diabetes as compared with healthy controls, which suggests testicular impairment in diabetes[8–10].

Correspondence: Dr M. Boyanov, Endocrinology Clinic, Alexandrovska Hospital, 1, G. Sofiiski Str., Sofia 1431, Bulgaria

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Moreover, men with type 2 diabetes tend to be middle-aged or older and are prone to the physiological decline in androgen production associated with aging, known as partial androgen deficiency in aging men (PADAM) or andropause[11,12].

Type 2 diabetes is also considered to be a phenotypic feature of the insulin resistance syndrome as described by Reaven[13]. This syndrome, also called the metabolic syndrome[14], is associated with visceral obesity, elevated blood lipids, hypertension, impaired glucose tolerance, type 2 diabetes mellitus and increased risk for cardiovascular disease.

The link of diabetes[15,16] and the metabolic syndrome[17] to cardiovascular disease is well established. Therefore, interventions that positively modify any of the symptoms of the metabolic syndrome may lower the overall cardiovascular risk.

Testosterone supplementation therapy is advocated in the treatment of symptoms of andropause[18]. Moreover, several intervention studies have demonstrated favorable effects of testosterone treatment on visceral obesity, insulin sensitivity, blood lipids and blood pressure in men diagnosed with symptoms of the metabolic syndrome[17,19–22].

We conducted an open-label controlled study to assess the effects of oral testosterone supplementation therapy on indices of glucose homeostasis and obesity, and on sexual function in middle-aged men with both type 2 diabetes and mild androgen deficiency. Our hypothesis was that, next to its effects on symptoms of androgen deficiency, testosterone supplementation would have additional beneficial effects on visceral obesity, glucose homeostasis and metabolic control in type 2 diabetic men.

SUBJECTS AND METHODS

Subjects

Forty-eight men with type 2 diabetes mellitus were included in the study. To be considered for inclusion, subjects had to be aged between 45 and 65 years, be married or living in a stable relationship with a female sexual partner for at least 6 months, have a waist–hip ratio (WHR) of at least 0.9, have symptoms of andropause or erectile dysfunction, and have serum testosterone levels below the normal range for young adults or in the lower third of this range (total testosterone < 15.1 nmol/l).

Subjects were excluded from the trial if they had concurrent illnesses other than diabetes or surgical interventions likely to impair sexual function, severe diabetic complications such as amputations or chronic renal failure, drug use other than antidiabetic medication or antihypertensives (angiotensin-converting enzyme (ACE) inhibitors), history of alcoholism or major psychopathology; or any sign or evidence of prostate enlargement or abnormalities.

Subjects were recruited from the men with type 2 diabetes referred to the Endocrinology Clinic of the Alexandrovska Hospital, Sofia, Bulgaria. The study was conducted in compliance with the principles of the Declaration of Helsinki and its revisions and current good clinical practice guidelines, and was approved by the institutional ethics committee. Informed consent was obtained from all participants prior to inclusion in the study.

Study design

The study was an open-label, randomized, no-treatment controlled study to assess the effects of oral testosterone supplementation therapy on indices of glucose homeostasis and obesity, and on sexual function in middle-aged men with both type 2 diabetes mellitus and mild androgen deficiency. Assessments were made at baseline and after 3 months of treatment.

The total group of 48 men was divided into a treatment group and a control group, each of 24 subjects. The participants in the treatment group received oral testosterone undecanoate (TU; Andriol®, Organon, Oss, The Netherlands) for 3 months, at a daily oral dosage of 120 mg, divided into 80 mg at breakfast and 40 mg at dinner (during the meals). The capsules were taken with water. Subjects in the control group received no treatment.

Measurements

Assessments were performed at baseline and after 3 months of treatment. All subjects underwent a structured medical interview and thorough medical examination at the start of the study.

Medical evaluation included assessment of age at onset and duration of diabetes, glycemic control (glycated hemoglobin (HbA_1c), fasting and postprandial blood glucose, mean daily blood glucose levels), diabetic treatment and complications. Special attention was paid to history of, or clinical evidence of, peripheral and autonomic neuropathy, retinopathy, nephropathy and coronary heart disease. Prior to inclusion all participants underwent transrectal digital and ultrasound examination of the prostate, and in seven cases prostate-specific antigen was also measured.

Symptoms of androgen deficiency were detected using the PADAM questionnaire developed at St. Louis University Medical School as described by Morley and Perry[11]. Symptoms of nervousness, fatigue, insomnia and sexual desire were scored by the subjects on a four-point scale (0, no symptoms (respectively, absence of sexual drive); 1, mild; 2, moderate; 3, severe (respectively, strong sexual desire)).

Erectile dysfunction was assessed using the abridged five-item version of the International Index of Erectile Function (IIEF-5)[23,24]. The severity of erectile dysfunction was classified into five categories: absent, mild, mild to moderate, moderate and severe, as proposed by Cappelleri and co-workers[25].

Anthropomorphic measurements included height, weight, body mass index (BMI) and WHR. Body composition (fat-free mass, body fat and total body water) was assessed in the fasting state by bioelectrical impedance on a tetrapolar body composition analyzer (Tanita TBF-215; Tanita Corporation, Japan).

Routine blood biochemistry, hematology, blood lipids, liver function tests, HbA_1c determinations and urine analysis were performed in the fasting state between 08.00 and 09.00, using standard laboratory methods. Total serum testosterone concentrations were determined at baseline and 10 h after administration of the last TU dose using immunofluorescence (Bayer Diagnostics, Germany).

Occurrence of adverse events was assessed by both spontaneous reporting and active questioning. Systolic and diastolic blood pressure were measured at three consecutive measurements after 10 min of bed-rest.

Statistical analysis

Data processing was performed using a SPSS 10.0 for Windows package. Statistical significance was set at $p < 0.05$. The different variables at baseline and at the end of the study were compared by two-sided t tests for paired and independent samples.

RESULTS

Clinical characteristics

All subjects completed the study in accordance with the protocol. There were no relevant demographic differences between the TU-treated group and the control group. Mean age of the subjects was 57.5 ± 4.8 years (median 57.2 years). The mean duration of the diabetic condition at the time of the study was 5.8 years (range 1–18 years). Mean age at diagnosis of diabetes was 52.9 years (range 46–58 years). Diabetic treatment in 62.5% was with oral hypoglycemic agents only (metformin in 25% of the subjects and metformin plus sulphonylurea in 37.5%), 12.5% of subjects received insulin monotherapy and 25% oral hypoglycemic agents in combination with insulin therapy (metformin in 12.5% and sulphonylurea in 12.5% of the subjects). The proportion of men with evidence of peripheral/autonomic neuropathy or retinopathy was 50% in both subgroups. One-third of the subjects showed evidence of nephropathy and 16.7% showed evidence of coronary heart disease. No concomitant medication (except for diabetes treatment and ACE-inhibitors) was taken during the study.

Table 1 summarizes the results of the anthropomorphic and blood pressure measurements, and bioelectrical impedance analysis at baseline and after 3 months of treatment. In the TU-treated group, body weight was reduced by 2.66% and BMI by 3.2%. In the control group, mean body weight and BMI changes were negligible. For body weight, the difference in change from baseline between the TU-treated group and the control group was statistically significant ($p < 0.05$). Waist–hip ratio decreased by 3.96% in the TU-treated group, as compared to a decrease of 0.97% in the control group ($p < 0.05$ for the intergroup difference). Body fat in the TU-treated group was decreased by 5.6%

Table 1 Anthropomorphic measurements, blood pressure and body composition (assessed by bioelectrical impedance) at baseline and after 3 months of treatment with testosterone undecanoate (TU). Data are expressed as mean ± SD

	TU group		*Control group*	
	Baseline	*Month 3*	*Baseline*	*Month 3*
Weight* (kg)	94.1 ± 19.3	91.6 ± 19.1	95.2 ± 19.9	94.6 ± 19.7
BMI (kg/m^2)	31.08 ± 4.79	30.08 ± 4.70	31.01 ± 4.90	30.88 ± 4.86
Waist–hip ratio*	1.01 ± 0.06	0.97 ± 0.07**	1.03 ± 0.06	1.02 ± 0.06
% Body fat*	31.04 ± 8.28	30.09 ± 6.88	32.92 ± 9.01	32.86 ± 8.96
Body fat* (kg)	29.21 ± 13.34	27.56 ± 12.43	31.34 ± 14.40	31.09 ± 14.12
Fat-free mass (kg)	64.89 ± 7.43	64.04 ± 8.41	63.86 ± 8.46	63.51 ± 9.02
Total body water (kg)	46.0 ± 5.46	46.01 ± 6.09	44.86 ± 6.02	44.92 ± 5.86
Systolic blood pressure (mmHg)	122 ± 8	120 ± 10	120 ± 8	122 ± 8
Diastolic blood pressure (mmHg)	80 ± 4	82 ± 4	76 ± 6	80 ± 4

*Significant difference at study end between changes from baseline in the TU-treated group and the control group ($p < 0.05$; unpaired t test); **$p < 0.05$ when compared to baseline (paired t test)

Table 2 Mean scores of symptoms of androgen deficiency and erectile dysfunction on a four-point self-administered scale. Data are expressed as mean ± SD

	TU group		*Control group*	
	Baseline	*Month 3*	*Baseline*	*Month 3*
Nervousness*	1.50 ± 0.88	0.375 ± 0.70**	1.75 ± 1.0	1.50 ± 0.75
Insomnia*	1.125 ± 0.80	0.50 ± 0.50**	1.25 ± 0.90	1.125 ± 0.84
Weakness (fatigue)*	1.125 ± 1.08	0.50 ± 0.50**	1.25 ± 0.96	1.00 ± 1.00
Libido*	1.25 ± 1.00	2.125 ± 0.61**	1.50 ± 1.00	1.675 ± 1.25
Erectile dysfunction*	2.25 ± 0.675	1.062 ± 0.90**	2.50 ± 0.75	2.25 ± 0.875

*Significant difference at study end between changes from baseline in the testosterone undecanoate (TU)-treated group and the control group ($p < 0.05$, unpaired t test); **$p < 0.05$ when compared to baseline (paired t test)

compared to 0.8% in the control group ($p < 0.05$). Fat-free mass and total body water did not change significantly in either group.

At baseline, ten subjects in the TU-treated group and nine in the control group had a systolic blood pressure between 135 and 150 mmHg and diastolic blood pressure values between 85 and 90 mmHg. The other subjects had normal blood pressure values both at baseline and at the end of the study. Eight subjects in the TU-treated group and nine in the control group took ACE-inhibitors (enalapril maleate) at a stable dose for the study period. There were no significant changes in either systolic or diastolic blood pressure during the study for the group as a whole.

The effects of treatment on symptoms of androgen deficiency and erectile dysfunction are presented in Table 2. All symptoms of androgen deficiency (nervousness, insomnia, fatigue and decreased libido) were significantly improved in the TU-treated group compared to baseline and compared to the control group, whereas these parameters remained virtually unchanged in the control group. The increase in libido in the TU group resulted in an increase in mean weekly copulations from 0.75 to 1.50. Mean scores of symptoms of erectile dysfunction changed from moderate to mild in the TU-treated group ($p < 0.05$ compared to baseline), whereas in the untreated controls no change could be observed.

The effects of treatment on blood glucose and lipid homeostasis are presented in Table 3. Fasting, postprandial and mean daily blood glucose values dropped significantly in the TU-treated group ($p < 0.05$). Reduced blood-glucose concentrations resulted in a relative decrease of mean HbA_1c by 17.3% (absolute decrease of 1.8%; $p < 0.05$). In the control group, blood glucose and HbA_1c

Table 3 Blood glucose parameters, lipid parameters and serum testosterone concentrations at baseline and after 3 months of treatment. Data are expressed as mean ± SD

	TU group		*Control group*	
	Baseline	*Month 3*	*Baseline*	*Month 3*
Fasting blood glucose (mmol/l)*	8.0 ± 2.6	6.0 ± 1.3**	8.4 ± 2.8	8.0 ± 2.4
Postprandial blood glucose (mmol/l)*	11.9 ± 3.2	8.7 ± 1.9**	11.0 ± 3.1	10.6 ± 3.0
Mean daily blood glucose (mmol/l)*	9.8 ± 2.2	7.2 ± 1.8**	9.6 ± 2.3	9.2 ± 2.2
HbA_1c (%)*	10.4 ± 1.6	8.6 ± 1.0**	10.3 ± 1.6	9.9 ± 1.4
Total cholesterol (mmol/l)	5.50 ± 1.41	5.42 ± 1.47	5.59 ± 1.49	5.55 ± 1.46
HDL-cholesterol (mmol/l)	1.20 ± 0.12	1.21 ± 0.22	1.16 ± 0.21	1.18 ± 0.23
LDL-cholesterol (mmol/l)	3.57 ± 1.14	3.60 ± 1.25	3.61 ± 1.22	3.69 ± 1.30
Triglycerides (mmol/l)	1.73 ± 0.87	1.39 ± 0.73	1.90 ± 0.92	1.70 ± 0.85
Total serum testosterone (nmol/l)*	9.56 ± 2.33	15.54 ± 3.41	10.76 ± 3.0	11.20 ± 3.16

*Significant difference at study end between changes from baseline in the testosterone undecanoate (TU)-treated group and the control group ($p < 0.05$, unpaired t test); **$p < 0.05$ when compared to baseline (paired t test); HbA_1c, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein
Reference ranges: total cholesterol, 3.60–5.20 mmol/l; HDL-cholesterol, 0.70–2.20 mmol/l; LDL-cholesterol, 2.2–3.8 mmol/l; triglycerides, 0.50–2.10 mmol/l; total serum testosterone, 8.36–28.7 nmol/l

remained elevated. Serum total cholesterol and cholesterol fractions did not change significantly in either of the subgroups. Serum triglycerides decreased insignificantly in both subgroups ($p = 0.1$).

As expected, total serum testosterone concentrations in the TU-treated group were significantly increased compared to baseline.

No adverse events were reported during the study. No treatment-induced changes in hemoglobin, hematocrit, total bilirubin, aspartate aminotransferase or alanine aminotransferase were observed. Serum γ-glutamyltransferase and alkaline phosphatase were significantly decreased at the end of the study (from 33.8 to 17.8 U/l and from 79.9 to 64.8 U/l, respectively), leading to a statistically significant difference in change from baseline between the TU-treated group and the control group ($p < 0.05$).

DISCUSSION

In our study, we investigated the effects of oral testosterone supplementation on glucose homeostasis, visceral obesity and sexual function in middle-aged men with type 2 diabetes mellitus and mild androgen deficiency. Oral treatment with 120 mg TU daily for 3 months led to improved metabolic control of diabetes, e.g. lower fasting, postprandial and mean daily blood glucose concentrations, and a decrease in glycated hemoglobin, in addition to weight loss (predominantly from the visceral fat depot). Weight loss was moderate but could solely be attributed to fat loss, since fat-free mass and total body water remained unchanged. This resulted in a decrease of visceral obesity as reflected by the decrease of waist–hip ratio. Serum lipid concentrations and blood pressure were not adversely affected by TU treatment. The association between obesity, elevated blood lipids, hypertension, impaired glucose tolerance/diabetes mellitus type 2 and increased risk for cardiovascular disease has been recognized as the metabolic syndrome[13]. Many publications have demonstrated that visceral fat accumulation seems to represent a higher risk for vascular events than general obesity alone[14]. Thus, our results indicating favorable effects of oral TU on the metabolic syndrome and visceral fat accumulation may suggest a favorable effect on cardiovascular risk. The results of this non-blinded pilot study should be confirmed by large, well-controlled prospective studies.

Our results are in line with those published by Mårin and colleagues[19–22]. Testosterone undecanoate treatment for 8 months in middle-aged abdominally obese men resulted in a decrease of visceral fat mass, without a change in body mass or lean body mass. Insulin resistance was improved and fasting blood glucose, diastolic blood pressure,

serum cholesterol and triglycerides were decreased. Using an *in vivo* isotope technique, testosterone treatment was shown to inhibit triglyceride assimilation in intra-abdominal depots, apparently directing this lipid fraction to the subcutaneous fat. *In vitro* studies showed that treatment with TU decreased lipoprotein lipase activity in the abdominal region. Rebuffe-Scrive and associates[26] also found that moderate doses of TU led to a decrease in abdominal lipoprotein-lipase activity, as well as a decrease in waist–hip circumference.

The observed beneficial changes in glucose control in our study cannot be attributed to direct actions of testosterone supplementation therapy itself. It is unlikely that testosterone alone could lead to such dramatic changes, which are much larger than those obtained by using any conventional antidiabetic drug. Testosterone may have acted on metabolic parameters as described above. Mechanisms involved in these changes might act via the effects on visceral fat accumulation, followed by metabolic improvement, and/or via direct effects on muscle insulin sensitivity[20]. There are also accumulating data on possible links between bioavailable testosterone and leptin levels[27], and therefore appetite and body weight regulation.

Our study also shows that testosterone supplementation therapy has a positive effect on feelings of depression and lack of motivation, and improves general well-being in older men. Improved or restored sexuality is often crucial for quality of life[28]. Results from our study show that testosterone supplementation has a positive effect on erectile dysfunction and on symptoms of andropause. This improved general well-being may lead to increased adherence to dietary recommendations and, subsequently, better metabolic control. It should, however, be kept in mind that our study was not placebo-controlled and therefore the results may be prone to bias, particularly concerning the self-reported symptoms of androgen deficiency before and after treatment.

The effects of testosterone supplementation on serum lipid concentrations remain controversial. In the past, androgens were notorious for their atherogenic effects when administered in supraphysiological doses[29,30]. However, when given to androgen-deficient men, androgens induced an improvement in lipid profile[31]. In our study, oral TU therapy did not significantly change serum lipid concentrations.

Oral TU treatment in our study was well tolerated. No adverse events following treatment were reported. There were no adverse affects on hematological, biochemistry (including liver function) or urinalysis parameters.

In conclusion, our study showed that oral testosterone undecanoate treatment in type 2 diabetic men with androgen deficiency and visceral obesity improved several features of the metabolic syndrome, including glucose homeostasis and body composition (decrease in visceral obesity) and improved symptoms of androgen deficiency, such as nervousness, insomnia, fatigue, reduced libido and erectile dysfunction.

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