Open Access Macedonian Journal of Medical Sciences. 2014 Dec 15; 2(4):601-607.
http://dx.doi.org/10.3889/oamjms.2014.107
Clinical Science

Influence of Testosterone Replacement Therapy on Metabolic Disorders in Male Patient with Type 2 Diabetes Mellitus and Androgen Deficiency

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Citation: Janjgava S, Zerekidze T, Uchava L, Giorgadze E, Asatiani K. Influence of Testosterone Replacement Therapy on Metabolic Disorders in Male Patient with Type 2 Diabetes Mellitus and Androgen Deficiency. OA Maced J Med Sci. 2014 Dec 15; 2(4):601-607. http://dx.doi.org/10.3889/oamjms.2014.107

Key words: Free testosterone; HbA1c; Lipid Profile; BMI; Leptin.

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Received: 24-Aug-2014; **Revised:** 24-Sep-2014; **Accepted:** 14-Oct-2014; **Online first:** 05-Nov-2014

Competing Interests: The authors have declared that no competing interests exist.

Abstract

INTRODUCTION: Multiple epidemiological studies have shown that low testosterone levels are associated with and predict the future development of T2DM.

AIM: The aim of study was to show the influence of testosterone replacement therapy on anthropometric characteristics, glycosylated hemoglobinlevel level, blood pressure and dyslipidemia in patients with T2DM and Androgen deficiency.

MATERIALS AND METHODS: From 125 male patients with T2DM were randomized 85 subjects with age 49.8 ± 6.74 and BMI from 35.83 ± 3.65 kg/m^2 in placebo-controlled study. We divided patients into two groups: 1) Treatment group, where was used testosterone replacement therapy. 2) Placebo group, where was used placebo. In both groups was added Life style modification, but Antidiabetic therapy was unchanged.

RESULTS: After six months of treatment we repeated the diagnostic assessments: lipid profile was improved in both groups but in group I it was statistically significant. Free testosterone level increased in all groups but in group I it was statistically significant. HbA1c decreased in both group but in group I we had the best result. Blood pressure was reduced in both groups, results were similar.

CONCLUSION: Our study demonstrated that it is possible to regulate blood pressure, lipid profile, HbA1c, BMI - by raising testosterone in diabetic men with androgen deficiency.

Introduction

Over the past few decades, obesity and type 2 diabetes mellitus (T2DM) has become a global health challenge. The number of people with obesity and T2DM has dramatically increased in the whole world, and Georgia is not the exception [1, 2]. Men with obesity, metabolic syndrome (MS), and T2DM have low total, free testosterone and sex hormone–binding globulin (SHBG) levels [3]. Conversely, the presence of low testosterone and/or SHBG predicts the development of metabolic syndrome and type 2 diabetes. Visceral adiposity, presented in men with low testosterone, metabolic syndrome, and/or T2DM, acts through pro-inflammatory factors. These inflammatory markers contribute to vascular endothelial dysfunction with adverse sequel such as increased cardiovascular disease (CVD) risk and erectile dysfunction (ED). Furthermore, studies show multidirectional impact of low testosterone level with obesity and MS and its negative effect on ED and CVD risk in men with T2DM [4].

Androgens play an important role not only in sex differentiation and development, but also in regulating the metabolism of glucose, protein, lipid and some inflammatory factors, all of which might have a great influence on insulin sensitivity. It is well known that reduced level of total testosterone (TT) in middle aged or in old men may contribute to abdominal obesity, increased insulin resistance, and diabetes mellitus. At least 6 large prospective clinical trials have suggested that reduction of TT predicted the increasing incidence of type 2 diabetes [5-6]. Low concentrations of endogenous androgens have been linked with insulin resistance, which is an important upstream driver for metabolic abnormalities [7-8]. Moreover, results from the Massachusetts Male Aging Study suggest, that low concentration of testosterone might play a role in the development T2DM [9-10]. Studies in laboratory animals support the hypothesis that diabetes has s detrimental effects on testicular

function; reduction in both Leyding cell number and testosterone secretion have been reported [11].

As it was previously shown the patients with type 2 diabetes have a frequent occurrence of hypogonadotrophic hypogonadism, as reflected in low plasma concentrations of testosterone and inappropriately low luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [12]. In addition, the lack of testosterone would also potentially promote further weight gain and loss of skeletal muscle and would thus promote insulin resistance [13-14].

In the European Male Aging Study database of 3,369 men between the ages of 40 and 79 years, three sexual symptoms (poor morning erections, low sexual desire, and ED) had a syndrome relationship with decreased testosterone levels [15]. Moreover, in the European Male Aging Study, low serum testosterone was more frequent in men with comorbidities such as obesity, metabolic syndrome, and type 2 diabetes. In studies from diabetes clinics, total, bioavailable, and free testosterone levels were low in men with type 2 diabetes [16-17]. When comparing testosterone levels in men with and without ED and type 2 diabetes, these investigators found significantly lower serum bioavailable testosterone (P = 0.006) and free testosterone (P = 0.027) in men with ED, but there was no significant difference in total testosterone levels. The lower the serum testosterone appears, the greater the severity of ED is suggested [16]. Corona et al. [18] evaluated 1,200 men with ED and reported that 16% had type 2 diabetes. Serum total testosterone levels were below the reference range (300 ng/dL or, 10.4 nmol/L) in 24.5% of men with diabetes versus 12.6% of non-diabetic subjects (P = 0.0001) after adjustment for age and BMI. In addition, hypogonadism in men with type 2 diabetes was associated with decreased sexual desire, more symptoms of depression, and lower luteinizing hormone levels. Multiple epidemiological studies have shown that low testosterone levels are associated with and predict the future development of T2D and the metabolic syndrome [19].

A meta-analysis by Ding *et al.* [20] analyzed 20 cross-sectional where total testosterone levels were consistently lower in diabetic men compared with non-diabetic controls in all individual studies. These findings were confirmed by a more recent meta-analysis of 28 cross-sectional studies including 1,822 men with diabetes and 10,009 non-diabetic controls by Corona *et al.* [21].

However, a cross sectional study from the Third National Health and Nutrition Examination Survey (NHANES) group including 1,413 adult men, 101 of which had diabetes, showed that men in the lowest fertile of calculated free testosterone, adjusted for age, ethnicity, and adiposity, were more likely to have prevalent diabetes [22]. In addition, a recent cross sectional analysis of 1292 men from the Norfolk population found that the 156 men with a hemoglobin A1c (HbA1c) of at least 6.5% or self-reported diabetes had, compared with men with an HbA1c no greater than 5%, a 2.4 nmol/liter lower circulating total and a 30 pmol/liter lower free testosterone level, respectively ($P = 0.001$) [23]. Studies from Australia [24], the United Kingdom [25], and the United States [26] consistently showed that 30–50% of aging, obese men with diabetes, in the absence of known testicular or pituitary pathology, have low total or free testosterone, at least relative to reference ranges based on healthy young men [24-26].

The aim of study was to show the influence of testosterone replacement therapy on anthropometric characteristics, glycosylated hemoglobin (HbA1c) level, arterial blood pressure and dyslipidemia in patients with T2DM and Androgen deficiency.

Materials and Methods

One hundred and twenty five male patients with T2DM were screened from the year 2010 till the end of the year 2013, at “National Institute of Endocrinology” (Tbilisi, Georgia). The study was approved by the Ethics Committee of this Institute. Written informed consent was obtained from all participants. Every possible side effect of the treatment was written in the inform consent. All patients had to meet inclusion criteria: T2DM; Body mass index (BMI) 27.0 – 48.0 kg/m^2; patient age range 30-65 years; positive screening questionnaire for androgen deficiency in males (Adapted from Morley JE, et al.), low free testosterone level (free testosterone and not total testosterone measurements was preferred by “National Institute of Endocrinology”).

Patients with following criteria were excluded from the study: diabetes mellitus type 1; hyperprolactinemia; BMI < 27 kg/m^2 and > 48 kg/m^2; kidney and liver active disease; adenoma of prostate II-III degree; secondary hypogonadism, treated by testosterone or testosterone stimulation therapy 3 month before screening; treatment with anti-obesity drugs within 3 months prior to informed consent; uncontrolled hyperglycemia with glucose level >240 mg/dl (> 13.3 mmol/L); any previous (or planned within next 12 months) bariatric surgery (open or laparoscopic) or intervention (gastric sleeve); current treatment with systemic corticosteroids at the time of informed consent or pre-planned initiation of such therapy (Note: inhaled use of steroids (e.g. for asthma/COPD) is no exclusion criterion, as this does not cause systemic steroid action); congestive heart failure (NYHA III or IV); acute or chronic metabolic acidosis (present condition in patient history); hereditary galactose intolerance; alcohol or drug abuse within the 3 months prior to informed consent

that would interfere with trial participation; acute coronary syndrome ≤ 6 weeks prior to informed consent; stroke or transitory ischemic attack (TIA) ≤ 3 months prior to screening; change in dose of thyroid hormones and dyslipidemia therapy within 6 weeks before screening; coumarin therapy within 6 months prior informed consent.

The following analyses were conducted at the screening visit: 1) anthropometric study: height and weight were evaluated in all subjects. BMI was calculated as weight (kg) divided by square of height (m²) and was expressed in kg/m². Waist circumference was measured midway between the iliac crest and the lower margin of the 12th rib. For measurement of supine blood pressure, subjects were in a supine or semi-recumbent position for minimum 5 minutes. After that blood pressure was measured twice with minimum 2 minute interval. The difference was not > 2 mmHg mark on the manometer. The final result was recorded. Blood pressure was measured with automatic manometer - Microlife BP100. All anthropometric measurements were done by investigator - Sh. J. 2) Venous blood samples were obtained from 9:00 to 11:00 a.m. after 10-12-h fast and stored at 4ºC. HbA1c, liver function tests, lipid profile were evaluated by liquicolor HUMAN test. All hormones: free testosterone, leptin, prostate specific antigen (PSA), thyroid stimulation hormone (TSH), follicle stimulation hormone (FSH), luteinizing hormone (LH) were performed by the fully automated enzyme-linked immunosorbent test (ELISA) analyzer Elisys Uno (HUMAN Diagnostics, Wiesbaden, Germany). 3) All patients filled the validation of a screening questionnaire for androgen deficiency in males (Adapted from Morley JE, et al.). 4) Ultrasonography of the abdomen and prostate were performed with a Siemens Acuson Antara. 5) 12 lead Electrocardiography (ECG) was performed with a Biocare ECG-3030.

A total of 85 subjects with age range 49.8 ± 6.74 years and BMI from 35.83 ± 3.65 kg/m^2 were randomized in placebo-controlled study. According to the laboratory and clinical condition we divided patients into two groups. 1) Treatment group (42 patients) and 2) placebo group (43 patients). Antidiabetic therapy was not changed in both groups. Lifestyle modification was the same in both groups: 1600-2000 calorie diet (30% fat, 30% protein and 40% carbohydrates) taken 4-5 times per day. No additional food intake was allowed. Walking - 150 min/week was recommended for all patients. The first group received testosterone replacement therapy (TRT) - testosterone undecanoate 1000 mg/4ml intramuscularly once in three month (Nebido - depot preparation of testosterone undecanoate used every 10-14 week, Jenafarm GmbH & CO.KG). The second group received placebo.

Diagnostic assessment (weight, waist circumference, blood pressure, HbA1c, lipid profile, liver function tests, free testosterone, leptin, PSA, TSH, FSH, LH) was done to all patients at baseline and after 6 month treatment period. all patients were given home blood glucose and blood pressure monitoring diaries and were informed to do the monitoring at least 2 times per week. If their fasting blood glucose level was >200 or <70 mg/dl or DBP (Diastolic blood pressure) >160 or SBP (systolic blood pressure) >90 mmHg, they had to contact their study doctor.

Shapiro-Wilk test was used to determine normality of data distribution. The results were presented as mean ± standard deviation (SD) and 95% confidence interval (CI 95%) for normally distributed data. Not normally distributed data were displayed as median with range (min – max values). Differences between the study group and control group patients were measured using independent samples T-test for normally distributed data and Mann-Whitney U test for not normally distributed variables. Pearson (r) correlation tests were used to determine the relationship between study parameters, depending on variable distribution. P-value < 0.05 was considered statistically significant. Statistical analysis was performed using the SPSS 15.0 software package (SPSS, Inc., Chicago, IL).

Results

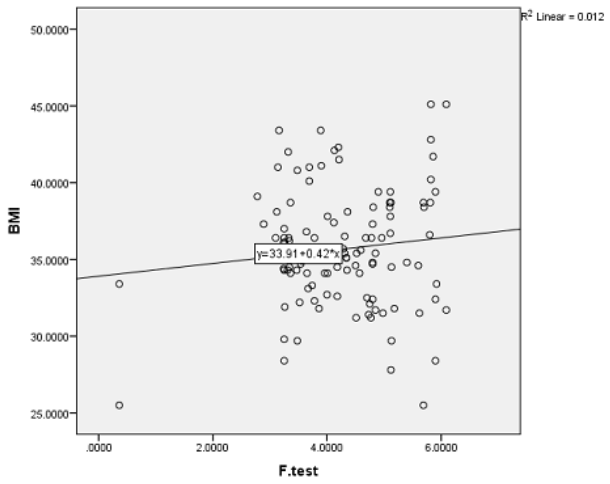
Average level of BMI was 35.83 kg/m2. In all investigated patients increased level of leptin and decreased level of free testosterone was observed at baseline and was in average 22.31 ng/ml (n. 0.2-5.0 ng/ml) and 3.85 ng/dl (n. 5.8-36 ng/dl) relatively. The average level of glycosylated hemoglobin (HbA1c) was 8.35%. Abnormal lipid profile was observed in each patient. 59 patients had arterial hypertension (Table 1).

Table 1: Descriptive characteristics form randomized patients.

Parameter	Mean ± SD (n =85)
Age (year)	49.8 ± 6.74
BMI (kg/m$^{2)}$	35.83 ± 3.65
WC (sm)	119.7 ± 15.98
SBP (mmHg)	130.11 ± 12.61
DBP (mmHg)	86.13 ± 10.33
F.test. (ng/dl)	3.82 ± 3.0.68
HbA1c (%)	8.35 ± 0.97
Leptin (ng/ml)	22.31 ± 8.97
Chol (mg/dl)	209.2 ± 15.05
TG (mg/dl)	183.88 ± 12.5
HDL (mg/dl)	54.74 ± 4.75
LDL (mg/dl)	101.25 ± 9.62
DM	85 ± 0
AH	59 ± 0

Data are expressed as mean ± SD. BMI: body mass index, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, F. test: Free testosterone, HbA1c: *Glycosylated hemoglobin,* Chol: Cholesterone HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, TG: triglyceride, TC: total cholesterol, DM: Diabetes Mellitus and AH: arterial hypertension.

Free testosterone level was inversely correlated with the degree of obesity (BMI) (Fig. 1) (r-0.10). There was no statistically significant correlation between free testosterone and waist circumference (r-0.56).



Correlation between BMI (kg/m$^{2)}$ and Free Testosterone(ng/dl) (R^2 Linear =0.012)

Figure 1: Correlation between BMI and free testosterone.

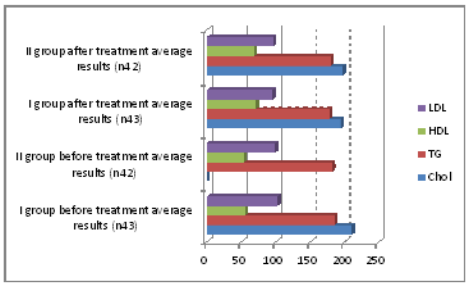
The patients were randomized in one side-blinded two groups 1) first group consisted of 42 patients, 2) second group consisted of 43. In first group existing anti-diabetic therapy remained unchanged, but was added lifestyle modification and testosterone replacement therapy (TRT). The second group received placebo.

Table 2: Descriptive characteristics: Before and after Treatment in both group.

	Group I: before treatment average results (n43)	Group II: before treatment average results (n42)	Group I: after treatment average results (n43)	Group II: after treatment average results (n42)	P value
BMI (kg/m$^{2)}$	35.65±3.78	36.60±3.57	29.68±3.10	31.88±3.16	0.046
F.test.(ng/dl)	3.85±0.57	3.8±0.78	12.06±3.57	6.64±1.07	0.047
HbA1c (%)	8.26±0.87	8.43±1.07	7.46±0.76	7.93±0.71	0.051
Leptin (ng/ml)	21.71±8.13	23.19±9.73	11.64±4.27	13.93±4.00	0.052
Chol (mg/dl)	211.17±15.68	207.28±14.35	194.64±7.62	198.02±6.77	0.05
TG (mg/dl)	185.6±11.66	182.21±13.20	178.31±9.4	180.23±10.25	0.047
HDL (mg/dl)	55.5±4.96	54±4.48	71.11±4.42	68.44±5.80	0.048
LDL (mg/dl)	102.95±9.60	99.58±9.46	95.62±9.72	96.3±10.27	0.049

Data are expressed as mean ± SD. BMI: body mass index, F. test: Free testosterone, HbA1c: *Glycosylated hemoglobin,* Chol: Cholesterol HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, TG: triglyceride, TC: total cholesterol.

After six month of treatment in both groups positive results were shown according to lipid profile: total cholesterol, triglyceride and LDL levels decreased, and HDL increased in both groups but statistically significant results were shown in the first group (Table 2, Fig. 2). Free testosterone level increased in both groups but statistically significant results was shown only in the first group (P = 0.047) (Table 2, Fig. 3). HbA1c decreased in both groups but in the first group results were better (P = 0.051) (Table 2, Fig. 4). BMI decreased in both groups but more reduction was seen in the first group (P = 0.046) (Table 2, Fig. 5). Leptin level after treatment was approximately same in both groups, but relatively best results were achieved in the first group (P = 0.052) (Table 2, Fig. 6). Blood pressure reduction was the same in both groups (Fig. 7).

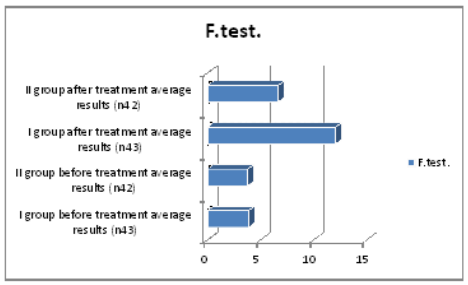


Chol: Cholesterone (mg/dl), HDL: high-density lipoprotein cholesterol (mg/dl), LDL: low-density lipoprotein cholesterol (mg/dl), TG: triglyceride (mg/dl).

Figure 2: Descriptive characteristics: before and after treatment.

Discussion

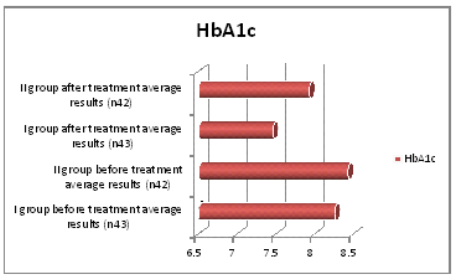
Serum testosterone, glycosylated hemoglobin (HbA1c), high-density lipoprotein cholesterol, triglyceride concentrations, BMI, and blood pressure improved in both groups after 6 month of the treatment. Our study showed that diabetic men have lower testosterone level then non-diabetic.



F.tets: Free testosterone (ng/dl).

Figure 3: Descriptive characteristics: Free testosterone before and after treatment in both groups.

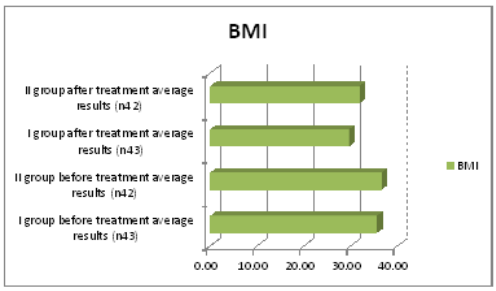
A meta-analysis by Ding *et al.* [20], who analyzed 20 cross-sectional studies with a total of 850 men with diabetes and 2000 non-diabetic controls, also showed that total testosterone levels were consistently lower in diabetic men compared with non-diabetic controls in all individual studies, with a mean pooled difference of 2.66 nmol/liter [95% confidence interval (CI), 3.45 to 1.86]. Our findings were also confirmed by a more recent meta-analysis of 28 cross-sectional studies including 1,822 men with diabetes and 10,009 non-diabetic controls by Corona *et al.* [21]; total testosterone was lower in men with diabetes compared with controls [mean difference, 2.99 nmol/liter (95% CI, 3.59 to 2.40)], and diabetes remained associated with lower total testosterone levels independent of age and BMI (adjusted r = 0.568; *P* = 0.0001) (6). Neither Ding *et al*. [20] nor Corona *et al*. [21] analyzed the association of free testosterone levels with diabetes, due to the lack of reliable data.



HbA1c: Glycosylated hemoglobin (%).

Figure 4: Descriptive characteristics: Glycosylated haemoglobin before treatment and after treatment in both groups.

We have shown that testosterone replacement therapy improves insulin resistance in hypogonadal men with diabetes. Testosterone therapy reduced the HbA1c, indicating an improved glycemic control. This study demonstrates that intramuscular testosterone replacement therapy (TRT) in hypogonadal men with type 2 diabetes improves HbA1c, the central biochemical defect associated with these conditions. Small-scale studies of testosterone treatment in men with metabolic syndrome or type 2 diabetes and marginal low or normal testosterone levels showed improvement in glycemic control. More studies have to be conducted to confirm our findings.



BMI: body mass index (kg/m^2).

Figure 5: Descriptive characteristics: BMI before and after treatment in both groups.

The low testosterone levels might have induced an increase in visceral obesity and severity of cardiovascular risk factors in T2DM. Increased age is one of the strongest predictors for coronary artery disease [29]. The studies have shown that hypogonadism is associated with dyslipidemia, there are only limited data supporting the effect of testosterone on lipids. Two studies reported a small rise in HDL cholesterol but no effect on TC or LDL cholesterol in hypogonadal men [27]. Our results showed that after TRT, total cholesterol, LDL-C, triglyceride had reduced and HDL increased by 16.53 mg/dl, 7.33 mg/dl, 7.29 mg/dl and 15.61 mg/dl respectively, which are consistent with other TRT trials′ results [28]. It is not yet fully understood whether hypoandrogenaemia causes the metabolic syndrome and T2DM or vice versa. Hypoandrogenaemia often precedes adult male obesity indicating that low androgen levels may be the precursor of insulin resistance, the metabolic syndrome and finally T2DM in obese men. A prospective study of 11 years duration revealed that low plasma testosterone levels independently predicts the development of the metabolic syndrome and T2DM and contribute to their pathogenesis [30].

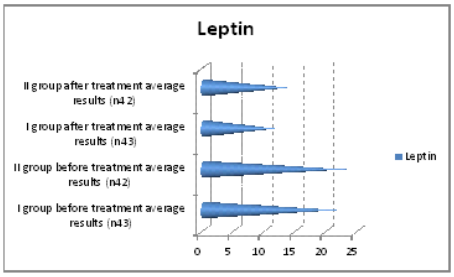
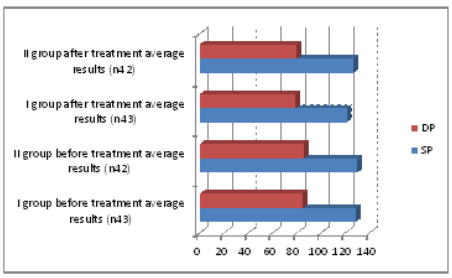


Figure 6: Descriptive characteristics: Leptin (ng/ml) level before and after treatment in both groups.

Lower levels of testosterone in men are associated with high blood pressure. Our study demonstrated a favorable effect of testosterone treatment on blood pressure in abdominally obese men. Other studies by Marin P et al and Yassin AA et al investigating the effects of testosterone treatment of men with osteoporosis found also a beneficial effect on blood pressure levels. In a study of 122 men receiving treatment with parenteral testosterone undecanoate over 15 month period, both systolic and diastolic blood pressure decreased significantly [31, 30]. The maximum effect was achieved after nine months of testosterone administration.



SP: systolic blood pressure (mmHg), DP: diastolic blood pressure (nnHg).

Figure 7: Descriptive characteristics: Systolic and diastolic blood pressure before treatment and after treatment in both groups.

Furthermore, leptin also may have some role in achieving positive results in treatment group. Leptin is an adipose tissue hormone with so called “double action”: it affects receptors on Leydig cells, lowering testicular testosterone secretion. In addition, leptin suppresses pituitary LH secretion. As it was shown hypogonadal diabetic men have increased leptin levels. Further evidence for the association between hypogonadism and insulin levels in men has been reported in studies on patients undergoing treatment for prostate carcinoma where androgen ablation is the main treatment [33]. In our study testosterone

replacement therapy reduced leptin levels in addition to the independent effects of weight loss in lowering leptin levels. A limitation of this study is the relatively small samples of subjects involved that can limit the generalizability of the study.

In conclusion, our study demonstrated that it is possible to regulate blood pressure, lipid profile, HbA1c, weight - by raising testosterone levels in diabetic men with androgen deficiency [34]. In addition to traditional CV risk factors, novel risk factors are also inversely related to testosterone levels. Re-instituting physiological levels of testosterone in hypoandrogenic men as our small study showed have an important role in reducing the prevalence of diabetic complication, but large-scale randomized placebo-controlled trials are needed.

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