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Research Article

A prospective Study of Serum Testosterone Level in Type 2 Diabetes Mellitus patients

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Abstract
Background: *Epidemiological studies have shown that low testosterone levels are an independent risk factor for type-2 diabetes (T2DM). The risk of both hypogonadism and T2DM increases with age.*
Aims and Objectives: To evaluate and study the relationship of serum testosterone level with conventional risk factors for atherosclerosis, duration of diabetes and HbA1c in T2DM patients.
Materials and Methods: *A total 120 subjects were studied after dividing them in to Cases (T2DM male patients, n=80) and Control (sex matched healthy male subjects, n=40) at Dept. of Medicine, G R Medical College & J.A. Group of Hospitals, Gwalior, between September 2011 and October 2012. Study cohort were studied based on the detailed history, anthropometric measurements, relevant blood investigations, HbA1C, ECG changes and estimation of serum total (STT) and free testosterone (SFT).*
Results: *Majority of the cases belonged to age group of 41-50 years (40%). Mean serum total testosterone (STT) (300.72±33.14 vs383.81±57.63, p=0.551) and serum free testosterone (SFT) (7.65±2.04 vs. 11.17±2.30, p=0.002) levels were lower among Cases compared to Control. Among Cases and Control, 28.75% and 25% subjects had decreased STT (p=0.020) whereas 57.5% and 25% subjects had decreased SFT (p=0.029) respectively. Among Cases out of 26 obese patients, 76.9% had low level of SFT whereas in Control group, out of 10 obese subjects 40% had low level of SFT. All the patients [18 (22.5%)] among cases who had total cholesterol ≥200 mg/dl had low level of SFT whereas among Control group, 50% out of 6 subjects had low level of SFT (p=0.015) Out of 53 patients who had TG ≥150 mg/dl, 67.92% had low level of SFT whereas in control group, out of 10 subjects, 30% subjects had low level of SFT (p= 0.0019). Out of 55 patients in cases and 13 subjects in Control who had HDL-C <40 mg/dl, 32 patients (58.18%) and 4 subjects (30.76%) had low level of SFT respectively (p<0.001).Among the patient with T2DM for >5 years (n=28), 12 (42.85%) and 18 (64.28%) had low levels of STT and SFT respectively. In cases with 2 or lesser risk factors for CAD, 5.26% and 42.16% patients had low level of STT and SFT respectively. In cases with 3 or more risk factors for CAD, 50% and 71.42% patients had low level of STT and SFT respectively.*
Conclusion: *Testosterone deficiency is common in T2DM patients who were in 4th and 5th decade of their life. Low serum free testosterone in T2DM patients was associated with reduced sexual desire, low HDL, increased BMI, high serum triglyceride, increase total cholesterol and LDL levels. Low serum free testosterone is also significantly associated with increased risk of CAD in T2DM patients.*
Keywords: *Testosterone deficiency, CAD, lipid profile, serum free testosterone.*

Introduction

Diabetes mellitus is most common endocrine disorder which involves multiple organs and leads to significant morbidity and mortality due to accompanying complications. Erectile dysfunction, reduced libido, orgasmic dysfunction, and retrograde ejaculation are established complications found with variable prevalence in men with diabetes. Various studies have shown that patients with type 2 diabetes have frequent occurrence of hypogonadism as reflected by their low plasma concentration of free testosterone. [1, 2]

Coronary artery disease (CAD) is a major cause of mortality and morbidity in developed world, and in developing countries, the incidence is rising. Atherosclerosis is the major cause of CAD. CAD manifests as acute coronary syndrome (ACS) and stable angina. [3]

Men are more than twice as likely as women to die from coronary heart disease, and this ratio is consistent in all population and is not related to differences in risk factors. [4] Low testosterone levels are associated with CAD [5] and low serum testosterone is associated with increased aortic atheroma[6]. Furthermore, low testosterone levels are associated with several risk factors for the development of CAD including systolic and diastolic hypertension, adverse lipid profile, and high levels of fibrinogen and procoagulable factors.[5]

The present study was undertaken in order to study the role of serum testosterone in patients with diabetes mellitus and its correlation with conventional risk factors for atherosclerosis.

Material and Methods

A case control study was performed including male T2DM patients attending medical OPD of G R Medical College &J.A. Group of Hospitals, Gwalior (Case group) and age and sex matched healthy subjects (Control group) were also taken from medicine OPD, between September 2011 and October 2012.The study cohort was divided into Case group (n=80) and Control Group (n=40).

Male patients with type 2 diabetes mellitus between the age group of 30-70 years were included. Patients taking drugs which are known to interfere with serum testosterone levels for example, glucocorticoids, hormone replacement therapy, ketoconazole, opiods, methadone, heroin and marijuana, patients with features associated with congenital GnRH deficiency (midline facial defects, synkinesis or a family history of GnRH deficiency or anosmia), patients with history of tumor, exposure to radiation, history of head trauma, spinal cord injuries, history of pelvic trauma and surgery, any disease other than diabetes known to cause autonomic dysfunction and any other chronic disease such as human immunodeficiency virus (HIV), end-stage renal disease, cirrhosis of liver and psychiatric disease were excluded from the present study.

Study cohort after written informed consent, were studied based on the detailed history, anthropometric measurements, relevant blood investigations, HbA1C, ECG changes and estimation of serum total and free testosterone. Estimation of cardiac markers was done wherever required.

A detailed history of present illness was recorded including duration of the onset of symptoms, complete ADAM questionnaire, past history and family history for hypertension, and DM and history of medications was asked. Personal history like early morning erection, smoking, alcohol consumption, decrease in libido, lack of energy, decrease in strength and/or endurance, loss of height, decreased enjoyment of life, feeling of sadness and/or grumpy, decreased strength of erection, recent deterioration in ability to play sports and a recent deterioration in work performance were noted.

A detailed clinical examination was done. Complete General physical examination was done. Systemic examination including cardiovascular, respiratory, gastrointestinal and neurological examination was done. Anthropometric indices measured were weight, height, body mass index, waist and hip

circumference and waist/hip ratio while the clinical indices measured were pulse rate, JVP and blood pressure.

All the subjects were evaluated for biochemical parameters including fasting and random blood sugar, haemoglobin, TLC, blood urea, s. creatinine, s. bilirubin and SGPT, HbA1C and lipid profile. HbA1C and serum total and free testosterone levels were done. Resting ECG was recorded in all the subjects.

Method of measurement of serum testosterone: In all men, the morning (08.00–10.00 hours) TT and FT levels were measured after an overnight fast. TT was measured by fully automated bi directionally interfaced chemiluminescent immunoassay and FT was measured by radio immune assay, with an intra-assay coefficient of variation of 2.6% and an inter assay coefficient of variation of 4.3%. Normal levels of TT were taken as 300-1000ng/dl and normal levels of FT as 9-40ng/dl.

Presence of hypertension was defined as per the Joint National Committee (JNC) 7 criteria. Presence of diabetes mellitus was defined as per American Diabetes Association Criteria 2018. Presence of chronic kidney disease defined as per National Kidney Foundation Criteria.

Dyslipidemia as per NCEP ATP III and ADA guidelines as total cholesterol >200mg/dl, triglyceride >150mg/dl, HDL <40mg/dl, LDL >100mg/dl and BMI calculated as per latest WHO guidelines.

All the data analysis was performed using IBM SPSS ver. 20. For different quantitative parameters mean and standard deviation was calculated. To compare the means between two groups, student unpaired 't' test is used. Chi square test is used to find the association between two qualitative variables. Level of significance is taken as $p<0.05$. Generation of graphs and tables etc. was done by using the Microsoft excel 2010 software.

Results

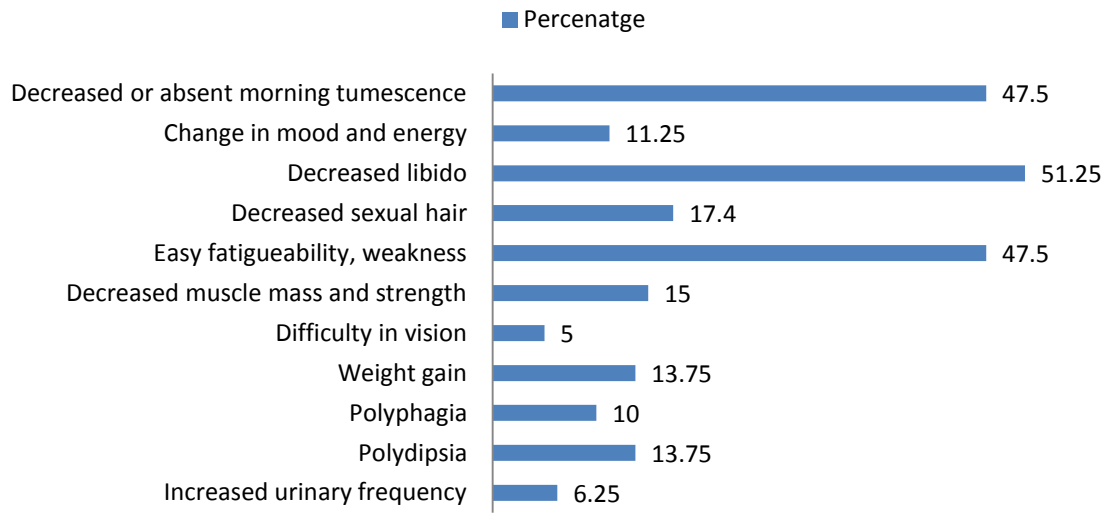
Majority of the cases belonged to age group of 41-50 yrs [32 (40%)]. Mean age in case group was 48.32±8.20 and 47.02±9.42 years in control group. Table 1 describe and compare the general characteristics of study cohort.

Table 1: Comparing general characteristics of study population

Parameters	Case	Control	P value
Age (years)	48.32 ± 8.20	47.02±9.42	0.842
WHR	1.04 ± 0.09	1.02±0.08	0.968
BMI (kg/m^2)	27.11 ± 4.57	27.07±3.70	0.432
Total testosterone (ng/dl)	300.72± 33.14	383.81±57.63	0.551
Free testosterone (ng/dl)	7.56± 2.14	11.17±2.30	0.002
Hemoglobin (g/dl)	11.04± 1.78	13.43±1.23	0.231
TLC	6905.37±1522.83	6605±1259.48	0.456
HbA1c (%)	8.05±1.44	5.07±0.44	<0.001
T. cholesterol (mg/dl)	201.95±26.96	188.12±17.39	0.002
Triglycerides (mg/dl)	153.57±12.41	124.45±31.15	0.726
LDL (mg/dl)	114.63±26.71	102.97±20.03	0.008
HDL (mg/dl)	36.16±5.62	45.8±7.20	0.575
FBS (mg/dl)	134.53±15.5	110±6.81	0.001
RBS (mg/dl)	195.2±35.84	145.07±6.76	0.002

Data is expressed as mean±SD, WHR; waist hip ratio, TLC: total leukocyte count, HbA1c; glycated hemoglobin, LDL; low density lipoprotein, HDL; high density lipoprotein, FBS; fasting blood sugar, RBS; random blood sugar

Graph 1: Incidence of Different symptoms in T2DM patients (n=80)



Most of the T2DM patients with low serum testosterone presented with decreased libido (65.2%) followed by decreased or absent morning tumescence (56.52%). Most common risk factor for T2DM in cases (47.5%) and controls (30%) was physical inactivity. Family history of T2DM and CVD was found in 18.75% and 25% of cases respectively. In the cases of T2DM with CAD (n=20), most common presenting symptom was chest pain (75%) followed by breathlessness (30%).

The serum total testosterone was decreased in 23 cases (28.75%) and 8 controls (25%) (p=0.020). The serum free testosterone was decreased in 46 cases (57.5%) and 8 controls (25%) (p=0.029)

Out of 20 T2DM patients who had CAD and 16 patients of T2DM only, 35% and 26.67% had subnormal level of serum total testosterone respectively (p=0.39).Whereas 13 patients of T2DM with CAD (65%) and 33 patients of T2DM (55.6%) had subnormal level of serum free testosterone (p=0.037).

Table 2: Comparing distribution of risk factors between groups

Risk Factor	Cases (n)	Controls (n)
Age (>45 yrs)	46	22
Obesity (>30kg/m^2)	26	10
Hypertension	13	01
Dyslipidemia	51	15
Smoking	18	08
Alcohol	09	04
Family History	12	05

Data is expressed as number

Maximum patients in Cases and Control were overweight [28 (35%)] and normal weight [16 (40%)] respectively. Mean BMI in case group (27.11±4.57) was higher than the control group (27.07±3.70) (p=0.432).In case group out of 26 obese patients (32.5%), 20 patients (76.9%) had low level of serum free testosterone whereas among control group, out of 10 obese males (25%), 4 subjects (40%) had low level of serum free testosterone.

In case group 18 (22.5%) patients had high total cholesterol (≥200 mg/dl) and all of them had low level of serum free testosterone. In control group, out of 6 subjects (50%) who had high total cholesterol (≥200 mg/dl), 3 (50%) had low level of serum free testosterone (p=0.015).

Out of 53 patients who had TG ≥150 mg/dl, 36 (67.92%) had low level of free testosterone

whereas in control group, out of 10 subjects who had TG ≥150 mg/dl, 3 (30%) subjects had low level of free testosterone (p= 0.0019).

In present study, out of 55 patients in cases and 13 subjects in control who had HDL-C <40 mg/dl, 32 patients (58.18%) and 4 subjects (30.76%) had low level of free testosterone respectively (p<0.001).

In case group, out of 43 patients with mild anaemia, 26 (60.4%) had low level of free testosterone and out of 11 patient with moderate anaemia, 7 (63.6%) had low level of free testosterone (p=0.231). Only 4 subjects in control group had mild anaemia with low level of serum free testosterone.

Among the patient with T2DM for >5 years (n=28), 12 (42.85%) and 18(64.28%) had low levels of serum total and free testosterone respectively. Mean serum total and free testosterone were lower in cases with lesser risk factor than the cases with 3 or more risk factors for atherosclerosis (p>0.05). In cases with 2 or lesser risk factors for CAD, 2(5.26%) and 16 (42.16%) patients had low level of serum total and free testosterone respectively. In cases with 3 or more risk factors for CAD, 21(50%) and 30 (71.42%) patients had low level of serum total and free testosterone respectively.

Table 3: Distribution of low serum testosterone with HbA1c level

Low serum testosterone	HbA1c							
	<6.5 (n=8)		6.5-8.4 (n=47)		8.5-10.4 (n=17)		>10.5 (n=8)	
	N	%	N	%	N	%	N	%
Total testosterone	03	37.5	13	27.66	03	17.65	04	50
Free testosterone	02	25	30	63.82	08	47.06	06	75

Discussion

Testosterone is the predominant sex hormone in man. Total testosterone levels are affected in setting of increasing age, obesity, diabetes mellitus, hyperthyroidism, some types of medications like estrogen and anticonvulsant use, chronic illness or congenital disorders.[7]

It has been documented in the literature that serum testosterone levels decreases with age. After age of 30 years, 1-2% of serum testosterone levels decreases every year as a part of normal aging process. But few recent studies have shown that decrease in serum testosterone level with age is not normal.[8] In agreement to that mean age in the present study was 48.32±8.20 in case group and 47.02±9.42 in control group. Majority of the cases (40.1%) and controls (37.5%) were in age groups of 41-50 years. In agreement to present study Koopman et al [9] and Gale et al[10] reported mean age of 46.01±1.27 and 42.5 years respectively.

In present study, 28.75% of the T2DM patients and 25% of the Control group patients had low level of STT whereas57.5% of T2DM patients and 25% of the Control group patients had low levels of SFT. Mean STT and SFT were lower in Cases compared to Control group. In a similar study, Ernani et al[11] also reported low levels of STT in patients with T2DM (34%) when compared to healthy control subjects (23%). Kapoor et al[12] found low levels of STT in 25% of patients with T2DM. Ernani et al[11] also reported that level of SFT was decreased in 46% of T2DM patients as compared to 24% in non-diabetics. Similarly Koopar et al[12], Chandel et al[13] and Mathis et al [14] reported a decrease in 42%, 58% and 57% of T2DM patients respectively.

In present study, out of 41 T2DM patients who had decreased sexual desire, 34.1% and 43.17% had low levels of STT and SFT respectively whereas out of 38 T2DM patients who had decreased or absent morning tumescence, 36.8% and 55.2% had low levels of STT and SFT respectively. Similar observations have been reported by Fedele et al[15] who observed erectile dysfunction, decreased or absent morning tumescence in T2DM to be 37%. Normal sexual

desire was observed in 39 (48.75%) patients and all of these patients had normal serum free testosterone.

In present study out of 26 obese T2DM patients, 61.51% and 76.9% had low level of STT and SFT respectively. Whereas Dhindsa et al[16] reported prevalence of low testosterone in obese diabetics to be 50%. The phenomenon of testosterone deficiency in diabetic patients with higher BMI could be due to increase in adipose tissues mass which results in increased aromatase activity, leading to enhanced conversion of testosterone into estradiol which further suppresses hypothalamic-pituitary-testicular axis and decreases testosterone secretion.[17]

In present study, all 18 patients who had TC >200 mg/dl, had low SFT level. In a similar study done by Muller et al[18] (226.6±1.11 mg/dl) reported a low level of SFT in patients with TC > 200 mg/dl. Results of both the studies are comparable to present study findings. In present study, out of 55 patients who had low HDL (<40 mg/dl) in T2DM patients, 85.18% had low SFT level. In agreement to present study Mathis et al[14] reported low testosterone levels in 28% cases. In present study 31 out of 80 T2DM patients had raised LDL-C (>100) levels, of these 74.1% had low level of free testosterone. Muller et al [18] reported that mean LDL-C level was 150.42±0.98 mg/dl and all those patients had low level of free testosterone levels. Prevalence of elevated triglycerides (>150 mg/dl) in diabetic patients with low free testosterone was 36 out of 53 (67.9%) in present study whereas Mathis et al [14] reported that prevalence of elevated triglyceride in diabetic patients with low testosterone levels was 45% in their study of 649 patients. These findings indicate higher incidence of dyslipidemia in patients with low serum free testosterone. Low free testosterone was more commonly found in patients with high serum cholesterol (100% vs. 16.6%), low HDL-C level (74.17% vs. 22.2%) and high serum triglyceride (68.755% vs. 58.18%) as compared to control group.

Testosterone stimulates erythropoiesis in bone marrow and increases hematocrit value. Prevalence of anemia (Hb<13 gm/dl) in T2DM patients with low free testosterone was 33 out of 46(71.7%) in present study. Bhatia et al[7] also reported prevalence of anemia in diabetic patients with low testosterone levels to be 37.83%, which is lower than the present study. The difference in the findings may be due to the small size of sample.

In present study, patients of diabetes mellitus with duration >5 yrs, 42.85% (12 out of 28) had low serum total testosterone and 64.28% (18 out of 28) had low free testosterone, also patients with duration of DM <1 years, 46.6% (14 out of 30) and with duration 1-5 years, 63.6% (14 out of 22) had low level of free testosterone. Umoh et al[19] reported no significant association between low level of free testosterone and duration of DM

Khan et al[20] showed no significant correlation between low level of free testosterone and duration of DM.

In present study, occurrence of good metabolic control with HbA1c < 7% in diabetic patients was 23 out of 80 (28.75%), of which 9 (39.13%) had low serum free testosterone level. Similar observations were reported by Farnkvist et al [21], who reported that prevalence of good metabolic control in diabetic patients was 33%. In present study, serum free testosterone was decreased in patients with T2DM with HbA1c level between 6.5-8.4% (63.82%) and >10.5 (75%). Serum total testosterone was decreased in patients with T2DM with HbA1c level <6.5 (37.5%) and >10.5 (50%). The difference was statistically not significant.

Main limitations of this study is the small size of sample, so statistical power of the study was low and thus results cannot be extrapolated to the general population. All the confounding factors might not have been removed. Other larger studies are required to confirm the findings of this study.

Conclusion

The present study showed that testosterone deficiency is common in diabetic patients in 4-5th

decade. This study shows that low serum free testosterone in diabetes correlates positively with reduced sexual desire, low HDL, increased BMI, high serum triglyceride, increase total cholesterol and LDL levels. Low serum free testosterone is also significantly associated with increased risk for coronary artery disease in diabetic patients. No significant association of serum testosterone with duration of diabetes and HbA1c level was found. Thus it is important to evaluate cases of diabetes with respect to free testosterone level for early detection and better sexual and mental function of such patients.

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