Original Article

Prevalence of hypogonadism in male Type 2 diabetes mellitus patients with and without coronary artery disease

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ABSTRACT

Aim: The present study is carried out to investigate hypogonadism using serum testosterone levels in male Type 2 diabetes mellitus (T2DM) subjects with and without coronary artery disease (CAD). **Subjects and Methods:** A total of 150 age and body mass index-matched male subjects in the age group of 30–70 years were recruited in three groups; Group A - subjects with normal glucose tolerance, Group B - T2DM subjects without CAD, and Group C - T2DM subjects with CAD (n = 50 each group). Subjects with CAD were diagnosed on the basis of electrocardiogram, treadmill testing, stress echocardiography, or coronary angiography. Total testosterone (TT), free testosterone (FT), bioavailable testosterone, calculated FT and glycemic parameters were measured and compared between all the three study groups. One-way ANOVA followed by *post hoc* Tukey's test and Pearson's coefficient of correlation tests were used for analysis. **Results:** Hypogonadism (TT <3 ng/ml) was observed in 40% (20/50) of subjects in Group C and 32% (16/50) of subjects in Group B as compared to only 14% (7/50) of subjects in Group A (Groups A vs. B; P = 0.055, Groups A vs. C; P = 0.006 and Groups B vs. C; P = 0.53). Group C subjects had significantly lower levels of TT (3.55 ± 1.46 ng/ml vs. 4.73 ± 2.17 ng/ml, P = 0.005), calculated FT (0.062 ± 0.0255 pg/ml vs. 0.0951 ± 0.0508 pg/ml, $P \leq 0.001$), and bioavailable testosterone (1.48 ± 0.65 ng/ml vs. 2.18 ± 1.20 ng/ml, $P \leq 0.001$) compared to control Group A subjects. There was no significant difference in any of the testosterone parameters between Groups A and B. Furthermore, an overall positive correlation was found between hypogonadism and CAD (r = 0.177, P = 0.030, n = 150). **Conclusion:** We observed hypogonadism as indicated by low testosterone levels in a significant proportion of male T2DM subjects with CAD.

Key words: Cardiovascular risk, coronary artery disease, diabetes, hypogonadism, testosterone

Introduction

In recent years, low testosterone levels have been recognized to be closely associated with increased cardiovascular (CV) risk.[1,2] Studies in the past have reported that testosterone deficiency is inversely associated with coronary intima-media thickness (CIMT),[3,4] a surrogate marker for atherosclerosis which leads to the development of coronary artery disease (CAD). Furthermore, it has been found that testosterone induces endothelium-independent relaxation of isolated rabbit aorta.[5] Studies have also reported that testosterone has beneficial effects on coronary blood flow in men with CAD.[6]

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Decrease in testosterone levels is also influenced by age,[7] obesity,[8] and insulin resistance (IR).[9] Subjects with diabetes have been reported to have low serum testosterone levels as compared with the healthy individuals.[10] Subjects with diabetes also possess a greater CV risk[11,12] and demonstrate CV risk biomarkers such as atherogenic dyslipidemia,[11,13] increased high-sensitivity C-reactive protein[14] levels, leptin,[15] adiponectin levels,[15] and leptin/adiponectin ratio.[16] An inverse relationship between serum free testosterone (FT) levels and plaque score has also been found in men with diabetes.[17] However, it is not clear if there is any association of hypogonadism and increased CV risk in subjects with diabetes. The present study was therefore carried out to find out the prevalence of hypogonadism in Indian male diabetes subjects with CAD.

Subjects and Methods

This study was approved by Institutional Ethics Committee-Human Research, University College of Medical Sciences, Delhi, India. All the investigations were performed as per the International Declaration of Helsinki and Tokyo. All the guidelines of the Ethics Committee were followed during the study. A total of 150 age and body mass index (BMI) matched male subjects in the age group of 30–70 years were recruited in three different groups; Group A - subjects with normal glucose tolerance (NGT), Group B - Type 2 diabetes mellitus (T2DM) subjects without CAD, and Group C - T2DM subjects with CAD (n = 50 each group).

Subjects who had fasting plasma glucose <100 mg/dl and 2 h postprandial plasma glucose <140 mg/dl (oral glucose tolerance test with 75 g anhydrous glucose) were labeled as NGTs in Group A. subjects with diabetes in Group B were recruited from the diabetic clinic of the institute/hospital. Diabetic subjects with CAD in Group C were recruited from preventive cardiology clinic of the institute/hospital under the supervision of subject specialists. A baseline 12 lead electrocardiogram, treadmill testing, stress echocardiography, or coronary angiography were used to look for any evidence of CAD.

Subjects suffering from any acute stress, coronary event or procedure (myocardial infarction, unstable angina, coronary artery bypass, surgery, or coronary angioplasty) in the previous 4 weeks, liver disease, serum creatinine levels >1.5 mg/dl, systemic disorders such as cancer, epilepsy, hypothyroidism, and evidence of any active infection including osteomyelitis, ulcers, and upper respiratory infection or any known history of hypogonadism or panhypopituitarism, and night shift workers were excluded from the study. History of mumps and alcohol consumption were also taken, and both were negative. All the subjects participated in the study were explained about the study and a written informed consent was obtained.

Informed consent was followed by a detailed medical history and clinical examination. BMI, systolic and diastolic blood pressure (supine and standing both) were recorded of all the recruited subjects. Fasting blood samples were collected for the estimation of plasma glucose, HbA1c, serum insulin, lipid profile, total testosterone (TT), FT, sex hormone binding globulin (SHBG), luteinizing hormone (LH), and follicle-stimulating hormone (FSH).

Commercially available kits were used for estimation of biochemical parameters, namely, plasma glucose (Accurex Biomedicals, India), total cholesterol and triglyceride (Merck-Labkit, Spain), high-density lipoprotein cholesterol (HDL-c) third generation direct homogeneous assay (Auto Pure, Accurex Biomedicals, India). Each time Quality Control Sera (Bio-Rad, USA) were run along with the samples. Results of the unknown samples and quality control sera were in range and reproducible. Serum TT, FT, insulin, SHBG, LH, and FSH were measured using radioimmunoassay kits (Immunotech, Beckman Coulter Inc., Czech Republic). HbA1c was measured by high-performance liquid chromatography method (Bio-Rad D10 instrument).

The normal value for TT was 3–12 ng/ml (sensitivity - 0.04 ng/ml), for FT: 8.69–54.69 pg/ml (sensitivity - 0.18 pg/ml), for SHBG 20–70 nmol/L (sensitivity - 0.2 nmol/L), for LH: 1.8–10 IU/L (sensitivity - 0.2 IU/L), and for FSH was 1.3–11.5 IU/L (sensitivity - 0.2 IU/L). Calculated FT (cFT) was calculated from SHBG, serum albumin, and TT using the method of Vermeulen *et al*.[18]

Hypogonadism was defined as TT values <3 ng/ml.[19] Hypogonadotropic hypogonadism (HH) was defined as TT levels <3 ng/ml and LH values <10 IU/L. Primary hypogonadism was defined as TT levels <3 ng/ml and LH levels >10 IU/L.

Measurements of adiposity, namely, waist, subcutaneous body fat - biceps, triceps, subscapular, and suprailiac, were also recorded. Body fat percent was calculated by applying the four skinfold measurements into the Durnin and Womersley formula.[20]

Statistical analysis

One-way ANOVA followed by *post hoc* Tukey's test was applied for comparison of parameters between the groups. Pearson's coefficient of correlation was calculated for

all the three groups together and separately for all the above-mentioned parameters. Data were considered significantly different if $P < 0.05$.

Results

Subjects in all the three groups ($n = 50$ each) were matched for age and BMI. Anthropometric and hemodynamic measures have been presented in [Tables 1 and 2]. There was no significant difference in the measure of central obesity (waist circumference) between any of the three groups. Fasting plasma glucose and HbA1c were found to be significantly higher in Groups B and C compared to control Group A [Table 2]. There was no significant difference in fasting plasma glucose and HbA1c between Groups B and C.

Lowest levels of TT, cFT, and bioavailable testosterone were found in Group C subjects, i.e. T2DM with CAD. Group B subjects, i.e. T2DM without CAD showed intermediate levels of these indices whereas control Group A subjects had highest levels of all of these testosterone parameters [Figure 1].

Serum levels of TT, cFT, and bioavailable testosterone were found to be significantly lower in Group C subjects compared to Group A subjects [Figure 1a-c]. FT levels were also found to be lower in Group C compared to Group A though this difference was not statistically significant [Figure 1d]. There was no significant difference in any of the testosterone indices between Group A and Group B [Figure 1].

Table 1: Anthropometric parameters in the three study groups

	Mean±SD			*P*
	Group A	Group B	Group C	
Age (years)	57.08±7.80	56.22±7.68	57.72±7.51	a=0.841 b=0.909 c=0.592
BMI (kg/m^2)	24.57±3.66	25.27±3.52	24.90±3.35	a=0.582 b=0.882 c=0.863
Waist (cm)	92.08±9.54	95.05±14.24	94.32±9.68	a=0.394 b=0.587 c=0.945
Triceps (mm)	7.97±3.45	11.59±5.21	7.93±4.08	a<0.001 b=0.999 c<0.001
Biceps (mm)	6.52±1.89	9.088±4.50	7.30±3.29	a=0.001 b=0.484 c=0.026
Sub scapular (mm)	17.30±4.48	21.98±7.87	21.46±6.27	a=0.001 b=0.004 c=0.912
Suprailiac (mm)	26.84±4.45	24.99±7.95	27.47±6.11	a=0.316 b=0.871 c=0.127
Fat mass	14.75±6.68	16.74±6.40	16.46±6.32	a=0.554 b=0.640 c=0.983
Calculated body fat percent	28.27±2.83	29.6±4.68	29.34±4.40	a=0.088 b=0.151 c=0.775

a: Groups A versus Groups B, b: Groups A versus Groups C, c: Groups B versus Groups C, BMI: Body mass index, SD: Standard deviation

Hypogonadism as indicated by low testosterone levels was found to be highest in Group C subjects (40%, 20/50) followed by Group B subjects (32%, 16/50) whereas only 14% (7/50) of the subjects in Group A had hypogonadism (Groups A vs. B; $P = 0.055$, Groups A vs. C; $P = 0.006$, and Groups B vs. C; $P = 0.53$). The majority of the subjects with hypogonadism in all the three groups had HH (19/20 in Group C, 11/16 in Group B and 6/7 in Group A). We did not observe any statistically significant difference in serum levels of SHBG, LH, and FSH between the three study groups [Table 2].

Subcutaneous body fat measurements, i.e. triceps, biceps, and subscapular were found to be significantly higher in Group B subjects compared to control Group A [Table 1]. Triceps and biceps were also found to be significantly higher in Group B subjects compared to Group C [Table 1]. However, fat percent, fat mass and suprailiac fat measurements were not significantly different between the three study groups [Table 1].

We observed an overall ($n = 150$) negative correlation of TT, FT, cFT, and bioavailable testosterone with body fat percent suggesting an inverse relationship between testosterone levels and obesity [Figure 2]. In addition, an overall positive correlation was found between hypogonadism and CAD ($r = 0.177$, $P = 0.030$, $n = 150$).

IR, as indicated by homeostatic model assessment (HOMA-IR), was found to be significantly higher in Groups B and C subjects compared to Group A subjects [Table 2]. Beta cell function (HOMA-β) was found to be significantly lower in both Groups B and C subjects compared to Group A subjects [Table 2]. No significant difference was found between serum triglyceride, total cholesterol and HDL-c between the three study groups except in Groups C and B where Group C showed significantly lower levels of HDL-c compared to Group B. Serum insulin levels were also found to similar between the three study groups.

Discussion

In this study, we compared testosterone profiles of diabetes subjects with and without CAD with nondiabetic healthy controls. We found the highest prevalence of hypogonadism

Table 2: Biochemical parameters

Biochemical parameters	Mean±SD			*P*
	Group A	Group B	Group C	
Fasting plasma glucose (mg/dl)	89.36±6.58	173.34±50.33	183.10±38.90	a<0.001 b<0.001 c=0.386
HbA1c (%)	5.64±0.36	8.38±1.93	8.60±1.75	a<0.001 b<0.001 c=0.753
Insulin (μIU/ml)	6.23±5.73	6.38±6.40	7.73±7.73	a=0.994 b=0.509 c=0.582
HOMA-IR	1.38±1.29	2.50±2.42	3.31±3.25	a=0.061 b<0.001 c=0.233
HOMA-β	91.00±86.32	32.03±45.87	27.90±32.37	a<0.001 b<0.001 c=0.938
SHBG (nmol/L)	38.74±14.45	38.20±16.49	42.99±19.01	a=0.98 b=0.41 c=0.33
LH (IU/L)	6.84±4.27	7.63±3.88	6.28±3.03	a=0.54 b=0.73 c=0.17
FSH (IU/L)	10.01±5.51	9.41±4.91	9.50±5.51	a=0.94 b<0.93 c=0.99

a: Groups A versus Groups B, b: Groups A versus Groups C, c: Groups B versus Groups C, SHBG: Sex hormone binding globulin, HOMA-IR: Homeostatic model assessment-insulin resistance, HOMA-β: Homeostatic model assessment-beta, LH: Luteinizing hormone, FSH: Follicle stimulating hormone, SD: Standard deviation

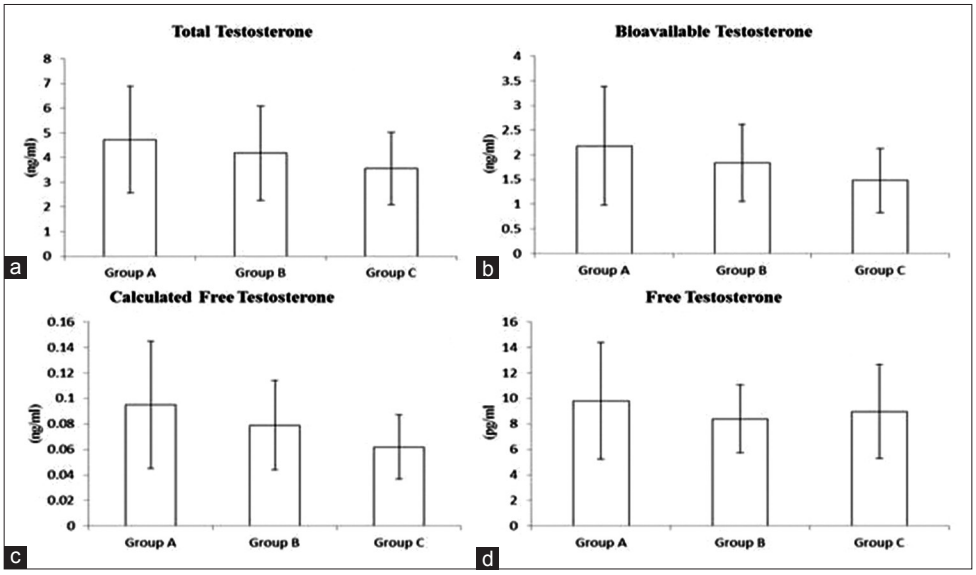

Figure 1: Various testosterone indices among the three study groups. (a) Group A versus Group B ($P = 0.29$), Group A versus Group C ($P = 0.005$), Group B versus Group C ($P = 0.21$); (b) Group A versus Group B ($P = 0.14$), Group A versus Group C ($P \leq 0.001$), Group B versus Group C ($P = 0.12$); (c) Group A versus Group B ($P = 0.12$), Group A versus Group C ($P \leq 0.001$), Group B versus Group C ($P = 0.06$); (d) Group A versus Group B ($P = 0.13$), Group A versus Group C ($P = 0.49$), Group B versus C ($P = 0.71$)

as indicated by low testosterone levels in diabetic subjects with CAD followed by diabetic subjects without CAD and then in controls. There was a significant difference in the prevalence of hypogonadism in diabetic subjects with CAD compared to controls whereas the difference fell just short of significance levels between diabetic subjects without CAD and controls.

We analyzed complete testosterone profile, namely, TT, FT, cFT bioavailable testosterone and SHBG in all the study subjects which allowed a comprehensive interpretation of testosterone status and provided a better understanding of internal validation. All testosterone measurements were carried out at 8 am which was fixed. This precaution was not taken in earlier studies. Hence, in our study, we also avoided

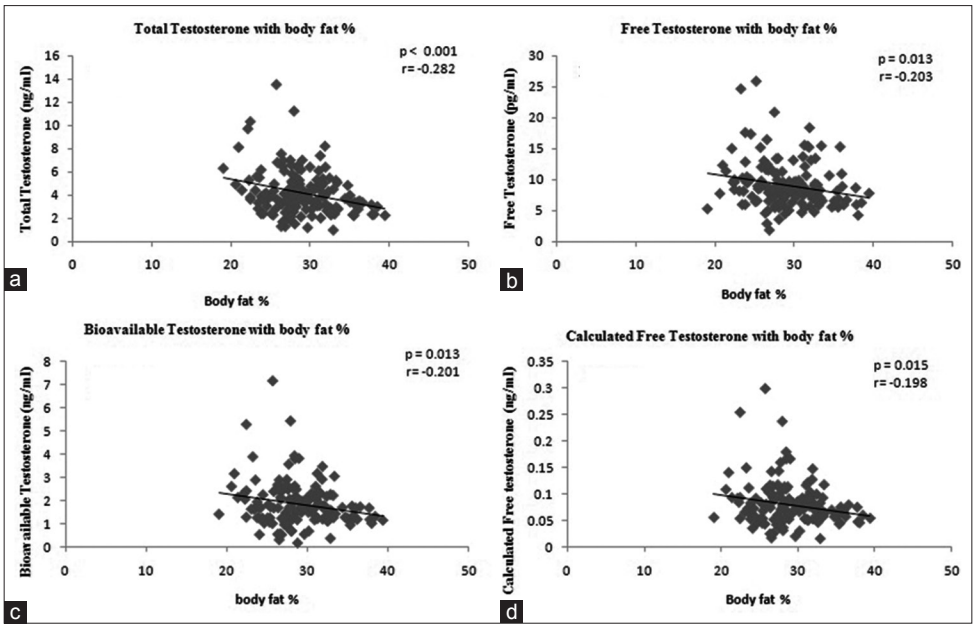

Figure 2: Correlation of testosterone indices with body fat percent (*n* = 150). (a) Total testosterone with body fat %, (b) Free testosterone with body fat %, (c) Bioavailable testosterone with body fat %, (d) Calculated free testosterone with body fat %

any fluctuations in testosterone levels due to variability in blood sampling timings. Body fat measurements were also included in our study to see if the effects of testosterone deficiency were related to its effects on lean body mass or fat content. However, we used single point sampling for testosterone examination and not repeated sampling which could have provided more accurate assessment of hypogonadism in males and it remains a limitation of the present study.

We found HH in the majority of subjects detected with testosterone deficiency (95% in diabetic with CAD group, 68 in diabetics without CAD group and 85% in NGTs). In previous studies, both higher[21] as well as lower[22] proportion of HH in hypogonadal diabetic males has been reported. It has been hypothesized that increased body fat content secondary to testosterone deficiency leads to increased conversion of testosterone to estradiol.[23] This results in enhanced suppression of hypothalamic GnRh[24-26] and LH[27] and consequent HH. Primary hypogonadism which has been reported less often is believed to occur secondary to microvascular damage in the testis.[28,29]

Testosterone indices (TT, bioavailable testosterone, and cFT) correlated negatively with the measure of central obesity, namely, waist circumference and body fat percent. TT levels also showed similar correlation with BMI and fat mass. These effects of testosterone deficiency may be contributing significantly to the associated CV risk in male T2DM subjects. Association of central obesity, higher adiposity and lower lean body mass with testosterone deficiency has been reported in earlier studies.[30-32] It has been hypothesized that low testosterone levels promote increased fat deposition and increase in adiposity.[23]

Several earlier studies have shown that deficiency in male sex hormones is associated with increased risk for CAD[3,33,34] besides its effects on lean body mass and adiposity. It has been reported that low testosterone levels are associated with markers of atherosclerosis such as increased CIMT.[4,18] A meta-analysis study showed that low testosterone levels are associated with increased CV risk and mortality.[35] This analysis also showed that testosterone replacement therapy in subjects with hypogonadism moderates metabolic components associated with CV risk.[35] Significant testosterone deficiency observed in diabetes subjects with CAD raises the important issue whether these subjects should be given testosterone replacement therapy in an attempt to reduce CV risk. This notion is also based on the findings of a recent retrospective study involving over 83,000 veterans.[36] Results of this study showed that normalization of TT levels with testosterone replacement therapy leads to a significant lowering of all causes of mortality, MI risk, and stroke.[36] Several other studies have also reported improved glycemic control, reduced IR and increased insulin sensitivity in subjects of T2DM receiving testosterone replacement therapy[37-40] which may subsequently lead to reduced CV risk in diabetes subjects. Further, it has been found that testosterone therapy reduces central obesity and consequent visceral fat mass and waist-hip ratio.[37] Effect of testosterone therapy on IR and insulin sensitivity is thought to be androgen receptor-mediated as androgen receptors are

found in much higher concentration in visceral fat depots than subcutaneous fat depots.[41]

Conclusion

The present study finds testosterone deficiency in a significant proportion of male T2DM subjects particularly those with evidence of CV disease. Low testosterone levels could contribute to a significantly higher CV risk in subjects with T2DM.

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Conflicts of interest

There are no conflicts of interest.

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