

SERUM TESTOSTERONE IN MALES WITH NEWLY DIAGNOSED TYPE 2 DIABETES AND ITS ASSOCIATION WITH GLYCEMIC STATUS AND OTHER METABOLIC INDICES

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ABSTRACT

BACKGROUND

Role of testosterone in the pathogenesis of metabolic syndrome and diabetes mellitus has been studied in recent years and an inverse relationship has been subsequently elicited. Low testosterone levels have been associated with insulin resistance and an increased risk of Type 2 diabetes (T2DM). However, limited data are available regarding association of testosterone with metabolic indices like Body Mass Index (BMI), waist circumference and lipid profile. This study was undertaken with the objective of evaluating levels of serum testosterone in newly diagnosed male T2DM and to correlate testosterone levels with the glycemetic status and other metabolic indices.

MATERIALS AND METHODS

A single point cross sectional case control study was conducted at MLN Medical College, Allahabad and its associated SRN Hospital, Allahabad during a period from March 2013 to July 2014 on 168 males between 18-60 years of age of whom 83 were diagnosed with T2DM within the past three months were taken as cases and remaining 85 patients without diabetes were taken as controls. Detailed history was obtained and clinical examination was done. Low testosterone was defined as total testosterone <241 ng/dl and its prevalence was calculated. The values of serum testosterone were correlated with Fasting Blood Sugar (FBS), Post-prandial Blood Sugar (PPBS), Glycosylated Hemoglobin (HbA1c), BMI, Waist circumference and Lipid profile of the patients.

RESULTS

Out of the 83 patients of T2DM, low serum testosterone was found in 37 (44.58%) while it was present in only 10 (11.8%) of 85 controls, which was found to be statistically significant (p value=<0.0001). The mean HbA1c in T2DM with low testosterone was 6.81±0.44% compared to 6.5±0.47% in normal testosterone group and the difference was statistically significant (p value=0.0029). Among cases there was statistical difference between low and normal testosterone values when BMI was compared (p=0.0162). It was significant among controls as well (p=0.0229).

CONCLUSIONS

Prevalence of hypogonadism was significantly higher in T2DM as compared to controls. Testosterone levels had significant negative correlation with HbA1c levels and BMI of the subjects.

KEYWORDS

Newly diagnosed type 2 Diabetes, Serum testosterone, Glycaemic status, BMI, Waist circumference, Lipid profile.

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BACKGROUND

In recent years, studies have shown an inverse relationship between testosterone, metabolic syndrome and T2DM.^[1] Testosterone has been found to play a significant role in obesity, glucose homeostasis, and lipid metabolism.

Cross-sectional epidemiological studies have reported a direct correlation between plasma testosterone and insulin sensitivity.^[2] and low testosterone levels have been

associated with an increased risk of T2DM, dramatically illustrated by androgen deprivation in men with prostate carcinoma.^[3] Several studies have suggested that men with low testosterone are at a greater risk of developing T2DM, and that low testosterone may even predict the onset of diabetes.^[4-8] Lower total testosterone and sex hormone-binding globulin (SHBG) predict a higher incidence of the metabolic syndrome. A systematic review by Ding, et al^[9] of 43 studies including 6427 men suggested that higher testosterone levels were associated with lower risk of T2DM and vice versa.

Similarly, Haffner et al^[8] demonstrated that low sex hormone-binding globulin (SHBG) and testosterone predict higher glucose and insulin levels and increased obesity. Osuna et al^[10] correlated waist circumference, body mass index (BMI), insulin, and homeostatic model assessment of insulin resistance (HOMA-IR) to testosterone levels and, in

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each case, found a significant negative correlation. Taken together, these findings raise the possibility that testosterone may have a protective function against diabetes in men.

Administration of testosterone to hypogonadal men has been found to reverse part of the unfavourable risk profile for the development of diabetes and atherosclerosis.^[11] Fukui et al^[12] demonstrated that serum testosterone levels are lower in a large number of Japanese patients with T2DM when compared with healthy men and suggested that testosterone supplementation in hypogonadal men could decrease IR and atherosclerosis. Boyanov et al^[13] also showed that men with T2DM receiving three months of testosterone supplementation have decreased fasting glucose, postprandial glucose, mean daily glucose and HbA1c values, compared with baseline. Kapoor et al^[14] reported that testosterone treatment in insulin-dependent patients reduced their insulin dosages by a mean of 7 units. Naharci et al^[15] demonstrated that long-term testosterone therapy improved insulin sensitivity and reduced body fat mass.

The present study has been undertaken to estimate the prevalence of low serum testosterone in newly diagnosed diabetic males and to find an association between low testosterone levels and glycaemic status of the patients. We further evaluated correlations between low testosterone levels and various metabolic indices, viz. BMI, waist circumference and lipid profile.

MATERIALS AND METHODS

The present case-control study was conducted on 168 subjects at MLN Medical College, Allahabad and its associated SRN Hospital, Allahabad from March 2013 to July 2014. 168 male subjects between 18-60 years of age were recruited for the study. Of these 168 subjects, 83 were T2DM who were diagnosed during the last 3 months, according to the 2012 American Diabetes Association guidelines and were considered as study subjects, either admitted to SRN Hospital or attending Medicine OPD. Rest of the 85 individuals were age matched non-diabetic healthy male volunteers who were considered for the control group.

Patients having Type 1 Diabetes, those who were on hormone replacement therapy, steroids or testosterone, patients with chronic renal or hepatic disease, HIV infection, surgically uncorrected cryptorchidism, malignancy and use of cancer chemotherapeutic agents or radiation therapy, prior infectious orchitis and those in whom surgical orchiectomy was done, were excluded from the study. A detailed history, clinical examination and relevant investigations were done in each patient. BMI and waist circumference were measured for each participant.

Serum testosterone levels (Morning sample) were measured using chemiluminescence immunoassay. Low testosterone was defined as serum total testosterone <241 ng/dl and the prevalence of its deficiency were calculated. Fasting blood glucose, post-prandial blood glucose, HbA1c and fasting lipid profile were done in the hospital laboratory.

Informed consent was taken from all the participants in the study.

Statistical Tests Applied

t test for independent samples and Chi-square test were applied on data collected to get the results.

OBSERVATIONS AND RESULTS

Table 1 shows distribution of serum testosterone in the cases and controls. Out of the 83 patients of T2DM, low serum testosterone levels were found in 37 (44.58%) while low levels were present only in 10 (11.8%) of 85 controls, which was found to be statistically significant ($\chi^2=20.84$, $df=1$, p value= <0.0001). The low testosterone subjects in BMI grouped cases and controls were tabulated (Table 2 and Fig. 1), and the difference between them was found to be statistically insignificant ($\chi^2=2.16$ $df=2$ $P=0.3396$). Among cases there was statistical difference between low and normal testosterone values when BMI matched ($\chi^2=8.25$ $df=2$ $P=0.0162$). It was significant among controls as well ($\chi^2=7.55$ $df=3$ $P=0.0229$) which showed that the difference in testosterone levels in controls might have been because of the difference in their BMI. There was significant difference in the mean testosterone levels among cases and controls when distributed as per BMI in 18.5-27.7 kg/m² category but not in ≥ 27.5 kg/m² which was likely due to small sample size in that category.

Table 3 and Fig 3 show the difference in the testosterone levels in cases with waist circumference ≥ 90 cms. and ≤ 90 cms. which was insignificant ($\chi^2=1.63$ $df=1$ $P=0.2017$). The difference in mean waist circumference among new T2DM with low testosterone was 90.7 ± 4.2 cm and normal testosterone was 89.98 ± 3.2 cm was insignificant (CI 95%, t value=0.8186, p value=0.4154). The mean HbA1c in T2DM with low testosterone was $6.81 \pm 0.44\%$ compared to $6.5 \pm 0.47\%$ in normal testosterone group and the difference between the two was statistically significant CI 95%, $t=3.0724$, $df=81$ with P value=0.0029. (Table 4 and Fig 4). The mean FBS in T2DM with low testosterone was 189.61 ± 68.2 mg% compared to 168.17 ± 49.63 mg% in normal testosterone group (Table 5 and Fig 5) and the difference between the two was not statistically significant CI 95%, $t=1.6564$, $df=81$ with P value=0.1015.

The mean PPBS in T₂DM with low testosterone was higher (278.3 ± 104.77 mg%) compared to (258.65 ± 63.78 mg%) normal testosterone group but the difference between the two was not statistically significant CI 95%, $t=1.0532$, $df=81$ with P value= 0.2954. (Table 6 and Fig 6). Serum cholesterol, triglycerides, LDL and VLDL were found to be slightly higher and serum HDL to be lower in the low testosterone subjects but none of this difference was statistically significant.

	Case n (%)	Control n (%)
Low Te	37 (44.58%)	10 (11.8%)
Normal Te	46 (55.42%)	75 (82.2%)
	83	85

Table 1. Serum Te in Case and Control Group

BMI (kg/m ²)	Cases		Controls	
	Low Te n (%)	Normal Te n (%)	Low Te n (%)	Normal Te n (%)
18.5-22.9	4 (10.8%)	16 (34.8%)	1 (10%)	27 (36%)
23-27.4	31 (83.8%)	25 (54.3%)	7 (70%)	46 (61.3%)
≥27.5	2 (5.4%)	5 (10.9%)	2 (20%)	2 (2.7%)
Total	37	46	10	75

Table 2. Te Levels in BMI Matched Cases and Controls

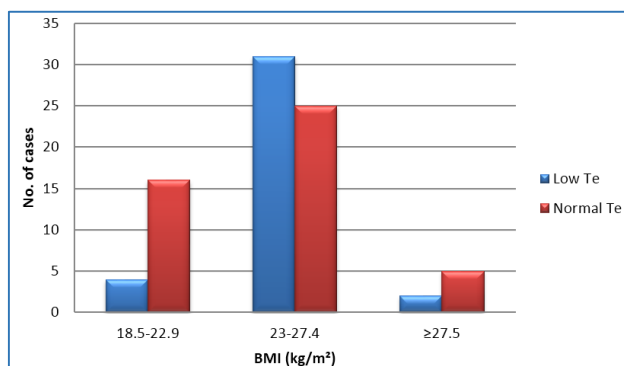


Figure 1. Bar Chart Showing Te Levels in BMI Matched Cases

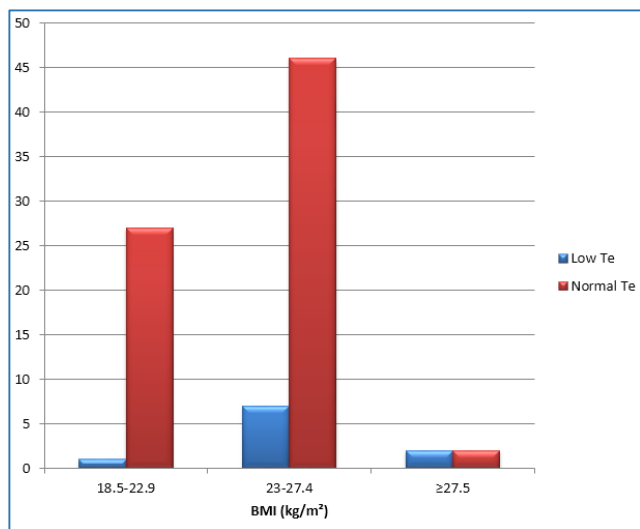


Figure 2. Bar Chart Showing Te Levels in BMI Matched Controls

Waist Circumference (cm)	Low Te n (%)	Normal Te n (%)
70-89.9	14 (37.8%)	25 (54.4%)
90-110	23 (62.2%)	21 (45.6%)
	37	46

Table 3. Waist Circumference and Te Levels

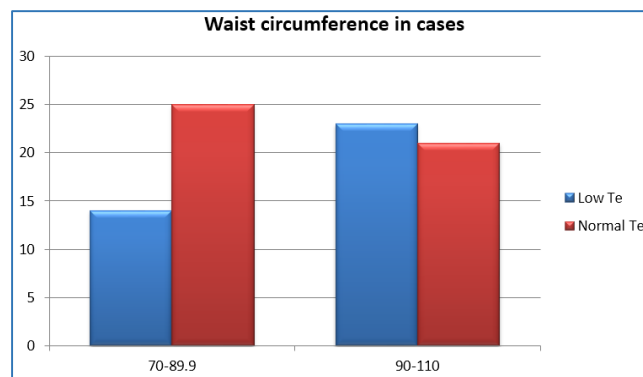


Figure 3. Bar Diagram Showing Waist Circumference in Cases

HbA1c	Low Te	Normal Te
Mean	6.81	6.5
SD	0.44	0.47

Table 4. HbA1c in Cases

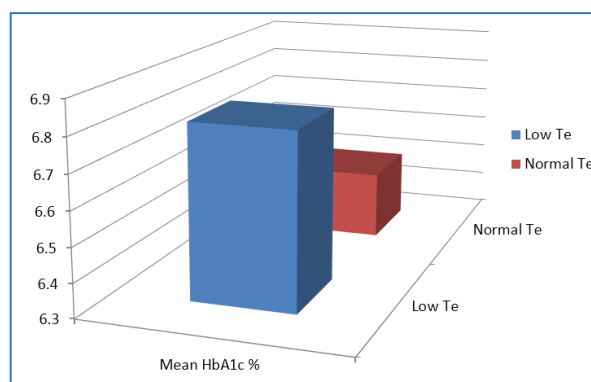


Figure 4. HbA1c in Cases

FBS mg%	Low Te	Normal Te
Mean	189.61	168.17
SD	68.2	49.63

Table 5. FBS in Cases

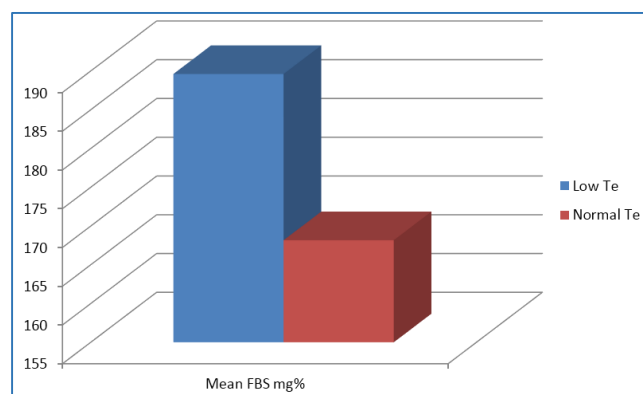


Figure 5. Mean FBS in Cases

PPBS	Low Te	Normal Te
Mean	278.3	258.65
SD	104.77	63.78

Table 6. PPBS in Cases

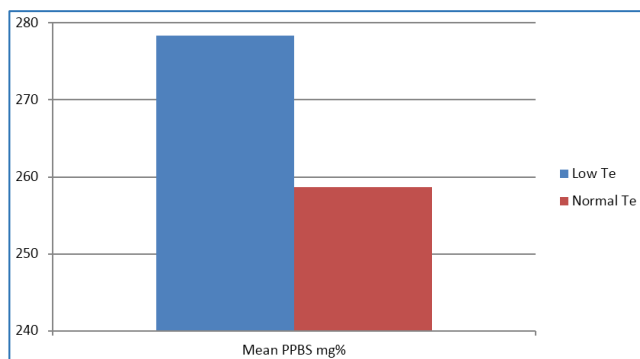


Figure 6. Mean PPBS in Cases

Lipid Profile (mg%)	Low Te (Mean±SD)	Normal Te (Mean±SD)	P value
Triglycerides	155.58±45.22	152.25±33.95	0.7026
Cholesterol	191.19±33.44	178.53 ±36.08	0.104
LDL	110.76 ±27.38	109.98±26.89	0.8967
HDL	48.28±8.05	49.44 ±8.75	0.5357
VLDL	28.09±11.05	25.58 ±8.84	0.2535

Table 7. Lipid Profile Levels and Te

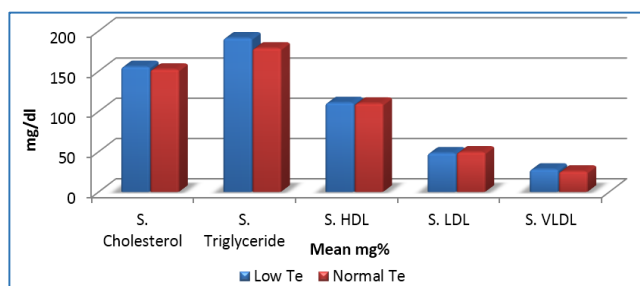


Figure 7. Lipid profile levels and Te

DISCUSSION

Low testosterone levels were found to be more prevalent in newly diagnosed T2DM (44.58%) as compared to controls (11.8%). In controls the low testosterone could be attributed to the normal ageing process which is associated with a decrease in total testosterone levels of the order of 0.5-2% per year. These observations are in conformity to those of several authors.^{16,6,17,18,19} Hayek et al²⁰ found that 36.5% of patients with T2DM had a testosterone level of <300 ng/dl, and 29% had symptoms of androgen deficiency. Kapoor et al²¹ in their study showed that 20% of diabetic men had testosterone <230 ng/dl and 31% had testosterone between 230-346 ng/dl. Grossman et al²² showed that 43% of all men with T2DM had low testosterone levels (<288 ng/dl) which reached to 61% in men aged ≥80. Testosterone biosynthesis is regulated primarily by pulsatile secretion of LH and serum testosterone levels reflect the integrity of the hypothalamic-pituitary-gonadal (HPG) axis.

Therefore low testosterone levels noted in cases of insulin resistance may indicate a defect at one or more functional levels of the HPG axis. In the insulin-resistance state, Leydig cell function, particularly steroidogenesis, may be impaired by changes in the production of hormones and

cytokines locally in the target tissue and in adipose tissue. Although several studies suggest that increasing insulin resistance may be attributed to a decrease in testosterone secretion in men, it is not fully clear how the HPG axis mediates the interplay between testosterone and insulin levels. Other potential mechanisms for low testosterone levels in T2DM include reduced or absent stimulatory effect of insulin on Leydig cells, increased leptin level causing Leydig cell dysfunction, increased TNF levels in inhibiting steroid biosynthesis in Leydig cells.

Mean testosterone levels fell progressively with increase in BMI, and the trend was significant across the groups. These findings were in conformity with the finding of several studies.²³⁻²⁵ Kapoor et al²¹ showed that testosterone significantly and negatively correlated with both BMI and waist circumference. Grossman et al²² showed that individuals with low testosterone levels were also more likely to have a BMI >30 kg/m². Among cases there was statistical difference between low and normal testosterone values when BMI matched suggesting higher BMI also to be involved in low testosterone in them. Obesity and associated hyperinsulinemia suppress the action of LH in the testis, which can significantly reduce circulating testosterone levels, even in men under the age of 40. The vicious circle of low testosterone and obesity has been described as the hypogonadal/obesity cycle. In this cycle, a low testosterone level results in increased abdominal fat, which in turn leads to increased aromatase activity. This enhances the conversion of testosterone to oestrogens, which further reduces testosterone and increases the tendency toward abdominal fat. Thus, data from our study suggest that obesity/insulin-resistance is associated with hypogonadism and low testosterone levels.

The difference in the mean waist circumference in low and normal testosterone group was statistically insignificant in the study which was also seen in a study by Umoh et al²⁶ Rhoden et al²³ showed in their study that association of low testosterone with waist hip ratio was significant. In newly diagnosed T2DM with low testosterone the mean HbA1c was higher as compared to normal testosterone group and this was statistically significant. The bidirectional relationship between testosterone and insulin resistance likely affects this finding and the severity of symptoms is a factor of the duration of disease process. No significant association was found between FBS, PPBS and testosterone in cases which were consistent with findings of Umoh et al²⁶ Kapoor et al²¹ in their study also had reported that testosterone was significantly associated with HbA1c values. There was no significant difference in the parameters of lipid profile among low testosterone and normal testosterone group in our study although the mean values of LDL, VLDL, triglycerides and cholesterol were higher in the low testosterone group.

Also the mean values of HDL were lower in the low testosterone group but this finding was not significant. Umoh et al²⁶ reported that HDL was the only lipid related with testosterone. In their study HDL showed inverse correlations with testosterone which were significant in male

individuals with metabolic syndrome and T2DM but not in controls ($p < 0.05$). Reports of Malkin, et al²⁷ in hypogonadal men with T2DM showed that testosterone correlated negatively with total cholesterol, but had no effect on other components of the lipid profile while Van Pottelbergh et al²⁸, Stanworth et al²⁹ Roger et al³⁰ in their work found a positive association between LDL-C and testosterone. Grossman et al²² also reported elevated triglycerides and reduced HDL cholesterol levels among hypogonadal T2DM. It is possible that reduced pituitary and gonadal function could reduce gonadotrophins and ACTH which ultimately results in reduced clearance and accumulation of HDL with low testosterone synthesis.

One of major strength of this study is its matched case control design which is controlled for age and BMI by design and analysis, thereby minimizing bias due to confounding. Cases were recruited on basis of diabetic status measured by objective laboratory values which avoided selection biases. Both cases & controls were selected from same source population. Moreover newly diagnosed (within 3 months) T2DM subjects were taken in the study and to minimize bias due to age subjects above 60 years were excluded from the study. Hence any low testosterone value in the study population was more likely due to the presence of T2DM rather than to fall due to increasing age.

Limitations of the Study

Our study also had various limitations. Firstly this was a cross-sectional design, which made it impossible to determine whether diabetes preceded or followed the decline in serum testosterone levels although this factor has been taken care of by taking newly diagnosed T2DM patients. A single low testosterone level is inadequate for making the diagnosis of hypogonadism, given the variability in serum testosterone levels that can result from circadian rhythms, the pulsatile nature of its secretion, use of concomitant medications and measurement variations. Free testosterone values are known to represent the actual evidence of hypogonadism but they were not measured as the conventional methods are not accurate enough to exactly measure their levels. Furthermore the cross sectional design of this study limits the ability to assess causality. Due to the constraints of a time bound study and because of the stringent selection criteria, the sample size was small and hence the results are subjected to Type II error and they cannot be generalized. Therefore, further studies containing large number of subjects both in patient and control group are needed to assess the association of low testosterone and even Free testosterone in new T2DM.

CONCLUSIONS

Prevalence of hypogonadism was significantly ($P < 0.0001$) higher in newly diagnosed T2DM as compared to controls.

As far as glycaemic status of the patient is concerned, testosterone levels had significant negative correlation with HbA1c levels but not with FBS and PPBS. In metabolic indices, only BMI had a significant negative correlation with

testosterone levels, both for diabetic and non-diabetic individuals.

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