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Testosterone Deficiency and Its Association with Impaired Blood Glucose: A Cross Sectional Study

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Abstract
Recent research indicates that men with impaired glucose regulation (pre-diabetes) or diabetes exhibit lower serum total testosterone (TT) levels compared to normoglycemic men. In India, there is a high incidence and prevalence of diabetes mellitus (DM) and pre-diabetes among the middle-aged population. While most studies have focused on serum TT levels in elderly men with pre-diabetes or diabetes, there is a notable lack of data concerning this association in middle-aged men. The objectives of this study were to investigate the serum TT levels in middle-aged men with DM or pre-diabetes and compare them with normoglycemic men. This cross-sectional, observational study included 178 nonsmoking, non-tobacco using and non-alcoholic men aged between 31 and 60 years. Anthropometric measurements, serum FBG levels and serum TT levels were assessed. Men with pre-diabetes and diabetes demonstrated significantly lower serum TT levels compared to non-diabetic men. Additionally, serum TT levels were found to negatively correlate with WC, BMI and blood glucose levels, with a significant correlation observed specifically with WC. Low serum TT levels are associated with both pre-diabetes and diabetes. Further prospective studies are needed to determine whether this association is causal.

INTRODUCTION

India exhibits a significant prevalence of Type 2 Diabetes Mellitus (T2DM) at 7.1%, with even higher rates in urban areas reaching 9%. Additionally, prediabetes also has a high prevalence and often remains undiagnosed for extended periods. The mean age of onset for T2DM is approximately 42.5 years[1,3]. Among men with T2DM, there is a notable prevalence of hypogonadism or low normal testosterone levels. Compared to the general population, diabetic men typically exhibit lower serum total testosterone (TT) concentrations. Moreover, low serum TT levels are associated with insulin-resistant conditions such as metabolic syndrome[4-6].

The majority of studies in this domain have focused on elderly patients and have frequently failed to exclude factors influencing serum testosterone levels. In our country, T2DM is prevalent among middle-aged men, adversely affecting their productive years. Our study aims to investigate the association between serum TT levels and impaired blood glucose levels in middle-aged men with T2DM or impaired fasting glucose (IFG). Additionally, we aim to compare serum TT levels between men with normal blood sugar levels and those with impaired blood sugar levels. Finally, we intend to determine the degree of correlation between serum TT and variables such as age, fasting blood glucose (FBG), body mass index (BMI) and waist circumference (WC).

MATERIAL AND METHODS

This research employed a cross-sectional and observational design. Participants were selected from individuals attending OPDs who met specific criteria. The inclusion criteria were men aged between 31 and 60 years who expressed a willingness to participate in the study. Exclusion criteria included smokers or individuals using tobacco, alcoholics, documented cases of hypogonadism and those with a history of infectious orchitis, testicular torsion, trauma, or untreated varicocele. Additional exclusions were individuals with liver or renal failure, those on sex hormone replacement therapy, or on medications such as statins, diuretics, flutamide, opiates, glucocorticoids, anticonvulsants, antithyroid drugs, spironolactone, carbamazepine and phenytoin. Participants with malignancies, thyroid disorders, diseases of the hypothalamus and/or pituitary gland, those who refused to provide informed consent and individuals with any acute inflammatory illness or chronic inflammatory disease were also excluded.

Upon meeting the criteria, participants were informed about the study's objectives and methods, and written consent was obtained from those who chose to participate. A comprehensive history was taken and anthropometric measurements, including weight, height and waist circumference (WC), were recorded. Body mass index (BMI) was calculated using the standard formula: BMI = weight in kilograms/ height in meters squared. WC was measured at the midpoint between the lower rib margin and the iliac crest using a non-elastic measuring tape, with measurements taken while the subject was standing and at the end of expiration.

A venous blood sample was collected from each participant after an overnight fast, between 8 AM and 10 AM, under aseptic conditions. Blood glucose levels were measured using the enzymatic colorimetric method on a fully automated Biochemistry analyzer. Fasting blood glucose (FBG) levels were classified as impaired if FBG was =100 mg/dL and participants were categorized as diabetic if FBG was >126 mg/dL.

Serum total testosterone (TT) levels were measured using the competitive immunoenzymatic method with the Testosterone ELISA kit. Absorbance readings were taken using the microplate reader. Reference values for TT levels provided by the manufacturer were: = 55 years: 212-601 ng/dL and >55 years: 11-725 ng/dL.

For statistical analysis, baseline parameters were expressed as mean±standard deviation (SD). Comparisons between participant groups were performed using the Student's t-test. Pearson correlation analysis was conducted to assess the relationship between TT and age, FBG, BMI and WC. Additionally, participants were divided into quartiles based on the distribution of TT levels and interquartile comparisons were made using analysis of variance (ANOVA) tests.

RESULTS AND DISCUSSIONS

The baseline characteristics of the study participants are summarized in Table 1. The mean age of the non-diabetic group was 54.3 years (SD±7.5), compared to 52.8 years (SD±8.5) in the prediabetic/diabetic group, with no statistically significant difference between the two groups (P = 0.23). In terms of waist circumference (WC), a significant difference was observed, with the prediabetic/diabetic group having a higher mean WC, which was statistically significant (P<0.01). Similarly, the mean body mass index (BMI) differed significantly between the groups. Fasting blood sugar (FBS) levels were markedly higher in the prediabetic/diabetic group. Finally, serum testosterone levels were significantly lower in the prediabetic/diabetic group, with a mean of 239.73 ng/dL (SD±135.65), compared to the non-diabetic group, which had a mean of 322.76 ng/dL (SD±189.24), indicating a significant difference (P<0.05).

The distribution of various parameters according to serum total testosterone (TT) levels is presented in Table 2. Serum testosterone levels showed a highly significant increase across the quartiles (P<0.01). The

Table 1: Comparison of baseline parameters among study participants

Parameters	Non-Diabetic (n=68)	Prediabetic/Diabetics (n=110)	p-value
Age; mean ± SD	54.3 ± 7.5	52.8 ± 8.50	0.23
WC(cm); mean ± SD	91.18 ± 9.18	99.19 ± 6.89	<0.01
BMI; mean ± SD	26.68 ± 2.73	25.5 ± 2.79	<0.01
FBS; mean ± SD	92.96 ± 9.98	123.41 ± 38.48	<0.01
S. Testosterone (ng/dL)	322.76 ± 189.24	239.73 ± 135.65	<0.05

Table 2: Distribution of parameters as per the distribution of serum TT levels

Parameters	1st quartile	2nd quartile	3rd quartile	4th quartile	p-value
Age; mean ± SD	50.2 ± 8.2	49.7 ± 8.0	46.3 ± 7.5	46.9 ± 5.4	0.35
No. of subjects (n)	80	77	12	9	-
WC (cm); mean ± SD	97.5 ± 8.2	94.8 ± 8.7	90.5 ± 3.3	91.0 ± 5.7	<0.01
BMI; mean ± SD	26.3 ± 3.1	25.4 ± 2.4	25.4 ± 1.0	24.3 ± 2.2	0.27
% of pre-diabetic/diabetic	75 (n=60)	57.14 (n=44)	16.67 (n=2)	22.22 (n=2)	<0.01
S. Testosterone (ng/dL)	137.6 ± 57.5	311.6 ± 55.1	544.6 ± 79.6	754.7 ± 80.6	<0.01

Table 3: Correlation of various parameters with serum total testosterone

Variables	Correlation coefficients	p-value
Age	-0.256	<0.01
Waist circumference	-0.171	<0.01
Body mass index	-0.154	<0.05
Fasting blood sugar	-0.132	0.17

mean serum TT levels were 137.6 ng/dL (SD±57.5) in the 1st quartile, 311.6 ng/dL (SD±55.1) in the 2nd quartile, 544.6 ng/dL (SD±79.6) in the 3rd quartile and 754.7 ng/dL (SD±80.6) in the 4th quartile. These results demonstrate that higher serum TT levels are associated with lower waist circumference, a lower percentage of pre-diabetic/diabetic individuals and a trend towards lower BMI, indicating a potentially protective role of higher testosterone levels against metabolic risk factors.

Table 3 presents the correlation analysis between various parameters and serum total testosterone levels. The analysis reveals significant inverse correlations between serum total testosterone levels and parameters such as age, waist circumference and BMI, indicating that lower testosterone levels are associated with older age, higher waist circumference, and higher BMI. The correlation with fasting blood sugar, though negative, did not reach statistical significance.

This study focused on middle-aged Indian men. Upon comparing diabetics and prediabetics with nondiabetic men, we discovered that the former group exhibited significantly lower mean serum TT levels. Dividing the study sample into quartiles based on serum TT levels revealed that the lower two quartiles had the highest prevalence of diabetes and prediabetes.

Several studies have reported an association of low serum TT with Type 2 Diabetes Mellitus (T2DM). Dhindsa *et al*. (2004) conducted a cross-sectional study on men with T2DM (mean age 54.7±1.1 years) and investigated low serum TT and hypogonadism. They found that 43.7% of study subjects had serum TT levels <300 ng/dL. Based on Free testosterone levels, 33% were hypogonadal. Additionally, BMI correlated significantly and inversely with serum total T and free T[6,7]. Al Hayek *et al.* (2013) in a descriptive cross-sectional study on diabetic men (mean age 52.6±11.2 yrs), found that 36.5% of the study sample had low serum TT (<300 ng/dL). Again, higher BMI was more likely to be associated with low serum TT levels[8]. Mattack *et al.* (2015) conducted a case-control study comparing diabetics with non-diabetics (age group 31-71 years). They observed that diabetics had significantly low serum TT as well as free testosterone compared to non-diabetics[4].

Several studies have also reported an association of low serum TT with high BMI and/or high WC. In 2010, Dhindsa *et al.* conducted a cross-sectional study to determine the prevalence of low serum TT, free testosterone and bioavailable testosterone in men with different BMI. Men with BMI in the obese and overweight categories had significantly low levels of serum TT, free testosterone and bioavailable testosterone, both in diabetics and non-diabetics[9]. Kupelian *et al.* (2008) conducted a cross-sectional study to study the relationship between testosterone levels and components of metabolic syndrome. Results showed that decreased levels of serum testosterone were associated with increased odds of having higher WC and high fasting blood sugar[10]. Akishita *et al.* (2010) conducted a cross-sectional study on middle-aged men (mean age 52.6±11.2 yrs) to determine the relation of serum TT levels with metabolic syndrome. They found a statistically significant negative association between low serum TT levels and higher WC. They also found a similar negative association between fasting glucose levels and serum TT levels[11].

Central obesity has long been recognized as a factor contributing to both insulin resistance and low testosterone levels in men. However, recent evidence has indicated a bidirectional relationship between obesity and low testosterone. Singh *et al.* (2008) observed that dihydrotestosterone inhibited the differentiation of human mesenchymal stem cells and preadipocytes into adipocytes[12]. Testosterone has been shown to enhance catecholamine lipolysis in vitro and reduce lipoprotein lipase activity and triglyceride

uptake in human abdominal adipose tissue in vivo[13]. Consequently, low testosterone levels may contribute to obesity development. Conversely, increased adiposity can lower testosterone levels by converting testosterone to estradiol in adipose tissue. Moreover, the secretion of proinflammatory cytokines by adipose tissue suppresses the hypothalamo-pituitary-gonadal axis at multiple levels, leading to hypogonadism[13]. This establishes a self-perpetuating cycle ultimately resulting in insulin resistance development.

The role of low serum testosterone levels in insulin resistance development is suggested by a prospective study conducted by Haring *et al.* (2009). They followed a cohort of men for 5 years and found that those with low baseline testosterone levels had a higher risk of developing metabolic syndrome. This risk remained significant even after adjusting for age, waist circumference and the effects of smoking and/or alcohol[14,15].

CONCLUSION

Impaired blood glucose levels are strongly associated with reduced serum testosterone (TT) levels in middle-aged men. This association is significant as low serum TT levels can lead to various adverse health outcomes, including decreased muscle mass, increased body fat, reduced bone density and diminished libido, potentially impacting overall quality of life and increasing the risk of metabolic syndrome and cardiovascular diseases. Understanding this relationship is crucial for public health strategies aimed at preventing and managing diabetes and its complications. By recognizing that impaired glucose regulation is linked to lower TT levels, healthcare providers can better educate patients about the importance of maintaining normal blood glucose levels.

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