Association of low total testosterone levels and impaired blood glucose levels in middle aged men – A cross-sectional study

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ABSTRACT

Background: Recent studies have shown that men with impaired glucose levels (pre-diabetes)/diabetes have lower serum total testosterone (TT) levels as compared to normoglycemic men. India has a high incidence and prevalence of diabetes mellitus (DM)/pre-diabetes in the middle aged population too. Most studies have researched about the serum TT levels in elderly pre-diabetic/diabetic men, but there is lack of information about such association in middle aged men. Aims and Objectives: These objectives of this study are to study the levels of serum TT in middle aged men with DM/pre-diabetes; to compare the serum TT levels in men with DM/pre-diabetes with normoglycemic men; and to observe the correlation between fasting blood glucose (FBG) and serum TT, body mass index (BMI), and waist circumference (WC). Materials and Methods: It is a cross-sectional, observational study. The study subjects were 150 nonsmoking, nontobacco addict, and nonalcoholic men aged between 31 and 60 years. Anthropometric measurements, serum FBG levels, and serum TT were measured. Results: The pre-diabetic and diabetic men had significantly low levels of serum TT as compared to non-diabetic men. Furthermore, serum TT levels correlated negatively with WC, BMI and blood sugar levels, but significant correlation was found only in the case of WC. Conclusion: Low serum TT levels are associated with pre-diabetes as well as diabetes. Whether the association is casual or not requires prospective study.

KEY WORDS: Diabetes Mellitus; Impaired Glucose Tolerance; Pre-diabetes; Total Testosterone

INTRODUCTION

India has a high prevalence of Type 2 Diabetes Mellitus (T2DM) (7.1%); which is even higher in urban areas (9%).¹ Not only diabetes but also prediabetes has high prevalence, which often goes undiagnosed for long periods.² Average age of onset is only 42.5 years.³ Men with T2DM have a high prevalence of hypogonadism or low normal testosterone levels.⁴ When compared with normal population diabetic men tend to have lower serum total testosterone (TT) concentrations.⁵ Low serum TT levels are also associated with insulin resistant conditions such as metabolic syndrome.⁶

Most of the studies in this field have examined elderly patients and have often not excluded factors affecting serum testosterone levels.

In our country, T2DM is rampant in middle-aged men taking a toll on the productive years of their lives.

We aim to study the association between serum TT levels and impaired blood glucose levels in middle aged men with T2DM or impaired fasting glucose (IFG). We also aim to
compare the serum TT levels between men with normal blood sugar levels and men having impaired blood sugar levels. Finally, we aim to find out the degree of correlation of serum TT with age, fasting blood glucose (FBG), body mass index (BMI), and waist circumference (WC).

MATERIALS AND METHODS

Ethical approval for conducting the study was obtained from the Institutional Ethical Committee. This is a cross-sectional and observational study.

The study subjects were selected from persons attending various specialty OPDs who fulfilled the following criteria:

Inclusion Criteria
1. Men aged between 31 years and 60 years of age
2. Willingness to participate in the study

Following were the Exclusion Criteria
- Smokers/Tobacco consumption
- Alcoholics
- Documented hypogonadism
- History of Infectious orchitis, testicular torsion, trauma, varicocele (untreated)
- Liver failure
- Renal failure
- Sex hormone replacement therapy
- Under medications such as statins, diuretics, flutamide, opiates, glucocorticoids, anticonvulsants, antithyroid drugs, spironolactone, carbamazepine, phenytoin.
- Malignancy
- Thyroid disorders
- Hypothalamus and/or pituitary gland diseases
- Refusal to give informed consent
- Any kind of acute inflammation illness or chronic inflammatory disease.

If the subjects satisfied the criteria, they were explained about the study objectives and methods. If they chose to participate, a written consent was obtained from them.

A detailed history, anthropometric measurements, namely weight, height and WC were recorded and BMI was calculated using standard techniques. Calculation of BMI was done by the formula (BMI = weight in Kilogram/Height in meter$^2$). WC was determined at a point midway between the margin of the lower rib and iliac crest with the help of a non-elastic measuring strip surrounding the body, horizontally. Measurement was taken while subject was standing erect and at the end of expiration.

A venous blood sample of the subjects was taken after an overnight fast between 8 am and 10 am under all aseptic precautions.

- Blood glucose was tested on by enzymatic colorimetric method on “Fully automated Biochemistry Analyzer XL 640” by Transasia Biomedical Ltd. Mumbai.
- Blood glucose was said to be “impaired” if the FBG level was ≥100 mg/dL IFG.[7]
- The subjects whose blood sugar was greater than 126 mg/dL were also grouped as diabetics.[7]
- Serum TT was tested by competitive immunoenzymatic method. (Testosterone ELISA Merilisa kit). Absorbancies were read by ChroMate Model 4300 microplate reader.
- Reference values for men as per the manufacturers:- ≤55 years = 212–601 ng/dL
  >55 years = 11–725 ng/dL.

Statistical Analysis

All baseline parameters are expressed as mean ± SD. Comparisons between groups of participants were performed using the Student’s $t$-test. Pearson correlation analysis was done for analyzing the degree of correlation between TT and age, FBG, BMI, and WC. For further analysis, population was divided into quartiles based on the distribution of TT levels. Interquartile comparisons were done with analysis of variance test.

RESULTS

All variables are presented as mean ± SD. Total number of study participants was 151. 93 men were prediabetic/diabetic. Out of 151 subjects, 44% had diabetes, 16.5% had IFG, and 38.6% had normal blood sugar levels.

Table 1 shows the comparison of characteristics between the non-diabetics and pre-diabetics/diabetics. The two populations did not differ significantly in age ($P = 0.2$), but significant difference was found between the two populations in case of serum TT ($P = 0.04^*$), BMI ($P = 0.002^{**}$) and WC ($P = 0.002^{**}$). BMI and WC were significantly higher, while serum TT was significantly lower in the prediabetics/diabetics.

Table 1: Comparison of variables among study participants

<table>
<thead>
<tr>
<th>Variables</th>
<th>Non-Diabetic (n=58)</th>
<th>Prediabetics/ Diabetics (n=93)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD)</td>
<td>51.7±7.7</td>
<td>50.3±8.10</td>
<td>0.2</td>
</tr>
<tr>
<td>Testosterone level (mean±SD)</td>
<td>307.39±199.3</td>
<td>251.29±142.79</td>
<td>0.04*</td>
</tr>
<tr>
<td>Fasting blood sugar level (mean±SD)</td>
<td>88.73±9.5</td>
<td>129.3±40.5</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>Body mass index (mean±SD)</td>
<td>25.4±2.6</td>
<td>26.84±2.94</td>
<td>0.002**</td>
</tr>
<tr>
<td>Waist circumference (cm) (mean±SD)</td>
<td>91.6±9.65</td>
<td>97.9±7.26</td>
<td>0.002**</td>
</tr>
</tbody>
</table>

*Significant, **Highly significant, ***Very highly significant
To analyze the association of serum levels of TT with prevalence of pre-diabetes/diabetes, BMI and WC, the population was divided into quartiles as per levels of serum TT [Table 2]. Variables were compared among the quartiles [Table 2]. In the lowest quartile of testosterone (TT ≤242 ng/dL), 75% men had pre-diabetes/diabetes. In the second quartile (TT = 243–462 ng/dL), 56% had pre-diabetes/diabetes. Only 20% and 25% men had pre-diabetes/diabetes in the 3rd and 4th quartiles, respectively. The trend was found to be highly significant across the quartiles. Men in the first two quartiles were older, and had higher central obesity as evidenced by higher mean WC. However, BMI was not significantly different among the quartiles.

Table 3 shows the correlation coefficients of the characteristics with serum TT. Serum TT correlated negatively with age (r = −0.244, P = 0.002**). Correlation of TT with fasting blood sugar and BMI were weak and insignificant, but that of TT with WC was significant, (r = −0.18, P = 0.02*).

**DISCUSSION**

This study focuses on middle-aged Indian men. On comparing the diabetics and prediabetics with nondiabetic men, we found that the former group had significantly lower mean serum TT levels. When the study sample was divided into quartiles based on serum TT levels, the lower two quartiles had the highest prevalence of diabetes and prediabetes.

Similar observations were noted in case of BMI and WC. On comparing diabetics and prediabetics with the non-diabetics, the former had significantly higher BMI and WC. Similarly, BMI and WC increased from 1st to 4th quartile of serum TT levels, but this trend was statistically significant for only the WC, and not for BMI.

The serum TT levels correlated inversely with FBS, BMI and WC. This correlation was significant only in the case of WC and not with BMI, indicating stronger association of TT with visceral obesity. Many of the diabetics who were under medication had normal blood sugars, so this may explain the weak correlation between serum TT levels and FBS.

Following are few examples of the studies that have found association of low serum TT with T2DM:

Dhindsa et al. (2004) conducted a cross-sectional study on men having T2DM (mean age 54.7 ± 1.1 years) and investigated the presence of low serum TT and hypogonadism. 43.7% of study subjects had serum TT levels <300 ng/dL. Based on Free testosterone levels, 33% were hypogonadal. Furthermore, BMI correlated significantly and inversely with serum total T and free T.[4]

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 study sample had low serum TT (<300 ng/dL). Again, higher BMI was more likely to be associated with low serum TT levels.[5]

Mattack et al. (2015) did a case control study comparing diabetics with non-diabetics (age group 31–71 years). They observed that the diabetics had a significantly low serum TT as well as free testosterone as compared to non-diabetics.[5]

Following are few examples of the studies that have found association of low serum TT with high BMI and/or high WC:

2010 Dhindsa et al. undertook 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 obese and overweight category had significantly low level of low serum TT, free testosterone and bioavailable testosterone. This was true in case of diabetics as well as non-diabetics.[9]

Kupelian et al. (2008) did a cross-sectional study to study 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) did a cross sectional study on middle aged men (mean age 52.6 ± 11.2 yrs) to determine relation of serum TT levels with metabolic syndrome. They found statistically significant negative association between low serum TT levels and higher WC. They also find similar

### Table 2: Distribution of variables according to the distribution of serum TT levels

<table>
<thead>
<tr>
<th>Variables</th>
<th>First quartile TT≤242 ng/dL</th>
<th>Second quartile TT=243–462 ng/dL</th>
<th>Third quartile TT=463–682 ng/dL</th>
<th>Fourth quartile TT=683–905 ng/dL</th>
<th>P ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>49.5±8.3</td>
<td>49.3±8.03</td>
<td>45.4±7.75</td>
<td>46.0±5.58</td>
<td>0.3 (NS)</td>
</tr>
<tr>
<td>Number of subjects (n)</td>
<td>68</td>
<td>65</td>
<td>10</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>Testosterone levels (ng/dL)</td>
<td>145.8±61.42</td>
<td>328.1±57.84</td>
<td>572.0±83.8</td>
<td>793.1±84.9</td>
<td>&lt;0.00001***</td>
</tr>
<tr>
<td>% of pre-diabetes and diabetics</td>
<td>75 (n=51)</td>
<td>56.92 (n=37)</td>
<td>20 (n=2)</td>
<td>25 (n=2)</td>
<td>0.005***</td>
</tr>
<tr>
<td>Body mass index</td>
<td>26.75±3.25</td>
<td>25.77±2.5</td>
<td>25.62±0.96</td>
<td>24.72±2.30</td>
<td>0.2</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>96.23±8.62</td>
<td>95.05±9.19</td>
<td>90.05±3.5</td>
<td>90.8±5.9</td>
<td>0.005**</td>
</tr>
</tbody>
</table>

*Significant, **Highly significant, ***Very highly significant. ANOVA: Analysis of variance, TT: Total testosterone
negative association between fasting glucose levels and serum TT levels.\(^{[11]}\)

Chrysohoou et al. (2013) did a cross-sectional study on the elderly Greek population to determine association between components of metabolic syndrome and serum TT levels. Men having low serum TT (<289 ng/dL) had significantly higher mean WC compared to men with higher serum TT levels.\(^{[6]}\)

Hence, an association among low serum TT, high blood sugar levels and high WC is existing as per the observations of these studies. Our study shows similar findings.

Central obesity has been known to be contributing to both insulin resistance as well as low testosterone levels in men. However, recent evidence has suggested that the relationship between obesity and low testosterone may be bidirectional. Singh et al. (2008) observed that dihydrotestosterone inhibited the differentiation of human mesenchymal stem cells and preadipocytes into adipocytes.\(^{[12]}\) Testosterone enhances catecholamine lipolysis in vitro and reduces lipoprotein lipase activity and triglyceride uptake in human abdominal adipose tissue in vivo.\(^{[13]}\) Hence, low levels of testosterone may be contributing to the development of obesity. On the other hand, increased adiposity lowers testosterone by conversion of testosterone to estradiol in the adipose tissue. Furthermore, secretion of proinflammatory cytokines by adipose tissue leads to suppression of hypothalamo-pituitary-gonadal axis at multiple levels, thus leading toward hypogonadism.\(^{[13]}\) Hence, this becomes a self-perpetuating cycle ultimately leading to the development of insulin resistance.

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

**Strengths of Study**

Our study had strict exclusion criteria and we included only those subjects who did not have the any factors influencing testosterone levels. Hence, we have attempted to lessen the confounding factors.

Furthermore, our study focuses on the middle-aged men only, which is not the case in many of the previous studies.

**Limitations of Study**

It is a hospital-based study, so it lacks the true representation of the extent of problem in the general population.

Free testosterone was not measured. The levels of TT also depend on SHBG.

**CONCLUSION**

Impaired blood glucose levels are associated with low serum TT levels in middle-aged men. Awareness of this association can be helpful to stimulate healthy lifestyle measures in population.

**REFERENCES**


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<table>
<thead>
<tr>
<th>Variables</th>
<th>Correlation coefficients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.244</td>
<td>0.002**</td>
</tr>
<tr>
<td>Fasting blood sugar level</td>
<td>-0.126</td>
<td>0.12</td>
</tr>
<tr>
<td>Body mass index</td>
<td>-0.146</td>
<td>0.07</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>-0.18</td>
<td>0.02*</td>
</tr>
</tbody>
</table>

*Significant, **Highly significant
association of testosterone and the metabolic syndrome in men is consistent across race and ethnic groups. J Clin Endocrinol Metab 2008;93:3403-10.


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