ORIGINAL ARTICLE

Testosterone Levels with Insulin Resistance in Type 2 Diabetes Mellitus in Men

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ABSTRACT

Objective: To determine the association of testosterone levels with insulin resistance in type 2 diabetes mellitus (T2DM).

Study Design: A Cross Sectional Observational Study.

Place and Duration of Study: This study was conducted at department of Chemical Pathology Army Medical College Rawalpindi from 11th Nov 2014 to 11th Nov 2015.

Materials and Methods: The study included 110 male participants. Two groups were made. Group A, included 55 patients of T2DM selected randomly from Endocrinology Department of Military Hospital Rawalpindi. Group B included healthy controls. Each group was further categorized on the basis of age and decade wise sub groups were made. Fasting plasma glucose (FPG), serum testosterone levels, serum sex hormone binding globulin levels (SHBG), glycosylated hemoglobin and fasting insulin levels were checked using fasting blood samples. The insulin resistance was calculated using Homeostatic Model for Assessment of Insulin Resistance (HOMA-IR). Data obtained was analyzed by SPSS version 20.

Results: Mean serum testosterone levels in group A (n=55) 9.36±5.06nmol/L was significantly lower ($P \leqslant 0.0001$) as compared to group B (n=55) 15.10±6.99nmol/L. Fasting plasma glucose (11.50±3.35 vs. 4.23±0.63nmol/L), HbA1c (6.86±0.35 vs. 5.05±0.45%), serum insulin (10.61±4.87 vs. 5.71±2.43µIU/ml) and insulin resistance calculated by HOMA-IR (5.51±3.73 vs. 1.07±0.45) were significantly higher in group A as compared to group B.

Conclusion: The present study shows that a lower levels of serum testosterone are found in diabetic patients. Moreover there is significant negative correlation of serum testosterone with insulin resistance.

Key Words: *Type 2 Diabetes Mellitus, Testosterone, Insulin Resistance, Homeostatic Model Assessment-Insulin Resistance.*

Introduction

Diabetes mellitus (DM) is a metabolic disorder with inappropriate glycemic levels either due to absolute insulin secretion deficiency or reduction in the insulin effectiveness.[1] Several studies during the past few years have shown that male patients of T2DM have a significantly higher prevalence of low testosterone levels as compared to age matched healthy males.[2,3] The Leydig cells of testes secrete male sex steroid hormone testosterone (95%). It circulates either as free form (2%) or bound to albumin and sex hormone binding globulin (SHBG) in the serum. There are three phases of testosterone surge in a man's life i.e. during fetal life, shortly after birth and finally at puberty till 20 years of age, thereafter it starts decreasing with advancement of age.[4] Testosterone exerts its physiological effects by activating androgen receptor either directly or through its metabolite 5α-dihydrotestosterone (5α-DHT). Testosterone may also be aromatized to estradiol which in turn exerts its effects through estrogen receptor α (ER α).[5]

The bioavailable or free amount of testosterone depends on the level of SHBG as it is specific carrier protein of testosterone. Higher SHBG levels will result in free testosterone levels to be low. Conversely, SHBG lower levels will in turn cause free testosterone levels to be high. Free testosterone being the active form makes this relationship important. Thus men with normal total testosterone but high SHBG may have symptoms of low testosterone as free testosterone levels are low. Men with low testosterone have low metabolic rate hence are prone to develop obesity, which in turn leads to

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IR.[6-8] Visceral adiposity also causes aromatization of testosterone to estradiol in fat cells. High circulating levels of estradiol will in turn suppress the production of testosterone causing its deficiency. Testosterone deficiency will then suppress lipolysis, reduce the metabolic rate leading to visceral fat deposition and insulin resistance.[3,9,10] Hence a vicious cycle is initiated which plays the key role in pathogenesis of T2DM.

Low testosterone and diabetes often goes hand in hand. In fact men with T2DM are much likely to have low testosterone levels as men who don't have T2DM.[11,12] Similarly numerous other studies have also highlighted IR and T2DM association with low serum testosterone levels.[13-15]

Such study has not been carried out in our population. Hence this study was planned to determine the association of testosterone levels with insulin resistance in type 2 diabetes mellitus (T2DM).

Materials and Methods

A cross sectional observational study was carried out at Chemical Pathology Department, Army Medical College Rawalpindi from 11th Nov 2014 to 11th Nov 2015. A total of 110 male individuals were included in the study by convenient sampling technique from the endocrinology department of Military Hospital Rawalpindi. They were divided into two groups. Group A consisted of 55 patients of T2DM and group B consisted of 55 healthy controls who had no major illness such as coronary heart disease, diabetes mellitus, thyroid disorders, and liver or kidney diseases. Each group was further categorized on the basis of age decade. Five ml venous sample was obtained from left median cubital vein after an overnight fast of 8-12 hours from the participants under aseptic conditions. Centrifugation of the blood was done at 4000 rpm for 5 minutes for separation of plasma. Analysis of Fasting plasma glucose (FPG) was done on fresh plasma. Serum was frozen at -30˚C for estimation of serum testosterone, insulin and SHBG levels. Two milliliter of whole blood was collected in Ethylenediaminetetraacetic acid (EDTA) containers for analysis of HbA1c.

Chemistry auto-analyzer Selectra E was used to measure FPG. Fully automated hormone analyzer, Immulite 1000, based on the principle of chemi-luminescence immunoassay technique was used to measure serum testosterone, insulin and SHBG levels. HOMA-IR formula (FPG levels x Fasting Insulin levels/22.5) was used to calculate insulin resistance. Ion exchange resin method was used to estimate HbA1c levels. The data was entered on data base program SPSS version 20 and results of the test were subjected to appropriate statistical analysis. Independent t-test was used for comparing the quantitative data. Pearson's Correlation co-efficient was used to analyze the association of serum Testosterone with other variables. P-value of < 0·05 was considered statistically significant.

Results

A total of 110 participants were included in the study. Out of those 55 were diabetics and 55 were age and gender matched healthy subjects.

Comparison of biochemical profile of different analytes in diabetic patients (Group A) and healthy controls (Group B) are summarized in Table I. The mean serum testosterone levels (mean ±SD) in diabetic patients is 9.36±5.06nmol/L as compared to healthy controls 15.10±6.99nmol/L with significant p-value of <0.001. The mean serum insulin levels (mean±SD) in diabetic patients is 10.61±4.87µIU/ml as compared to healthy controls 5.71±2.43µIU/ml with significant p-value of <0.001. The insulin resistance of diabetic patients is significantly higher i.e 5.51±3.73 as compared to healthy controls 1.07±0.45 (P-value <0.001).

Table I: Comparison of the biochemical profile of the studied groups (n=110)

Variables (with reference range)	Group A (Diabetic) n=55	Group B (Control) n=55	P-Value
Testosterone(nmol/L) (8.86-36.47)	9.36±5.06	15.10±6.99	<0.001**
SHBG (nmol/L) (13.3-90.0)	40.59±16.87	59.26±18.30	<0.001**
FPG (mmol/L) (3.3-5.6)	11.50±3.35	4.23±0.63	<0.001**
HbA1C (%) (4.0-6.0)	6.86±0.35	5.05±0.45	<0.001**
Insulin (µIU/mL) (5-25)	10.61±4.87	5.71±2.43	<0.001**
Insulin Resistance (<1.0)	5.51±3.73	1.07±0.45	<0.001**

Note: *P-value<0.05, **=P<0.01

Comparison of serum testosterone levels at different age groups in diabetic patients (Group A) and healthy controls (Group B) are summarized in Table II. Significantly lower levels of serum testosterone was noted in all age groups of diabetic patients as compared to healthy controls.

Table II: Comparison of testosterone levels at different age groups

Age (years)	Group A (Diabetic)	Group B (Control)	P-Value
30-40 (n=15)	9.01±8.09	16.06±7.78	0.022*
41-50 (n=11)	9.87±4.06	14.59±5.07	0.026*
51-60 (n=16)	8.75±3.64	16.28±9.65	0.007**
61-70 (n=13)	8.96±1.38	12.08±1.71	0.016**

Note: *P-value<0.05, **=P<0.01

Correlation of serum testosterone levels with FPG, HbA1c, serum insulin and insulin resistance in different age groups of diabetic patients is summarized in Table III. These results clearly shows significant negative correlation of serum testosterone with FPG, HbA1c, serum insulin and insulin resistance.

Table III: Correlation of testosterone levels with various parameters in diabetics

Age category	SHBG	FPG	HbA1c	Insulin	IR
Age (years)	r	r	r	r	r
30-40 (n=15)	-0.268	-0.044	-0.013	-0.311	-0.217
41-50 (n=11)	0.370	-0.358	-0.030	-0.058	-0.166
51-60 (n=16)	0.259	-0.441	-0.073	-0.433	-0.668
61-70 (n=13)	0.756	-0.053	-0.350	-0.111	-0.296

Discussion

This study was under taken to assess the association of testosterone levels with insulin resistance in type 2 diabetes mellitus in men. The principal observation of this study is that mean testosterone levels in diabetic patients is significantly lower as compared to the healthy controls. This finding is in agreement with studies carried out by Stellato et al, Goto et al, Ho et al and various others with similar results.[11-18] This study therefore establishes that serum testosterone levels are lower in type 2 diabetic males as compared to healthy controls.

Another important finding of this study is significant negative correlation of serum testosterone with insulin resistance. Serum insulin levels are much higher in diabetic patients as compared to healthy controls. Moreover there is significant insulin resistance in diabetic patients as calculated by HOMA-IR. This finding is also in agreement with studies carried out by Oh et al, Grossman et al and Goto et al.[14-19] Another important observation of the study was negative association of fasting plasma glucose (FPG) and HbA1c with serum testosterone. This finding is in line with studies carried out by Dhindsa et al and Elsagheir et al.[20,21]

The main limitation of our study is relative small sample size and financial constraints in carrying out costly endocrine tests. Further well designed studies with larger sample are suggested to assess the management strategies of T2DM to address the testosterone deficiency.

Conclusion

The present study shows lower levels of serum testosterone in diabetic (male) patients. Moreover there is significant negative correlation of serum testosterone with insulin resistance.

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