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Serum Testosterone Level in Type 2 Diabetes Mellitus

Mubeena Laghari[1*], Shazia Murtaza[2], Zuha Talpur[3], Khalil Ahmed Memon[4], Aneela Tehzeen[5] and Mohsina Hamid[6]

[1]Department of Biochemistry, LUMHS, Pakistan.
[2]Clinical Trial Unit, Prince Naif Health Research Center, King Saud University Medical City, Riyadh, KSA.
[3]Isra University Hyderabad, Pakistan.
[4]Pathology Department, LUMHS, Pakistan.
[5]Gynae and Obstetrics Department, Gambat Institute of Medical Sciences (GIMS), Pakistan.
[6]Department of Biochemistry, Independent Medical Collage, Faisalabad, Pakistan.

Authors' contributions

This work was carried out in collaboration among all authors. Authors ML and ZT designed the study, Authors KAM and MH performed the statistical analysis. Authors SM and AT wrote the protocol and wrote the first draft of the manuscript. Authors AT, MH and KAM managed the analyses of the study. Author SM managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aim: To determine the serum testosterone levels in the type 2 diabetes mellitus and its correlation with biochemical parameters of glycemic and lipid metabolism.
Methodology: A cross sectional study was conducted at Department of Biochemistry and Department of Medicine, A cross sectional study was conducted at the Department of Biochemistry, Diabetic outpatient department and Department of Medicine, Liaquat University Hospital. Male type 2 diabetics (n=100) and age matched male (n=100) were included as cases and control for study purpose. Diagnosed cases of type 2 DM, male gender and 40 – 60 years of age were included in the study protocol. Physical examination of male type 2 diabetics was performed by a consultant physician. Sera were separated from blood and stored in refrigerators at

**Corresponding author: E-mail: drmubeena2002@gmail.com;*

– 20^{0}C. Blood glucose, A1C, and blood lipids (cholesterol, triglycerides, LDLc and HDLc) were detected by standard laboratory methods. Serum testosterone was measured by ELISA (competitive immuno- assay) assay commercial kit. Data was entered in Statistical software SPSS 21.0 version (IBM, Incorp, USA) for statistical analysis (P≤0.05).

Results: Mean±SD age of male type 2 diabetics was 53.2 ± 11.1 years compared to 54.5±10.4 years in control (P=0.056). Serum Testosterone in cases was 10.85±4.7 mmol/L compared to 13.39±3.8mmol/L in control (P=0.0001). Low testosterone level was noted in 46% male.Serum Testosterone shows inverse correlation with RBG (r= -0.31, P=0.003), A1C (r= -0.23, P=0.014), Cholesterol (r= -0.24, P=0.014), TAGs (r= --0.78, P=0.0001) and HDLc(r= -0.70, P=0.0001). Serum testosterone proved positively correlated with LDLc(r= 0.670, P=0.0001).

Conclusion: The present study finds low serum testosterone in male type 2 diabetes mellitus patients

Keywords: Testosterone; type 2 diabetes mellitus; cholesterol.

1. INTRODUCTION

Diabetes mellitus (DM) is primarily a disorder of glucose metabolism characterized by chronic hyperglycemia [1,2]. It is caused by relative or absolute deficiency of hormone secreted by the β-cells of Islets of Langerhan's in Pancreas called the insulin. DM is of two types called; the type 1 and type 2 DM. DM is a multifactorial disorder regarding its etiology. Glucose metabolism is characterized primarily by hyperglycemia and secondarily by the hyperlipidemia and dyslipidemia. Type 2 DM (T2DM) affects different organ systems of body in particular the insulin independent cells of body causing end organ damage in nerve cell, kidneys, etc.[1,2] Several studies [3-6] have reported low testosterone levels in type 2 diabetics resulting in hypogonadism. It has been debated that the testosterone has relationship with onset of DM as risk factor that has not been proved. It has been shown type 2 diabetics have low circulating testosterone levels that might affect the glycemic status of diabetics. Low testosterone levels in type 2 diabetics have been said to predict the onset of diabetes. Testosterone is a cholesterol derived hormone that might be affected by the dyslipidemia and hyperlipidemia in diabetics. It has been reported that the Leydig cells of testes are adversely affected by the diabetic hyperglycemia and dyslipidemia resulting in their dysfunction and reduced secretion of testosterone in male population. As the testosterone plays vital role in different biological functions in the male life hence its low level has been predicted affecting the sexual life of male adversely. Numerous studies [7-9] have narrated negative association of serum testosterone, hyperglycemia and insulin resistance in the male diabetic's. As the DM is an endocrinopathies it may produce other endocrinopathy such as those of low testosterone resulting in disturbed biological functions in the male population. There seems to be highly significant association between these two endocrinopathies influencing each other mutually. Low serum testosterone occurs because of a number of mechanisms, such as hyperglycemia, dyslipidemia, increased oxidants load, Leydig cell injury, enzyme defects, androgen enzymopathy, androgen receptor polymorphism, etc. Visceral obesity of diabetics may contribute to hypogonadism. Sex hormone binding globulins (SHBGs), disturbed gonadotropin synthesis and secretion by Leydig cells have been implicated mechanisms. Oxidative load increases the cytokine secretion of TNF-α (tumor necrosis factor – α), Interleukins (IL-1β, IL-6), disturbed aromatase activity results in estrogen excess and male sex dysfunction [7-9]. Various studies have narrated strong association of low testosterone with metabolic syndrome in Caucasian and Asian men [7-9]. Currently, research has focused on Leydig cell dysfunction in type 2 diabetics, [9] it was concluded that testosterone deficiency and the DM burden is increasing in Pakistan [1,2] hence there is need for further research studies to be conducted at national level to make data available for highlighting the problem of male hypogonadism in type 2 diabetics. The present study was conducted to estimate serum testosterone levels and its correlation with biochemical parameters of glycemic and lipid control in the type 2 male diabetics.

2. MATERIALS AND METHODS

The present cross sectional study was conducted at the Department of Biochemistry, Diabetic outpatient department and Department of Medicine, Liaquat University Hospital. Study

covered duration of January 2018 to February 2019. Sample size was calculated by using Rao software. Diagnosed cases of type 2 DM of male gender were selected according to inclusion and exclusion criteria. One hundred male type 2 diabetics and one hundred age matched male were included in study purpose. Male type 2 diabetics were inducted through non-probability purposive technique. Records of Diabetes mellitus were checked to fulfill the inclusion criteria (dianogsed DMT2, both sexes mal and female). Diagnosed cases of type 2 DM, male gender and 40 – 60 years of age were included in the study protocol. Normal healthy male of similar age were included as control. Participants were asked of volunteer inclusion in the study protocol. They were informed interviewed the purpose of study, advantages and disadvantages. They were informed that the study will to improve the male sex function in the future and will not cause any physical or economic loss. Volunteers who gave full voluntary willingness qualified for inclusion in the study protocol. They were informed that the expenses of Laboratory investigations will be paid by the researcher. Physical examination of male type 2 diabetics was performed by a consultant physician. Findings were noted in a pre – structured proforma. Participants handling was as per the "Helsinki`s Declaration" of human research. Patient data was kept confidential in lockers. Only principal researcher had access to the personal data. Volunteers were informed of giving consent for blood sampling. Venous blood sample was done by a disposable syringe preferably from the ante – cubital fossa after applying tourniquet. Five ml venous blood was taken in disposable syringe and divided into two parts. 2 ml was put in the sodium fluoride tubes and 3 ml was centrifuged at x3000 rpm for 15 minutes. Sera were separated from blood and stored in refrigerators at – 20^0C. Blood glucose, A1C, and blood lipids (cholesterol, triglycerides, LDLc and HDLc) were detected by standard laboratory methods. Serum testosterone was measured by ELISA (competitive immuno-assay) assay commercial kit. Cobas chemistry analyzer was used for biochemical analysis at the laboratory. Lower limit of serum testosterone was taken as <3 ng/ml [9]. Values of cholesterol (≥200 mg/dl), TAGs (≥150 mg/dl), LDLc (≥100 mg/dl) and HDLc (≤50 mg/dl) were taken as hyperlipidemia/dyslipidemia [10]. Data was entered in Statistical software SPSS 21.0 version (IBM, Incorp, USA) for statistical analysis. Numerical data was analyzed by Student`s t-test and results were presented as mean±SD. Linear Pearson`s correlation was run to check association/ correlation of serum testosterone with the glycemic and lipid parameters. Level of significance was at 95% confidence interval (P≤0.05).

3. RESULTS

Mean±SD age of male type 2 diabetics was 53.2 ± 11.1 years compared to 54.5±10.4 years in control (P=0.056). Fasting (FBG) and random blood glucose (RBG), A1C (%), Cholesterol, TAGs, LDLc, and HDLc differed statistically highly significant between cases and control (P<0.05). Serum Testosterone in cases was 10.85±4.7mmol/L compared to 13.39±3.8mmol/L in control (P=0.0001) (Table 1 and Fig. 1). Of 100 male type 2 diabetics, 46% male had low serum testosterone. Correlation output of serum testosterone with different study variables is shown in Table 2. Serum Testosterone shows inverse correlation with RBG (r= -0.31, P=0.003), A1C (r= -0.23, P=0.014), Cholesterol (r= -0.24, P=0.014), TAGs (r= --0.78, P=0.0001) and HDLc(r= -0.70, P=0.0001). Serum testosterone proved positively correlated with LDLc(r= 0.670, P=0.0001) (Table 2).

Table 1. Age and laboratory findings in cases and control

	Cases (n=100)	Control (n=100)	P-value
Age (years)	53.2 ± 11.1	54.5±10.4	0.056
FBG (mg/dl)	162.7 ± 25.3	82.5 ± 10.3	0.001
RBG (mg/dl)	299.3 ± 5.7	142.5 ±31.3	0.003
A1C (%)	8.4 ± 1.7	5.5 ± 0.24	0.0001
Cholesterol (mg/dl)	8.402 ± 1.2	5.752 ± 0.24	0.0001
TAGs (mg/dl)	702.5±11.3	602.5±12.3	0.0001
LDLc (mg/dl)	137.6±10.9	99.6±3.3	0.0001
HDLc (mg/dl)	32.9±7.3	42.9±5.3	0.0001
Testosterone (mmol/L)	10.85 ± 4.7	13.39 ± 3.8	0.0001

Table 2. Correlation of serum testosterone with glycemic and lipid parameters

FBG	r-value*	0.197
	p-value**	0.03†
RBG	r-value*	-0.31
	p-value**	0.003†
A1C	r-value*	-0.23
	p-value**	0.014†
Cholesterol	r-value*	-0.24
	p-value**	0.014†
TAGs	r-value*	-0.78
	p-value**	0.0001†
LDLc	r-value*	0.67
	p-value**	0.0001†
HDLc	r-value*	-0.70
	p-value**	0.0001†

*†. Correlation calculated at 0.05 level; *. r-value - Correlation co-efficient; *. P-value - Significance leve*

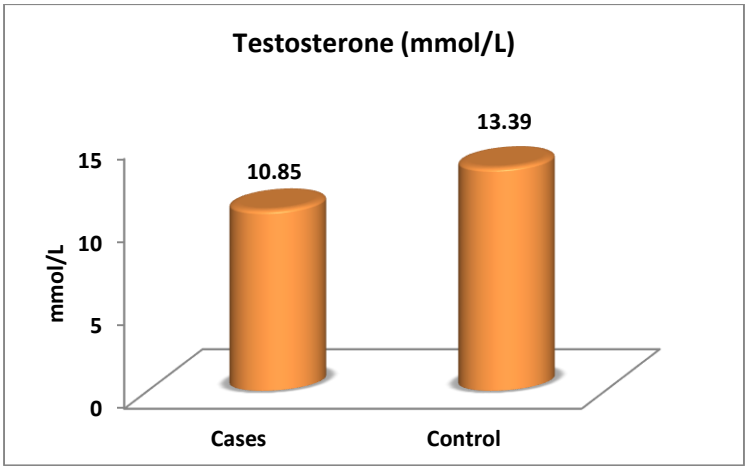

Fig. 1. Mean serum testosterone level in cases and control

4. DISCUSSION

The present study is first cross sectional study analyzing the serum testosterone levels in the type 2 diabetes mellitus and its correlation with biochemical parameters of glycemic and lipid metabolism. Major objective of present research was to estimate the serum testosterone levels in type 2 diabetic male cases comparing with the normal healthy age matched control. Serum testosterone is most important gonadal androgen hormone that plays role in mediating the various physiological functions in the human body. Interestingly, the present study found low serum testosterone levels in type 2 male diabetics compared to control (p-value < 0.0001). In present study, the Mean±SD age of male type 2 diabetics was 53.2 ± 11.1 years compared to 54.5±10.4 years in control (P=0.056). Age finding of present study is in agreement with previous studies [6,7,9]. In present study, the Serum Testosterone in cases was 10.85±4.7 mmol/L compared to 13.39±3.8 mmol/L in control (P=0.0001) (Table 1 and Fig. 1). A previous study by Kundu et al. [9] reported mean serum testosterone in male type 2 diabetics was 3.51±1.26 ng/ml compared to 5.88±2.34 ng/ml in non-diabetics showing low serum testosterone in male type 2 diabetics that is in line keeping with the present study. Out of 100 male type 2 diabetics, 46% male had low serum testosterone that is in agreement with a previous study.[9] Farooq et al. [10] analyzed serum testosterone in 300 male type 2 diabetics Kashmiri patients and reported serum testosterone deficiency was found in 42%. Tiwari et al. [11] estimated serum testosterone in 83 type 2 diabetics and reported deficiency in 44.58% of male diabetics. The findigns are in keeping with the present study that noted testosterone deficiency in 46% of male type 2 diabetics. Kim et al. [12] analyzed 464 male type 2 diabetics and reported low serum testosterone in 34.9% that is lower compared to present and other previous study [9-11]. Similar

findigns of low serum testosterone have been reported by Yeap et al. [13] They reported diabetic male had had twice low serum testosterone compared to non – diabetic male [13]. Yao Q et al. [14] and Ding et al. [15] conducted a systematic review and meta – analysis of thousands of male type 2 diabetics and confirmed low serum testosterone levels were found. Kupelian et al. [16] suggested low serum testosterone may be considered a marker of type 2 DM with insulin resistance. Yialamas et al. [17] suggested reflection of serum testosterone and insulin resistance that was associated through body composition and it was concluded the testosterone might also regulate insulin sensitivity. Other previous study reported direct association of low testosterone with the insulin resistance in type 2 DM [18] and remission of type 2 DM after testosterone therapy [19]. It has been suggested the testosterone decline is slow and constant physiological process occurring over decades and begins in early life peaking after the third or fourth decade of life [9]. Exact cause of testosterone reduction occurring through decades is not known [9]. We found high glycemic and lipid parameters in present study (Table 1), the findings are in agreement with previous studies [9-13]. We found inverse correlation of serum testosterone with RBG (r= -0.31, P=0.003), A1C (r= -0.23, P=0.014), Cholesterol (r= -0.24, P=0.014), TAGs (r= --0.78, P=0.0001) and HDLc (r= -0.70, P=0.0001). Serum testosterone proved positively correlated with LDLc (r= 0.670, P=0.0001) (Table 2). The findings are in agreement with previous studies [9-13]. Previous studies [9-12] found inverse association of serum testosterone with fasting and random blood glucose. Kim et al. [12] reported the negative association of serum total testosterone with blood glucose (r=– 0.142, P=0.002) and A1C values (r=– 0.097, P=0.040) in male diabetics. Findings are in line keeping with the present study. Similar finding of negative linear correlation of fasting blood glucose and A1C with the testosterone is reported by another previous study [10]. They showed a significant negative correlation of serum testosterone level with Fasting glucose ($r = -0.252$, $p = 0.001$) and A1C ($r = -0.697$, $p = 0.001$) [10]. The findings of present study are worth to report the low serum testosterone occurs in male type 2 diabetics showing association with glycemic and lipid parameters. Limitations of present study are; first- small sample size, and second – cross sectional study design. The study sample belonged to peculiar ethnic group of male diabetic population hence findings cannot be generalized to other settings.

5. CONCLUSION

The present study finds low serum testosterone in male type 2 diabetes mellitus patients. Negative correlation of serum testosterone is noted with blood glucose, glycemic control, cholesterol, triglycerides and high density lipoprotein. Serum testosterone proved positively correlated with low density lipoprotein cholesterol in present study. Further research with large sample size in indigenous male diabetics is warranted.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

All authors declare that ‘written informed consent was obtained from the patient.

ETHICAL APPROVAL

Study was conducted after the approval of Ethics committee.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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