PREVALENCE OF TESTOSTERONE DEFICIENCY IN PATIENTS OF DIABETES MELLITUS LESS THAN 40 YEARS OF AGE

Praveen K. Malik[1], Archana Rani[2]

[1]Assistant Professor, Department of Internal Medicine, ESIC Medical College and Hospital, Faridabad.
[2]Assistant Professor, Department of Anaesthesiology, Hamdard Institute of Medical Sciences and Research, New Delhi.

ABSTRACT

BACKGROUND

Diabetes mellitus is common endocrine disorder which involves multiple organs and leads to significant morbidity and mortality due to accompanying complications. Erectile dysfunction, reduced libido, orgasmic dysfunction, and retrograde ejaculation are established complications found with variable prevalence in men with diabetes.

METHODOLOGY

In the present study, total 90 male patients of diabetes mellitus of age below 40 years were taken from medical outpatient department and indoor patients of medical wards of a tertiary care teaching hospital of South Delhi. They were evaluated for complains regarding sexual dysfunction. Hormonal assays of serum free testosterone, LH, FSH, C-peptide, HbA1c and lipid profile were carried out in all patients.

RESULT

Present study shows that testosterone deficiency is quite common in young diabetic patients. Low serum free testosterone was more common in type 2 diabetes as compared to type 1 diabetes (38.46% Vs 29.41%). BMI has significant effect on serum free testosterone levels. Patients with higher BMI had negative correlation to free testosterone although testosterone deficiency was also seen in few lean patients. High serum triglyceride and low serum HDL were seen more frequently in patients with low free testosterone.

CONCLUSION

This study reveals that hypogonadism is not a rarity even at initial stages of diabetes. This study, although small, highlights importance of assessment of young diabetic patients for sexual dysfunction and hypogonadism.

KEYWORDS

Diabetes mellitus, Hypogonadotropic hypogonadism, Erectile dysfunction, Serum testosterone.

MeSH TERMS

Diabetes mellitus, Hypogonadism, Erectile Dysfunction, Testosterone.

HOW TO CITE THIS ARTICLE: Malik PK, Rani A. Prevalence of testosterone deficiency in patients of diabetes mellitus less than 40 years of age. J. Evid. Based Med. Healthc. 2016; 3(9), 275-278. DOI: 10.18410/jebmh/2016/66

INTRODUCTION: Diabetes mellitus is a heterogeneous metabolic group of diseases which is chronic, lifelong in nature. It involves almost all organ of human body including reproductive system leading to varied manifestations varying from loss of libido, erectile dysfunction to infertility.

Diabetes is becoming rampant in India so much so that by 2030 it is predicted that by 2030 diabetes mellitus may afflict up to 79.4 million individuals in India, while China (42.3 million) and the United States (30.3 million) will also see significant increases in those affected by the disease.[1] Unfortunately, the incidence of diabetes is increasing in young people also which may have hugely adverse effect in their reproductive and sexual life.

The prevalence of hypogonadotropic hypogonadism is high and expected in patients with diabetes mellitus in various surveys. It is still known whether it is the low serum testosterone level which is responsible for the development of diabetes or vice versa. The purpose of this review is to find the clinical and biochemical assessment of hypogonadism in young diabetic male patients.

METHODOLOGY: The present study titled "Prevalence of testosterone deficiency in patients of Diabetes Mellitus less than 40 years of age" was undertaken in the Department of Medicine, in a tertiary care teaching medical college of South Delhi. The study sample included diabetic male patients of age less than 40 years who presented in ward and outpatients in the Department of Medicine.

All diabetic male patients of age under 40 years were selected without any bias for duration and education status. Patients with HIV infection, chronic renal disease, testicular

Submission 04-01-2016, Peer Review 15-01-2016,
Acceptance 23-01-2016, Published 30-01-2016.
Corresponding Author:
Dr. Praveen K. Malik,
Assistant Professor,
Department of Internal Medicine,
ESIC Medical College and Hospital,
Faridabad, Haryana.
E-mail: drpraveenmalik@gmail.com
DOI: 10.18410/jebmh/2016/66

disease and cirrhosis are to be excluded from the study. Informed consent was sought from all possible participants and willing persons were requested to fill the questionnaire regarding sexual and reproductive health. Prior permission was taken from the institutional ethical committee.

The diagnosis of diabetes was made as per recommendations of WHO[2] and National Diabetes Data group (American Diabetes association, 2014)[3]

FPG≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
A1C≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose≥200 mg/dL (11.1 mmol/L).
Table 1: Criteria for the diagnosis of diabetes

*In the absence of unequivocal hyperglycaemia, results should be confirmed by repeat testing.

The diagnosis of types of diabetes based on serum C-peptide level. Type 1 diabetes have low or missing level of C-peptide <206pmol/L or 0.618ng/ml[4] while in Type 2 diabetic patients, C-peptide level is either normal or high. Normal range of C-peptide is 0.78–1.89ng/ml.[5] The diagnosis of hypogonadism based on serum free testosterone level. For diagnosis of hypogonadism, serum free testosterone level is < 6.9pgm/ml.[6]

All patients are to be evaluated for complaints regarding sexual dysfunction. Hormonal assay of serum free testosterone, LH, FSH, C–peptide, HbA1c and lipid profile were carried out in all patients. All the data were collected and analysed using SPSS statistical package. Data are expressed as mean values (SD). Statistical analysis was performed by using one way ANOVA, Paired T test, 2 sample test and Kruskal Wallis for non-parametric data. A probability value of <0.05 was considered significant.

RESULT AND DISCUSSION: In our study which was conducted in a teaching medical college between January 2015 to October 2015. Total of ninety male diabetics' patients less than 40 years willingly participated in the study. Out of ninety 27 were between the age group of 21-30 years whereas 63 were in 31-40 age group. In present study, among patients with type 1 diabetes 15 of 51(29.41%) had low level of free testosterone, while among type 2 diabetes 15 of 39(38.46%) had low level of free testosterone in serum.

Following table summarizes incidence of low free testosterone in different studies as compared to present one.

Study	Low free testosterone in type 1 diabetes (%)	Low free testosterone in type 2 diabetes (%)
Tomar et al, 2006[7]	6%	26%
Chandel et al, 2008[8]	8%	58%
Grossmann et al, 2008[9]	20.3%	57%
Present study,2015	29.41%	38.46%
Table 2		

In present study, out of 90 patients 57(63.3%) had decreased sexual desire and absent morning tumescence. Out of these 57 patients 30(52.6%) had low serum free testosterone. Prevalence of low free testosterone with decreased sexual desire and absent morning tumescence in type 1diabetes was 15 out of 51(29.4%) while in type 2 it was 15 out of 39(33.3%). Similar observations have been reported by Fedele et al, who observed prevalence of erectile dysfunction in type 1 diabetes to be 26% while in type 2 diabetes it was 37%.[10]

Occurrence of low free testosterone with decreased sexual desire and absent morning tumescence in type 1diabetes was 50% while that in type 2 diabetes was 55.6%, the difference observed between type 1 and type 2 was insignificant. Normal sexual desire was observed in 33 (36.7%) patients and all of these patients had normal serum free testosterone.

In present study, out of 90 patients 18(20%) were obese (BMI >30Kg/mt^2). Among these 18 patients, 12(66.7%) had low serum free testosterone. Whereas Dhindsa et al reported prevalence of low testosterone in obese diabetes to be 50%.[11] The phenomenon of testosterone deficiency in diabetic patients with higher BMI could be due to increase in adipose tissues mass which results in increased aromatase activity, leading to enhanced conversion of testosterone in to estradiol which further suppresses hypothalamic-pituitary-testicular axis and decreases testosterone secretion.[12] Adipose tissue, which is considered an endocrine organ and produces a host of hormones and cytokines, may modulate insulin action and regulate Leydig cell function. Leptin production is tightly coupled to insulin resistant and may play a key role in steroid biogenesis and reduced testosterone levels. Leptin levels have been shown to be inversely correlated with serum testosterone levels,[13,14] and increased circulating leptin may be involved in the pathogenesis of Leydig cell dysfunction.[15] Other possible mechanism involved in pathogenesis of obesity related low testosterone is insulin resistance.[11]

Low BMI (<18.5Kg/mt2) was observed in 6 out of 90(6.67%) patients, of which 3(50%) had low free testosterone. Whereas, Dhindsa et al observed that testosterone deficiency in lean diabetes patients was 44%.[11]

This observation indicates that testosterone deficiency can occur even in diabetic patients with low BMI.

In present study, prevalence of high cholesterol (>200 mg/dl) in diabetic patients was 12 out of 90(13.3%), of which 6(50%) had low serum free testosterone level. Prevalence of low serum free testosterone among patients with high serum cholesterol in type 2 diabetes was 66.7% while no patients of type 1 diabetes had high serum cholesterol with low free testosterone.

In present study, prevalence of high triglyceride (>150 mg/dl) in diabetic patients was 48 out of 90(53.3%), of which 21(43.75%) had low serum free testosterone level.

Triglycerides Level	Patients with low free testosterone (n=30)	%
High (≥150mg/dl)	21	70%
Normal (<150mg/dl)	9	30%
Table 3		

Prevalence of elevated triglycerides (>150mg/dl) in diabetic patients with low free testosterone was 21 out of 30(70%) in present study whereas Grossmann et al reported that prevalence of elevated triglyceride in diabetic patients with low testosterone levels were 45% in their study of 649 patients.[9]

In present study, occurrence of low HDL (<40mg/dl) in diabetic patients was 66 out of 90(73.3%), of which 21(31.8%) had low serum free testosterone level.

HDL level	Patients with low free testosterone (n=30)	%
Low (<40mg/dl)	**21**	70%
Normal (≥40 mg/dl)	9	30%
Table 4		

Prevalence of low HDL (<40mg/dl) in diabetic patients with low testosterone was 21 out of 30(70%) in present study whereas Grossmann et al reported low testosterone levels in 28% cases.[9] These finding indicate higher incidence of dyslipidaemia in patients with low serum free testosterone. Low free testosterone was more commonly found in patients with high serum cholesterol (50% vs 30.76%) and high serum triglyceride (43.75% vs 21.4%) as compared to patients with normal serum cholesterol and normal serum triglyceride respectively. Difference was statistically insignificant.

In present study, all patients with low serum free testosterone level (n=30) had normal serum FSH level. Out of 90 patients, one patient (1.11%) had low serum FSH, which had normal serum free testosterone. Regarding LH and testosterone, most patients with low FSH levels also have low LH and low testosterone levels. A few cases of isolated FSH deficiency exist in which LH and testosterone levels are within reference ranges but the sperm count is low.[16]

Prevalence of low serum LH(<1.5mIU/ml) in diabetes was 3 out of 30(3.33%), which also had low serum free testosterone. Prevalence of patients with normal serum LH in diabetes was 69 out of 90(76.7%), of which 24(34.8%) had low serum free testosterone level, indicating absence of primary hypogonadism in bulk of cases to be cause of low free testosterone levels in diabetic patients.

LH level	No. of patients with low serum free testosterone (n=30)	%
Normal(1.5–9.3mIU/ml)	24	80%
Low(<1.5mIU/ml)	3	10%
High(>9.3mIU/ml)	3	10%
Table 5		

In present study, out of 30 patients with low free testosterone 3(10%) had high serum LH level with normal serum FSH. This may be due to primary gonadal involvement while in 27 patients low free testosterone was due to diabetes.

Leydig cell function is under regulation by LH and other hormones therefore, it is possible that increased insulin resistant or hyperglycaemia may result in reduced testosterone biogenesis because of decreased central stimulation.[17] Interestingly, Pitteloud et al did not observe any correlation between insulin sensitivity and parameters of LH secretion or LH response to exogenous GnRH, suggesting that low testosterone levels associated with insulin resistant are not attributable to a major decrease in hypothalamic or pituitary hormone secretion.[18] Oltmanns et al presented data suggesting that hypoglycaemia and not insulin suppresses testosterone secretion and that this is mediated by pituitary decrease in LH output.[19] Adipose tissue, which is considered an endocrine organ and produces a host of hormones and cytokines, may modulate insulin action and regulate Leydig cell function. Leptin production is tightly coupled to insulin resistant and may play a key role in steroid biogenesis and reduced testosterone levels. Leptin levels have been shown to be inversely correlated with serum testosterone levels[13,14] and increased circulating leptin may be involved in the pathogenesis of Leydig cell dysfunction.[15] The expression of leptin receptors in Leydig cells and the inhibition of hCG stimulated testosterone secretion from rat Leydig cells by leptin suggest a role of this hormone in the biogenesis of testosterone.[20]

CONCLUSION: To conclude, present study shows that testosterone deficiency is quite common in young diabetic patients. Low serum free testosterone was more common in type 2 diabetes as compared to type 1 diabetes (38.46% vs 29.41%). BMI has significant effect on serum free testosterone levels. Patients with higher BMI had negative correlation to free testosterone although testosterone deficiency was also seen in few lean patients. High serum triglyceride and low serum HDL was seen more frequently in patients with low free testosterone. This study reveals that hypogonadism is not a rarity even at initial stages of diabetes. This study, although small, highlights importance of assessment of young diabetic patients for sexual dysfunction and hypogonadism.

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