

A Hospital Based Evaluation of Hypogonadism Among Male Type 2 Diabetic Patients in Eastern Part of Rural India

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a common metabolic disorder in India. It is recognised that the low testosterone level is associated with reduced insulin sensitivity and type 2 diabetes (T2DM)¹. Testosterone level is comparatively lower in diabetic²⁻⁵. But data in this relation is lacking particularly in rural India. So the aim of this study was to evaluate the prevalence of hypogonadism among T2DM patients in rural India with an objective to assess and compare serum total Testosterone (TT), Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) level of male T2DM patients and age matched healthy control group. **Methods and Material:** It was an open label observational descriptive cross sectional study. Fifty male type 2 diabetic patients and 50 healthy control subjects were selected randomly following inclusion and exclusion criteria for this study. Blood sample was collected aseptically and properly for assessment TT, FSH, LH, and glycosylated haemoglobin. **Results:** Hypogonadism (TT < 12 nmol/l) was found in 68% of diabetic subjects and in 20% of healthy control group. Of those with diabetes 72.72% of diabetic whose serum TT level < 12 nmol/l had LH level < 10 nmol/l. **Conclusion:** Testosterone levels were frequently low in men with T2DM compare to the healthy normal individuals of the same age group. Majority of them were suffering from hypogonadotropic hypogonadism (HH).

Keywords: Type 2 DM, Serum Total Testosterone, LH, FSH, HH

INTRODUCTION

The prevalence of hypogonadism is largely unknown among type 2 diabetics in Asian

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countries, including India. T2DM is a common metabolic disease in India and Insulin resistance is an important feature of type 2 diabetes⁶. It is being increasingly recognised that low testosterone levels in men are associated with reduced insulin sensitivity and type 2 diabetes¹. An inverse relationship exists between testosterone levels and insulin concentration in healthy men⁷. Low testosterone levels have also been found to predict insulin resistance and the future development of type 2 diabetes⁸⁻¹⁰. Furthermore, it has been reported that testosterone levels are lower in diabetic men compared with non-diabetic subjects²⁻⁵. The association between hypogonadism and diabetes mellitus has recently received considerable attention. Most of the studies in diabetic men have defined hypogonadism solely on the basis of testosterone levels^{8,9}. It is also not known whether the lower testosterone levels in diabetes are associated with changes in LH and FSH. Previously published data shows that the commonest form of gonadal dysfunction is hypogonadotropic hypogonadism^{5,11,12}. It is not clear whether there is a definite predictable relationship between the glucose tolerance and testosterone level in type 2 DM. This study was deployed with an aim to evaluate the association and prevalence of hypogonadism among the male T2DM.

The objective of this study was to assess and compare the serum testosterone, FSH and LH level between T2DM patients and normal non-diabetic subjects.

MATERIALS AND METHODS

This study was carried out in a rural tertiary care hospital in West Bengal. It was an open label observational descriptive cross sectional study. Fifty male type 2 diabetic patients (following ADA criteria) with no other co morbidity as case had been selected randomly following prefixed inclusion and exclusion criteria from the out patients department and 50 non-diabetic healthy age matched male subjects from the community had been taken as control. The total 100 (case 50+control 50) study subjects were in the age group of 40-79 yrs and had been divided into four groups according to the age. These were as follows 40-49 yrs, 50-59 yrs, 60-69 yrs, 70-79 yrs for both case and control. Exclusion criteria were 1) Concurrent illness other than diabetes or surgical interventions likely to impair sexual functions or any interventions producing symptoms of hypogonadism. 2) Serious diabetic complications 3) hepatic and renal disease, 4) Drugs used other than anti-diabetics 5) History of chronic alcoholism 6) history of other hormonal disorder except diabetes mellitus. Prior to this study ethical approval had been obtained from the institutional ethics committee and written informed consent had been taken from both the patients and control subjects.

There is no clear consensus for an accepted lower limit of normal testosterone. Recently, published recommendations for the diagnosis of late-onset hypogonadism from a panel of European and American testosterone experts recommended that patients with total testosterone <8 nmol/l should be treated with testosterone therapy, those with total testosterone of 8–12 nmol/l and hypogonadal symptoms should be given a trial of testosterone replacement therapy, and those

with total testosterone >12nmol/l are not hypogonadal and should not be treated. Observing the above statement TT level <12nmol/l was considered as hypogonadism of which <8nmol/l was considered as overt hypogonadism and 8-12nmol/l as border line and >12nmol/l as eugonadism. A venous blood sample amounting 20 ml was drawn aseptically between 8:00 and 10:00 AM after an overnight fast from each patient for biochemical assessment. The blood sample then immediately centrifuged, and serum was separated and stored at -20 degree C for measurement of TT, FSH, LH and glycated haemoglobin (HbA1c). Total testosterone was assessed by using radioimmunoassay. LH, FSH, HbA1c were measured by using ELISA method. All these test were conducted in the Department of Biochemistry, Burdwan Medical College.

STATISTICS

Data has been expressed here with mean \pm standard deviation. Test of significance has been done here by using one-way ANOVA test, unpaired t test, relative risk (RR), odds ratio (OR). $P < 0.05$ has been considered here as significant. Statistical software used spss version 20.

RESULTS

Minimum, maximum and Mean age with standard deviation of diabetic subjects was 40, 79 and 58.40 ± 10.89 years respectively; and for control group it was 40, 76 and 58.88 ± 9.86 years respectively. The median and mode of the ages was 57yrs and 66yrs respectively for both cases and control. There was no significant difference of the mean age between these case and control groups ($p = .809$). The distribution of age group in study population also bears no significant difference. ($p = .943$). The study subjects were divided into four groups as a function of age i.e 40-49yrs, 50-59yrs, 60-69yrs and 70-79yrs; and they were 12(24%), 17(34%), 13(26%), 8(16%) in numbers respectively.

Mean TT, FSH and LH level among T2DM subjects were 12.10 ± 8.20 nmol/l, 9.94 ± 5.91 nmol/l and 6.46 ± 4.48 nmol/l respectively and among healthy controls were 22.77 ± 8.43 nmol/l, 25.56 ± 12.62 nmol/l, 7.79 ± 3.57 nmol/l respectively. Among T2DM cases overt hypogonadism (TT < 8 nmol/l), borderline hypogonadism (TT 8-12 nmol/l), eugonadism (TT > 12); were 18 (36%), 16 (32%) and 16 (32%) respectively; and same in control group were 4(8%), 7(14%), and 39(78%) respectively. Therefore hypogonadism (68%) was significantly (p -value < 0.0001) more with the T2DM cases. On the other hand eugonadism (80%) was significantly (RR-3.4, 95% CI 1.89-6.10, z-statistic 4.09, $p < 0.0001$) more with the non-diabetic control group.

The mean values of TT (nmol/l) in the defined age groups (in years) i.e. 40-49, 50-59, 60-69, 70-79yrs were 19.12 ± 9.30 , 11.62 ± 7.25 , 9.29 ± 6.90 , 7.41 ± 3.38 among diabetics cases and 21.11 ± 7.73 , 27.40 ± 5.47 , 23.35 ± 9.00 , 16.46 ± 8.46 among nondiabetic healthy control group respectively. There was significantly ($p < 0.05$) reduced TT levels among diabetic subjects in comparison to non-diabetic individuals when compared within the groups except 40-49yrs. age group.

Table 1: Values of HbA1c, TT, LH, FSH of cases and controls according to the different age related groups of cases and controls

Age(yrs)	Study subject	No	HbA1c(%)	TT*(nmol/l)	LH**(nmol/l)	FSH*** (nmol/l)	P value
40-49	Case	12	7.95±2.38	19.12±9.30	6.28±3.26	12±6.91	0.500*0.200**0.009****
	control	12	4.39±0.69	21.11±7.73	8.38±3.90	24.61±9.85	
50-59	Case	17	7.04±2.00	11.62±7.25	6.34±4.79	11.05±6.26	0.000*0.672**0.000****
	control	17	4.13±0.53	27.40±5.47	6.84±2.70	25.52±10.65	
60-69	Case	13	6.48±1.62	9.29±6.90	6.65±5.96	8.3±5.48	0.001*0.711**0.000****
	control	13	4.14±0.4	23.35±9.00	7.24±2.75	25.19±11.61	
70-79	Case	8	8.25±2.94	7.41±3.38	6.65±3.64	7.22±2.70	0.034*0.257**0.022****
	control	8	4.27±0.61	15.46±8.46	9.53±5.08	27.40±20.61	
total	Case	50	7.31±2.23	12.10±8.20	6.46±4.48	9.94±5.91	0.000*0.089**0.000****
	control	50	4.24±0.55	22.77±8.43	7.79±3.57	25.56±12.62	

HbA1c- Glycated haemoglobin, TT-testosterone, LH-luteinising hormone, FSH-follicle stimulating hormone

The mean values of FSH(nmol/L) for the same groups were 12 ± 6.91 , 11.05 ± 6.26 , 8.3 ± 5.48 , and 7.22 ± 2.70 in diabetic cases and 24.61 ± 9.85 , 25.52 ± 10.65 , 25.19 ± 11.61 , 27.40 ± 20.61 in non-diabetic healthy control with means 9.94 ± 5.91 and 25.56 ± 12.62 respectively and there is significantly ($p<0.05$) reduced FSH levels among diabetic cases than non-diabetic individuals when compared within the groups as well as means.

The mean values of serum LH for these same groups are 6.28 ± 3.26 , 6.34 ± 4.79 , 6.85 ± 5.96 , 6.65 ± 3.64 in diabetic cases and 8.38 ± 3.90 , 6.84 ± 2.70 , 7.24 ± 2.75 , 9.53 ± 5.08 in non-diabetic healthy control with means 6.46 ± 4.48 and 7.79 ± 3.57 . the reduction of LH levels among diabetic cases than non-diabetic individuals when compared within the groups as well as means were statistically insignificant ($p>0.05$).

DISCUSSION

This study was carried out at a rural based teaching hospital of West Bengal. T2DM is a common metabolic disorder and its association with hypogonadism is well known from different study throughout the world. It is also a prevalent disease in India but the prevalence of hypogonadism among T2DM subjects is largely unknown. This present study was undertaken to evaluate the prevalence and association of hypogonadism in male T2DM patients in comparison with the age matched healthy subjects. In our study it has been observed that 34 T2DM patients (68%) had the total testosterone level below $<12\text{nmol/dl}$ in comparison to 10 persons (20%) in non-diabetic healthy subjects and such difference was statistically significant (OR-8.5, 95% CI 3.41-21.17, z statistic-4.59, $p<0.0001$). This indicates the significant association of hypogonadism with T2DM. Serum TT and FSH in different age group is significantly ($p<0.05$) low in diabetic group compare to non-diabetic healthy group except TT in 40-49 yrs age group. This is suggestive of age independent prevalence of hypogonadotropic hypogonadism. This finding was not consistent with the findings revealed by Ali *et.al*¹³. They found high serum and urinary FSH and LH among diabetics with low total and free testosterone levels. However, Tenover *et al*¹⁴ found that the majority of hypogonadal men over the age of 60 yrs. had low or inappropriately normal LH levels. On the other hand, Chandelet *al.*,¹⁵ observed that LH and FSH concentrations in T2DM patients were in the normal range but free testosterone concentrations was low. Our study showed a higher prevalence of hypogonadotropic hypogonadism (low LH and FSH) than that reported by Kapoor *et al.*,⁶. A study carried out in Taiwan⁷ showed that the prevalence of both androgen deficiency and the prevalence of symptomatic androgen deficiency were 24.1% and 12%, respectively. On the basis of normal ranges and international recommendations, overhypogonadism (level of TT $<8\text{nmol/l}$) was 36%, borderline hypogonadism (TT $8-12\text{nmol/l}$) was 32% and eugonadism (TT $>12\text{nmol/l}$) was 32% among T2DM cases; and in control group it was 8%, 14%, and 78%. respectively.

Serum mean TT and mean FSH level decreases gradually as age advances from 40 yrs to 70 yrs in diabetes cases in this study. This may be due to increase induration

of diabetes mellitus and also may be age depended because similar decrement of mean TT level was also found in control healthy non diabetic subjects. So, it can be concluded from our study that patients with T2DM is commonly and significantly associated with hypogonadism than that of non-diabetic healthy group and hypogonadotropic hypogonadism is more prevalent among diabetics. A larger study is required to establish the association of hypogonadism and T2DM.

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