Original Article

Study on hypogonadism in male with Type 2 Diabetes Mellitus

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Type 2 diabetes is associated with subnormal free testosterone concentrations in conjunction with inappropriately low LH and FSH concentrations in at least 25% of men suffering from this disease. In this study, we have evaluated the prevalence of hypogonadism in young non obese people with T2DM in our population and explored whether testosterone therapy would be able to reduce insulin resistance. Two hundred and seven male with Type 2 diabetes with age between 30 years and 50 years, on usual therapy with stable dose of drugs for last 3 months with HbA1C less than 9% and BMI less than 30kg/m^2 were selected and assessed for total serum testosterone. Twelve patients with serum total testosterone levels <350 ng/dl were treated with injection testosterone treatment. LH, FSH, HOMA-IR at baseline was done before giving testosterone. Serum total testosterone levels were re-assessed at 3 and 6 months in this group. After 6 months, glycemic status, BMI, waist circumference, HOMA-IR and lipid profile were re-evaluated. Prevalence of hypogonadism (serum total Testosterone <350ng/dl) was found to be 8.7% which was not increasing either with age or duration of diabetes. Prevalence of hypogonadism showed significant positive relation with BMI but not with HbA1c. After testosterone replacement, improvement was noticed in BMI, HbA1c, HOMA-IR and HDL level. Non obese young male with type 2 diabetes with good glycemic control and without complications may not have higher risk of developing hypogonadism compared to those reported in western literature. However, chance of erectile dysfunction is much higher which is probably due to other independent risk factors for ED. [*J Indian Med Assoc* 2017; **115:** 17-9]

Key words **: Male hypogonadism, type 2 diabetes, non obese.**

It is being increasingly recognized that low testosterone levels in men are associated with reduced insulin sensitivity and type 2 diabetes. Studies over the last few years have clearly established that at least 25% of men with type 2 diabetes have subnormal free testosterone concentrations in association with inappropriately low LH and FSH concentrations suggestive of hypogonadotropic hypogonadism[1]. Subnormal testosterone concentration with increased LH and FSH levelisalso demonstrated in another 4% of men with type 2 diabetes. Whether male hypogonadism is a cause[2] or effect of the insulin resistance and subsequent diabete smellitus is not clear. Low or subnormal testosterone concentration is strongly associated with metabolic syndrome, particularly visceral adiposity. Dhindsa *et al*[3] also demonstrated that 33% of men with type 2 diabetes had significantly lower levels of free testosterone. In Indian context, as many patients with T2DM are non obese, we evaluated the prevalence of hypogonadism in T2DM and whether testosterone therapy in those with low or subnormal testosterone concentrations would be able to reduce insulin resistance.

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Materials and Methods

The study was conducted over a period of 2 years at IPGME&R, Kolkata after having approval from Institutional Ethical committee. Two hundred and seven male persons with Type 2 diabetes who were on usual therapy with stable dose of drug for last 3 months with HbA1C less than 9% and BMI less than 30 kg/m^2 were selected from diabetes clinic of this institute. Persons presenting with history of malignancy, cirrhosis of the liver, renal failure, known hyperthyroidism or hypothyroidism ,already on testosterone, psychiatric disorders, including depressive disorders, history of testicular trauma /irradiation/surgery, recent acute illness, chronic heart failure, chronic lung disease were excluded. Also, those who are taking drugs like ketoconazole, spiranolactone, glucocorticoids and anabolic steroids were excluded.

History in details including features suggestive of hypogonadism was taken from each patient. In addition, ADAM questionnaire[4] (Androgen Deficiency in the Aging Male) was used.

This is a 10-item screening questionnaire used to evaluate androgen deficiency in aging males. A positive response is based on decreases in libido or strength of erections or anythree nonspecific questions that include fatigability, decreases in muscle strength, mood changes, and loss of height. This questionnaire has 88% sensitivity and 60% specificity. Patients were assessed clinically for various parameters including body mass index and waist circumference. All persons were evaluated for total serum testosterone at 9 AM and other baseline investigations eg, complete hemogram, HbA1C, FBS, 2 Hours PPBS, serum creatinine, liver function test, fasting lipid profile, ECG.

Hypogonadism was defined as having morning total testosterone below 350 ng/dl.

Twelve patients with serum total testosterone levels <350 ng/dl were treated with Injection testosterone treatment. LH, FSH and HOMA-IR at baselinewere assessed before giving testosterone.Serum total testosterone levels were re-assessed at 3 and 6 months in this treated group. After 6 months, FBS, PPBS, HbA1c, BMI, waist circumference, HOMA IR and lipid profile were re evaluated.

Testosterone, LH and FSH were measured by Chemiluminescent Immunometric Assay (CLIA) in Immulite-1000 platform (siemens).

Statistical Methods

The summary parameters were expressed as mean ± standard deviation. Student's independent sample t test was used to compare the mean of study parameters between two groups distributed normally. ANOVA was used to compare multiple means. Chi-square/ Fisher Exact test was used to find the significance of study parameters on categorical scale between two or more groups. Correlation coefficient was assessed by Pearson's correlation test or Spearmen correlation test depending on the distribution of data.

Results

Two hundred and seven male persons were included in the study. Mean age was 41.49 ± 4.83 years and average duration of diabetes was 5.50 ± 4.26 years. Average BMI was 23.85 ± 2.26 Kg/m^2. Proportion of obese (BMI>25 kg/m^2) people with type 2DM was 33.17% (N=68) and rest 34.83% (N=139) was non-obese. Average waist circumference of this whole group was 90.03 ± 8.12 cm. One hundred and six (53.27%) subjects had waist circumference < 90 cm and 93 (46.73%) subjects had waist circumference > 90 cm. One hundred and twenty three (59.42%) reported erectile dysfunction, mostly partial. Prevalence of hypogonadism (Fig1) (serum total testosterone <350ng/dl) was found in18 subjects (8.7%). No significant correlation was found between ages with either erectile dysfunction (ED) or low serum total testosterone.

ED was present in 25(83.3%), 48(48.48%), 18(51.43%) and 24(77.42%) subjects having diabetes for less than 1 year, 1-5years, 6-10 years, 11-20 years duration, respectively (Table 1). With increasing duration of diabetes, ED was significantly increased except in group having diabetes for less than 1 year.

Low serum total testosterone (<350 ng/dl) was present in 3(8.33%), 9(9.09%), 3 (8.57%) and 3(9.68%) subjects having diabetes for <1 year, 1-5 years, 6-10 years, 11-20 years, respectively.No significant correlation was found between duration of diabetes and low serum total testosterone (<350 ng/dl).

Normal BMI group had lesser prevalence (4.49%) of low serum total testosterone (<350 ng/dl) than both overweight (14.58 %) and obese (7.35%) group (Table 2).

ED and Non ED cohort had fasting plasma glucose 134.17±40.34 mg/dl and 124.07±29.21 mg/dl; and 2 hours post prandial glucose 224.91 ± 75.4 mg/dl and 193.17±58.62 mg/dl, respectively. ED cohort had significantly higher FPG (p=0.038) and PPG (p=0.001) than Non-ED. HbA1C was also higher in the ED cohort (Fig 2).

There were no significant difference in FBS (P=0.80), PPBS (P=0.31) and HbA1c in between two groups having serum total testosterone more than 350 ng/dl and less than 350 ng/dl.

Twelve out of those eighteen subjects with serum total testosterone <350 ng/dl was treated with injection testosterone with dose adjustment for next 6 months. Serum LH and FSH of those 12 persons ranged in between 1.7 - 6.8IU/ml and 2.1 -8.4 IU/ml, respectively. Follow-up testosterone (418.17 ± 39.69ng/dl) was significantly higher than baseline (285.5 ± 46.54 ng/dl) (p<0.001). Follow-up BMI (23.5 ± 1.14 Kg/m^2) was significantly lower than baseline (23.91 ± 1.22Kg/m^2) (p<0.04). Follow-up HbA1c (7.22 ± 0.73%)were significantly lower than baseline (7.35 ±

Table 1 — *Relation of ED with duration of T2DM*

Duration of Diabetes in years	Erectile Dysfunction		Total	P
	Absent	Present		
Less than 1	6 (16.7 %)	30 (83.3 %)	36	
1-5	51(51.52 %)	48(48.48 %)	99	
6-10	17(48.57 %)	18 (51.43 %)	35	0.001
11-20	7(22.58 %)	24(77.42 %)	31	
	81	120	201	

Table 2 — *Relation between low serum testosterone (<350ng/dl) & BMI*

BMI (Kg/m^2)	Hypogonadism		Total	P
	Absent	Present		
18.5-22.9	85 (95.51 %)	6(4.49%)	91	
23-24.9	41 (85.42%)	7(14.58%)	48	0.108
≥25	63(92.65%)	5(7.35%)	68	

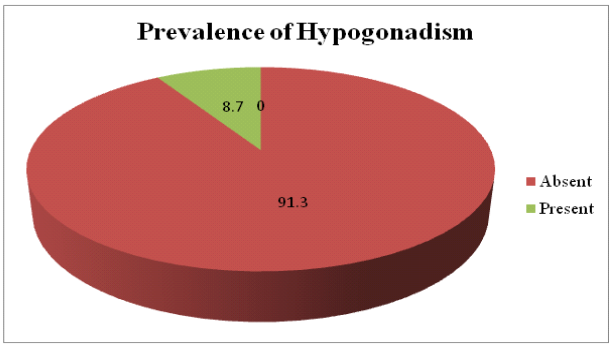

Fig 1 — Prevalence of hypogonadism (serum Testosterone <350ng/dl)

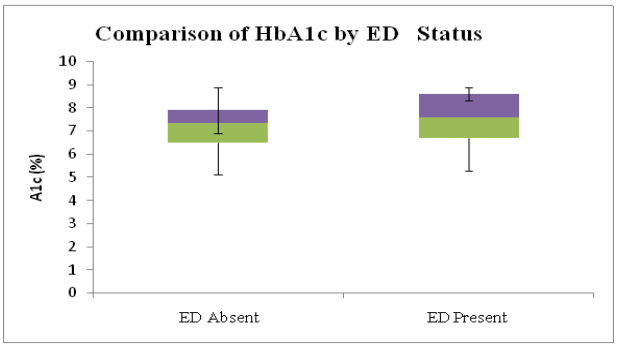

Fig 2 — Relation in between HbA1C and ED.

0.82%) (p<0.04) and follow-up HOMA IR(1.59 ± 0.55) were significantly lower than baseline (1.92 ± 0.48) (p<0.001)(Fig 3).

Discussion

Prevalence of hypogonadism (serum total testosterone <350ng/dl) in our study was found 8.7% (N=18) which is much lower than previous finding. Dhindsa *et al*[3] demonstrated that 33% of men with type 2 diabetes had significantly lower levels of free testosterone. But, themean age in that study was 54.7 ± 1.1 year, the meanweight 104.1± 2.6 kg, the mean BMI 33.4±0.8 kg/m^2, the mean HbA1c 8.4 ± 0.2% and the mean duration of diabetes was 7.7 ± 0.7 year. This suggests that the population studied were more aged and were more obese compared to our population. Kapoor *et al*[5] found overt hypogonadism in 17% of men with total testosterone <8 nmol/l and 14% with bioavailable testosterone <2.5 nmol/l in a cross-sectional study of 355 men with type 2 diabetes aged more than thirty years. These independent risk factors for hypogonadism wereworse than our cohort which can explain the lower prevalence of low serum testosterone in our study[3,5]. There were no significant difference in FBS (P=0.80), PPBS (P=0.31) and HbA1c in between two groups having serum total testosterone above or below 350 ng/dl, similar to findings of Kapoor *et al*[5]. LH and FSH value are suggestive of hypogonadotro-phichypogonadism as suggested by earlier study[3].

Follow-up BMI, HbA1c and HOMA-IR were signifi-

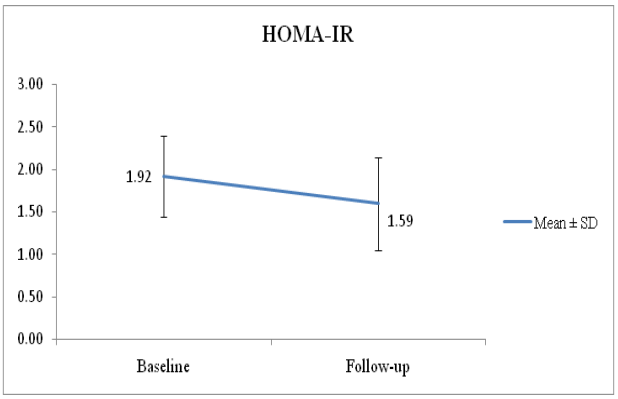

Fig 3 — HOMA IR level before and after therapy

cantly lower than baseline (p<0.04, p<0.04, p<0.001 respectively) in treated group similar to earlier interventional studies[6,7,8].

Conclusion

Non obese young male with T2DM without complications and HbA1c under control may not have that higher risk of developing hypogonadism. However, chance of erectile dysfunction is much higher which may be explained by other independent risk factors for same.

Acknowledgment

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