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ASSESSMENT OF HYPOGONADISM WITH REFERENCE TO CLINICAL FEATURES AND SERUM TESTOSTERONE LEVELS IN INDIAN MALE TYPE 2 DIABETICS AMONG PATIENTS ATTENDING DIABETIC CLINIC

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Conflicts of Interest: Nil

ABSTRACT:

Objective: To Assess the prevalence of Hypogonadism with Reference to Clinical Features and Serum Testosterone Levels in Indian Male Type 2 Diabetics (T2DM)among patients attending Diabetic clinic in a rural medical college setup.

Material and methods: In the cross-sectional study of 50 diabetic patients of 30-66 years age group preferably without chronic illness, total testosterone, serum FSH, serum LH, HbA1c, Body Mass Index (BMI), Waist Circumference (WC) and Blood Pressure (BP) were measured. History of duration of diabetes, hypertension and smoking were also noted. Overt Hypogonadism was defined as the presence of clinical symptoms of hypogonadism and low testosterone level (total testosterone <2.31 ng/ml). Borderline hypogonadism was defined as the presence of symptoms and total testosterone of 2.31-3.46ng/ml.

Results: A low serum testosterone level was common in diabetic men and a significant proportion of these men had symptoms of hypogonadism. Overt hypogonadism was seen in 28% of men with total testosterone levels <2.31 ng/ml and borderline hypogonadism was found in 24% of men with total testosterone levels 2.31- 3.46 ng/ml. Total serum testosterone levels significantly and negatively correlated with both BMI (p <0.001) and WC (p = 0.025628), with the association being stronger for BMI. HbA1C also significantly and negatively correlated with serum testosterone levels (p <0.01). Significance was also noted with respect to hypertension (<0.001) and ADAM score(0.04528). Smoking and duration of diabetes did not have correlation with serum testosterone in our study.

Conclusions: Testosterone levels are frequently low in men with T2DM and the majority of these men have symptoms of hypogonadism, even in the younger age group (early-onset hypogonadism). Obesity and BMI are also associated with low testosterone levels in Indian diabetic men. Early recognition and treatment reduces the adverse effects on Metabolic and cardiovascular profile and restore sexual functions.

Keywords: Type 2 diabetes, serum testosterone, overt hypogonadism, obesity

Introduction

Diabetes mellitus is a leading health problem and world is witnessing a pandemic. The estimated number of patients with diabetes was 371 million in 2012 and will reach approximately 552 million by 2030[(1)]. Aging population, high consanguinity, obesity, together with socioeconomic changes and westernization has resulted in the great rise in the prevalence[(2)].

Insulin resistance is an important feature of type 2 diabetes. Subnormal free testosterone concentrations in association with inappropriately low LH and FSH concentrations and a normal response to GnRH of LH and FSH in Type 2

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Diabetes were first described in 2004[3]. This association of hypogonadotropic hypogonadism (HH) with type 2 diabetes has now been confirmed in several studies and is present in 25-40% of these men[4,5]. Obesity is associated with type 2 diabetes and reduced testosterone levels[6]. Hypogonadotrophic hypogonadism is linked to major conditions associated with insulin resistance, Type 2 Diabetes and Metabolic syndrome.

Erectile Dysfunction (ED) is a common and distressing complication of diabetes. Advancing age, duration of diabetes, poor glycaemic control, hypertension, hyperlipidemia, sedentary lifestyle, and smoking are associated with ED in diabetic patients[7].

Testosterone is the principal sex hormone in men. It is important not only for normal sexual function but also for maintaining bone and muscle strength, mental and physical energy, and overall well-being. Low testosterone is associated with diminished libido, erectile dysfunction, increased fat mass, decreased muscle, bone mass and energy, depression, and anaemia. Type II diabetes may be one of the commonest causes of hypogonadism – a lack of function in the testes, which adversely affects testosterone production.

This study was conducted to correlate the Serum Testosterone levels with clinical hypogonadism in Type 2 Diabetes Mellitus; and correlate the Serum Testosterone levels with other variables like age, duration of diabetes, smoking, BMI, waist circumference, blood pressure and HbA1C levels in Type 2 Diabetes Mellitus.

MATERIALS AND METHODS

This single center, Cross-sectional, analytical and observational study was conducted at PESIMSR, Kuppam, to evaluate clinical and biochemical hypogonadism, in fifty men suffering from Type 2 Diabetes Mellitus and attending medical OPD and Endocrine clinic. Only patients above 30 years of age, and diagnosed as diabetic within the past three years were selected.

The exclusion criteria included, Type I diabetics, patients on medications which are known to interfere with the diabetic status, history of carcinoma, radiation, any kind of trauma and surgery, patients with superimposed diseases which may cause autonomic dysfunction, and patients suffering from chronic diseases. Ethical approval was obtained from the Institute Ethical Committee.

Total of 50 patients were taken. A detailed history of present illness was recorded including duration of the onset of symptoms. Past history and family history for hypertension and DM and history of chronic medications use were asked. Personal history like smoking & alcohol consumption were also noted. Complete Androgen Deficiency in the Ageing Male (ADAM) questionnaire was asked for clinical assessment of hypogonadism[8]. (Table no.1)

Table 1: ADAM Questionnaire

	Answer YES or NO to each of the following questions:	Yes	No
1.	Do you have a decrease in libido (sex drive)?		
2.	Do you have a lack of energy?		
3.	Do you have a decrease in strength and/or endurance?		
4.	Have you lost height?		
5.	Have you noticed a decreased "enjoyment of life?"		
6.	Are you sad and/or grumpy?		
7.	Are your erections less strong?		
8.	Have you noticed a recent deterioration in your ability to play sports?		
9.	Are you falling asleep after dinner?		
10.	Has there been a recent deterioration in your work performance?		

Table no.1: ADAM Questionnaire

A detailed clinical examination was done. General examination including height, weight, BMI, WC (defined as the point midway between the iliac crest and the costal margin) and blood pressure (BP) were measured. Systemic examination including cardiovascular, respiratory, gastrointestinal and neurological examination was performed.

In all the patients, blood sample were collected between 8 a.m. and 10 a.m. Serum sample was obtained by centrifugation. Samples were collected and stored at –20°C for hormonal analysis. Using Enzyme linked Immuno-Fluoroscent Assey (ELFA), the Total Testosterone, Follicle stimulating hormone and Luteinizing hormone levels were determined. HbA1C, other routine hemogram, and organ function tests were retrieved from patient data.

STATISTICS

SPSS version 20 was used for statistical analysis. All values were expressed as a percentage of each group or as mean ± SE (standard error) unless otherwise stated. The independent sample't' test was used to compare testosterone levels in men with ED and without ED. Independent sample't' test was also used to compare testosterone in others variables like glycosylated hemoglobin (HbA1C), BMI, WC, smokers and hypertension. Results were considered statistically significant at $p < 0.05$.

RESULTS

Of the 50 patients in the study group, 28% (14 patients) had overt hypogonadism, and 24% (12 patients) had borderline hypogonadism. The mean age in our study group was 46.48 years with minimum of 30 years and maximum of 66 years. The average duration of diabetes in study population was 6.66 years. The mean and standard deviation of variables like serum testosterone, HbA1c, waist circumference and BMI is tabulated in Table no.2

Descriptive Statistics					
	N	Minimum	Maximum	Mean	Std. Deviation
AGE (YRS)	50	30	66	46.48	7.614
SERUM TESTOSTERONE(ng/ml)	50	0.30	7.40	2.961	1.24537
HbA1c (%)	50	5.4	11.6	7.876	1.6687
BMI (kg/m2)	50	18.4	32.0	24.87	4.2142
WAIST CIRCUMFERENCE (cm)	50	69	115	91.68	10.877
DURATION (YRS)	50	3	20	6.66	3.503

Table 2 : The Baseline Characteristics of Subjects

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Majority of the patients were in the age group of 40-49 years representing 46% of the total, and the least were in >60 years age group representing 6%. Analysis of symptoms showed that osmotic symptoms were the most common of all representing 68%, and the symptom important to our study comprising impotence and sensory symptoms were seen in 24% of the patients. The distribution of all symptoms among the study group in represented in figure no.1

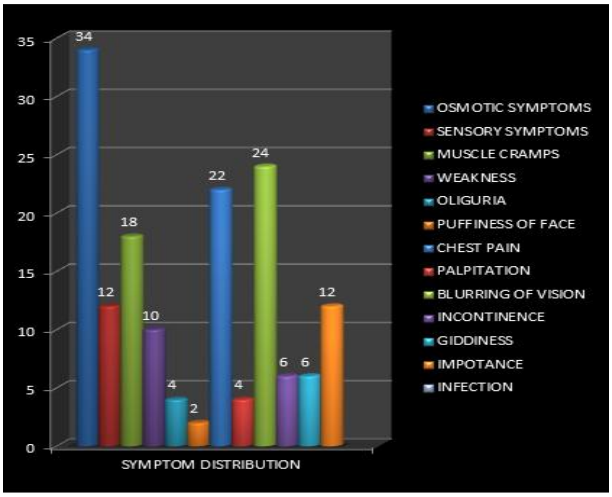

Figure no.1: Symptom distribution

Figure 1: Symptom distribution

Of all the patients in the study group, 46% were hypertensive, 50% were alcoholic and 58% were smokers. 34% of the patients had a family history of diabetes mellitus and 40 % had family history of hypertension. 42% of the patients had fulfilled the criteria for clinical hypogonadism based on ADAM score which entirely relies on history given by the subjects. Majority of patients in our study fall in to the category of overweight and obese contributing to 58% of the total subjects. Underweight patients represented only 4% of the total. And 54% of the subjects had waist circumference above 90 cm which is a marker of central or visceral obesity.

Prevalence of low testosterone levels:

Twenty eight percent (14 men) had testosterone level <2.31 ng/ml and twenty four percent (12 men) had testosterone between 2.31-3.46 ng/ml. Prevalence of low testosterone levels was not uncommon in all age groups but it was maximum in age group of 40-49 years.

Prevalence of overt hypogonadism in diabetic patients with positive ADAM score was 20% (10 men) and borderline hypogonadism was 16% (8 men) based on symptoms as suggested by ADAM questionnaire and low serum testosterone Levels. ED and loss of libido were the common symptoms, 46% and 52%, respectively, in these patients with low testosterone levels (<3.46 ng/ml.). Only 26% patient had other symptoms.

Association of Low Testosterone Level with all Clinical Variables studied in this present study was tabulated in the Table no.3. Significance has been taken with p value < 0.05

Table 3: Association of Low Testosterone Level with all Clinical Variables

Parameter (n)	<2.31 ng/ml	2.31-3.46 ng/ml	>3.46 ng/ml	P value
BMI >23 kg/m2 (28)	14	13	1	<0.001
WC >85 cm (26)	11	12	3	0.025628
HbA1C >9% (27)	13	13	1	<0.01
Hypertension (21)	13	8	0	<0.001
Smoking (29)	10	13	6	0.282344
Erectile dysfunction(ADAM score)(21)	10	8	3	0.045
Age				
<40 (9)	0	6	3	
40-49 (23)	8	7	8	
50-59 (15)	7	5	3	
>60 (3)	0	3	0	

Table no.3: Association of Low Testosterone Level with all Clinical Variables

Association of body composition and testosterone levels in diabetic patients:

Total serum testosterone levels significantly and negatively correlated with both BMI ($p < 0.001$) and WC (p value = 0.0256). In patients having BMI >23 kg/m2, 28% diabetic men had low testosterone <2.31 ng/ml. To this, when the patients in the group falling between 2.31-3.46 ng/ml were added, it increased to 54% ($p < 0.01$). In patients with WC >85cm, the serum testosterone levels was ≤3.46 ng/ml in 46% of the cases (p value= 0.0256).

Correlation between HbA1C and low testosterone:

HbA1C significantly and negatively correlated with serum testosterone levels ($p < 0.001$). 96% patients with HbA1C >9% had low testosterone levels, while 39% diabetics with HbA1C <9% had serum testosterone <3.46 ng/ml showing statistical significance ($p < 0.001$).

Correlation between hypertension and low testosterone:

hypertension significantly and negatively correlated with serum testosterone levels ($p < 0.001$). All patients with hypertension had low testosterone levels, while 51% diabetics with no hypertension had serum testosterone <3.46 ng/ml showing statistical significance ($p < 0.001$) .Statistical correlation and significance between hypogonadism and diabetes duration and smoking history could not be established in the present study ($p > 0.05$).

DISCUSSION

Hypogonadism, a clinical condition comprising both symptoms and biochemical evidence of testosterone deficiency is associated with T2DM. The purpose of this study was to determine the prevalence of clinical hypogonadism based on both symptoms and biochemical measure of testosterone deficiency in men of T2DM in Rural Indian perspectives.

In present study, we observed that there is a high prevalence of symptomatic hypogonadism in men with T2DM. Previous studies[11] have shown that about one-third of men with T2DM have low serum testosterone levels. In our study, we found that a high proportion of diabetic men had low levels of serum testosterone. There is no widely accepted consensus as to what constitutes the levels of testosterone below which treatment is to be considered. But on the basis of normal ranges and international recommendations overt hypogonadism <2.31 ng/ml and borderline hypogonadism 2.31-3.46 ng/ml serum testosterone level was considered

In the present study, 28% subjects with T2DM had symptoms and associated serum testosterone level <2.31ng/ml, which was called as overt hypogonadism. Further 24% of diabetic men had symptoms of hypogonadism with testosterone level in the range of borderline hypogonadism i.e. 2.31-3.46 ng/ml. These findings support the study done by Kapoor and colleagues[(9)].

Aging is associated with decline in testosterone levels even in healthy men according to Nieschlag, Behre and colleagues[(10)]. In this Baltimore Longitudinal Study on aging, 8, 12, 19 and 28% of men aged >40, 50, 60 and 70 years, respectively had serum total testosterone levels below the normal range of <11.3 nmol/l in that study. Using the criteria in that study, we found a higher prevalence of hypogonadism across all age group 66.6% in <40, 65.2% in 40-49, 80% in 50-59 and 100% in >60years. Kapoor et al also

found similar results in all diabetic age groups (42, 44, 39 and 56% in the age-groups 40-49, 50-59, 60-69 and 70-79 years, respectively)[9]. Although hypogonadism increases with age, it is also common in younger diabetic age groups. Dhindra and colleagues have shown low testosterone level in T2DM. Frequency of symptoms in all defined groups of their study was studied.

It is important to note that the ADAM questionnaire lacks specificity and this questionnaire is useful only in the presence of a biochemical evidence of low level of serum testosterone. Asian-Indians are known to have a lower BMI than Europeans[11]. For any given BMI, Asian-Indians have a greater waist-to-hip ratio than Europeans. To clarify the issue, a study done in patients with T2DM and sex- and age-matched nondiabetic controls checked for Visceral, subcutaneous and total abdominal fat, which was measured by computed tomography (CT), while dual-energy X-ray absorptiometry (DEXA) was used to measure central abdominal and total body fat. Diabetic subjects had significantly higher visceral and central abdominal fat compared to controls. Both measurements correlated well with each other as well as with the WC. Therefore, WC is a valid measure of visceral adiposity in this population([12]. To clarify the anthropometric variables in Asian-Indian adults, 19,025 adults over 20 years of age were given an oral glucose tolerance test using World Health Organization (WHO) criteria. The calculations were done to stratify subjects with diabetes against subjects without diabetes using multiple logistic analyses. The upper limit of the stratum in which the risk became clinically significant was considered the cut-off for normal values. The normal cut-off for BMI was 23 kg/m2 in both sexes. The cut-off for WC was 90 cm for men and 80 cm for women. The present study showed that there is strong negative correlation between WC and hypogonadism in cases of diabetes ($p = 0.025628$) and between BMI and hypogonadism in these cases ($p < 0.01$)[13]. The study supports the results of previous study done by Kapoor and colleagues according to which there was strong correlation between body composition and total testosterone levels[12].

It was observed in our study, that serum testosterone decreased more in uncontrolled diabetic men showing correlation and statistical significance ($p < 0.01$). In this study, we did not find any association between the duration of diabetes and history of smoking with hypogonadism. Previous studies also have not shown any clear cut relation with these findings[12,13]. Further studies with a large number of subjects may determine the clear cut association.

Testosterone therapy has important role in treatment of ED and also in management of Insulin Resistance. Men with ED who failed to respond to phosphodiesterase inhibitors have been shown to have low testosterone levels. Testosterone replacement therapy in two studies was found to convert sildenafil nonresponders to responders. Interventional studies have shown a beneficial effect of testosterone replacement therapy on IR. A study in healthy men with low total testosterone reported an improvement in insulin sensitivity with testosterone or dihydrotestosterone treatment[14]. Testosterone treatment has also been shown to reduce IR in obese men, men with heart failure and T2DM subjects. Studies on T2DM men have shown an improvement in glycemic control with testosterone replacement therapy[15].

CONCLUSION

Testosterone levels are frequently low in men with T2DM and the majority of these men have symptoms of hypogonadism, even in the younger age group (early-onset hypogonadism). Obesity and BMI are also associated with low testosterone levels in Asian-Indian diabetic men.

Control of diabetes and associated risk factor should be the goal of therapy. More studies are required to establish the benefit of testosterone replacement therapy on quality-of-life and the diabetic state in Indian men.

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