

Prevalence of Low Serum Testosterone among Type 2 Diabetes Mellitus: A Predictor of Micro Vascular Disease

¹Vijayamahantesh N N, ²Deepak C L, ³Sudeep K, ⁴Venkatesha B M.

Father Muller Medical College Hospital

Abstract: Diabetes Mellitus is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease. A high prevalence of low serum testosterone (LST) and hypogonadism(HG) in men with type 2 diabetes have been reported worldwide.

Objective: To assess the prevalence of androgen deficiency and hypogonadism and their relation to associated complications of T2DM.

Materials and Methods: This was a cross-sectional study, conducted among 50 men (aged 30-60 years) with type 2 diabetes who consecutively attended endocrine OPD at Father Muller Medical College Hospital Mangalore, between August 2013 and February 2015. The patients' demographic characteristics were collected using a basic questionnaire. Duration of diabetes, smoking habits, presence of retinopathy and nephropathy were collected from the medical records. Hypogonadism was assessed with the help of Androgen Deficiency in Ageing Male (ADAM) questionnaire. Venous blood samples were collected to test for total testosterone (TT), follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), serum lipids, and glycosylated hemoglobin (HbA1c). LST was defined as TT <3 ng/ml. These parameters were compared with the complications associated with T2DM.

Results: Overall, 18% of patients with diabetes had TT level <3 ng/ml and 40% had symptoms of androgen deficiency. Of those with serum testosterone level <3ng/ml, 66.6% had symptoms of androgen deficiency, 11.1% had primary hypogonadism (HG), and 88.9% had secondary HG. High incidence of retinopathy and nephropathy was found among patients with low testosterone. On analyzing, significant relationship was found between smoking, hypertension, duration of diabetes, diabetic nephropathy and diabetic retinopathy and low testosterone levels.

Conclusions: Smoking, hypertension, duration of diabetes mellitus, diabetic nephropathy and diabetic retinopathy were found to be associated with LST. So LST can be considered as a indicator of microvascular complications of T2DM.

Keywords: Diabetes mellitus, low serum testosterone, Hypogonadism, prevalence.

1. INTRODUCTION

Diabetes Mellitus is one of the non communicable disease which has flourished to reach epidemic status in India with more than 62 million diabetic individuals currently diagnosed with the disease.^{1,2} In 2000, India (31.7 million) had highest number of people with diabetes mellitus followed by China (20.8 million) and the United States (17.7 million). 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.^{3,4}

Epidemiological studies have reported that 30%– 50% of men with T2DM have testosterone deficiency⁵, and up to 75% of them have sexual dysfunction, particularly erectile dysfunction (ED).⁶

LST is linked to visceral adiposity and insulin resistance (IR), vascular disease,⁷ hypertension, and dyslipidemia, as well as osteoporosis. These metabolic derangements are linked to increased morbidity and mortality in patients with LST.⁸ ED and HG have recently been recognized as possible predictors of forthcoming metabolic diseases and cardiovascular events.⁹

The main symptoms of LST are reduced libido/erectile dysfunction, reduced muscle mass and strength, increased adiposity, osteoporosis/low bone mass, depressed mood, fatigue, low energy, and impaired quality of life.

Hypogonadism (HG) is a clinical condition consisting of both symptoms and biochemical signs of testosterone deficiency. However, many studies in men with diabetes have defined LST solely on the basis of testosterone levels. Previously published data show that the commonest form of gonadal dysfunction was hypogonadotropic HG.¹⁰ Ando et al.,¹¹ reported low TT and normal LH levels in diabetics; whereas, Ali et al.,¹² found that subjects with diabetic neuropathy had low testosterone, high LH and FSH levels.

The present study had been carried out to verify the prevalence of LST and HG in men with T2DM and to assess its relation to glycemic control and complications associated with T2DM.

2. MATERIALS AND METHODS

A total of 50 men (aged 30-60 years) with type 2 diabetes who attended endocrine OPD at Father Muller Medical College Hospital Mangalore, between August 2013 and February 2015 were included. This was a cross-sectional study of 60 men with type 2 diabetics, aged 30- 60 years, who visited endocrinology clinic at Father Muller Medical College Hospital. All patients gave written informed consent, and the local research ethics committee approved the protocol. The participants included in this study were married men who met the American Diabetes Association criteria for type 2 diabetes. Medications for DM, hypertension or other medical disorders were not discontinued during the study. The exclusion criteria for the patients were: anatomical abnormalities of the genitals (for example, penile fibrosis) that impaired erection, significant mental disorder, history of severe hematological, renal or hepatic disease, history of alcoholism or substance abuse within the past 12 months, history of stroke or myocardial infarction within the past 6 months, serious cardiovascular disease within the past 6 months including heart failure, unstable angina pectoris or life-threatening arrhythmia, abnormal blood pressure (BP <90/50mmHg, systolic blood pressure (SBP) >170mmHg or diastolic blood pressure (DBP) >100mmHg at rest), history of malignant hypertension, inflammatory disease or infection, patients on medications with potential to cause erectile dysfunction and hypogonadism as adverse effect.

The patients' demographic characteristics were collected using a basic questionnaire. Information on the duration of diabetes, presence of retinopathy, and nephropathy were collected from their medical records. Smoking habit and alcohol intake history was collected. Study participants were asked to complete the androgen deficiency in ageing male (ADAM) questionnaire. This questionnaire has 88% sensitivity and 60% specificity.¹³ A positive response is based on a decrease in libido or the strength of erections, or any three nonspecific questions that may include a decrease in muscle strength, fatigability, mood changes, and loss of height.

Body mass index (BMI) and Blood pressure were noted. Blood sample was analyzed for TT, FSH, LH, prolactin (PRL), glycosylated hemoglobin (HbA1c), total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride. TT was assessed using radioimmunoassay. LH, FSH, and PRL were measured by chemiluminescent immunometric assays. HbA1c was analyzed using high performance liquid chromatography (HPLC) method. Total cholesterol, triglyceride, HDL, and LDL were assayed for all patients

In this study, LST was defined as TT <3.0 ng/ml. Symptomatic androgen deficiency was defined as TT <3.0 ng/ml in addition to a positive response to ADAM questionnaire. Primary HG was defined as LH >10 MIU/ml with TT <3.0 ng/ml, while the secondary HG was defined as LH <2 MIU/ml with TT <3.0 ng/ml.¹⁴ The diagnosis of DM was based on the American Diabetes Association (ADA) criteria.¹⁵ Nephropathy as diagnosed in relation to urine protein creatinine ratio. Patients with ratio of more than 0.1 were considered to have nephropathy. Retinopathy was diagnosed with the help of ophthalmologist. Patients were classified into nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR).

Overweight was defined as BMI 25-29.9 kg/m², and obesity was defined as BMI ≥30 kg/m². Among type 2 diabetic patients, lipid levels were considered abnormal according to ADA criteria. Hypercholesterolemia referred to a total cholesterol level ≥200 mg/dl. HDL was considered low when the level was <40 mg/dl. LDL was considered high when

the level ≥ 100 mg/dl. Hypertriglyceridemia was considered high when TG level was ≥ 150 mg/dl. Dyslipidemia was considered present when one or more of the previous abnormalities were found in serum lipids, or if the patient was receiving medication for any of the above conditions. Patients with HbA1c $< 7\%$ were considered controlled.¹⁵

Statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS version 23). In addition to descriptive analysis, Chi-square tests or independent t-test were done to find out associations.

3. RESULTS

This study included a total of 50 patients with type 2 diabetes, aged between 30 and 60 years with a mean age of 47 ± 6.9 years.

The sociodemographic and clinical characteristics of participants are shown in Table 1.

Table 1: Demographic, clinical, and relevant characteristics of study participants (n=50)

variable	N (%)
Age(years)	
30-39	8
40-49	24
50-59	18
Dm duration(years)	
,<5	25
5-10	7
>10	18
BMI (kg/m ²)	
<25	18
Overweight	27
obese	5
Hypertension	
Hypertension	17
No hypertension	35
Smoking	20
Smoking no smoking	30
OHA only	34
Insulin and OHA	16
D. Retinopathy	23
D. Nephropathy	28

The mean BMI was 25.57 ± 2.7 kg/m² and 8% of diabetics were obese and 54 % were overweight. About 36% had diabetes for more than 10 years. More than half of the patients (78%) were on oral antidiabetic agents and only 18% were on insulin. One-thirds of the diabetic population (34%) was on antihypertensive treatment.

Table 2: The mean (SD) values of serum gonadal hormones level among patients with diabetes according to age group

Age Parameters	30-39 years	40-49 years	50-59 years
Testosterone(ng/ml)	5.31(1.6)	4.56(1.4)	4.02(1.4)
Follicle stimulating hormone (MIU/ml)	7.3(4.1)	7.1(4.5)	8.2(4.6)
Leutinizing hormone (MIU/ml)	6.1(2.4)	6.2(2.6)	6.4(3.1)
Prolactin(ng/ml)	9.2(7.2)	9.6(6.0)	9.4(7.4)
HbA1c	8.85(1.8)	8.4(1.9)	8.28(2.1)

Table 2 shows the variations in the mean serum gonadal hormone levels by different age groups. It seems that total testosterone decreased with increasing age. Overall, 18% of patients with diabetes had TT level < 3 ng/ml and 40% of study participants had symptoms of androgen deficiency.

Table 3 indicates the prevalence of LST level (TT <3 ng/ml) by groups of different variables. The prevalence of low total serum testosterone was 27.7% in age group 50-59, and 8.3% in age group 40-49, and 25% in age group 30-39. Of those with serum testosterone level <3 ng/ml, 77.7% had symptoms of androgen deficiency, about 11.1% had primary HG, and 88.9% had secondary HG. The statistics analyses indicated significant differences among the smoking ($P = 0.004$), hypertension ($p=0.001$), duration of diabetes ($P = 0.005$), diabetic nephropathy ($P = 0.005$) and diabetic retinopathy ($P = 0.005$). There was no significant differences among age, BMI, Dyslipidemia and HbA1c ($P = 0.157$).

Table 3: Prevalence of low serum testosterone level (total testosterone <3 ng/ml) for patients with type 2 diabetes mellitus according to relevant characteristics.

variables	Testo (> 3ng/ml)	Testo (< 3 ng /ml)	P value
Age			
30-39	5.71	2.75	0.325
40-49	4.98	2.45	0.420
50-59	4.43	2.44	0.318
Duration	5.03	12.67	0.003
BMI	25.74	29.74	0.033
Smoking	12	8	0.005
Hypertension	9	8	0.001
HbA1c	8.3	9.3	0.157
Dyslipidemia	9	6	0.062
Diabetic retinopathy	14	9	0.001
Diabetic nephropathy	19	9	0.004

4. DISCUSSION

Due to a higher prevalence of low testosterone in diabetics, the possibility that LST might contribute to diabetes-related sexual dysfunction has recently been reevaluated.¹⁶ The present study found that 18% of patients with T2DM had a TT level of <3 ng/ml, and 40% had symptoms of androgen deficiency.

The term secondary (hypogonadotropic) HG denotes an inadequate release of gonadotropin-releasing hormone (GnRH) and is characterized by low-normal or low levels of FSH, LH, and testosterone. The present study indicated that TT decreased with age. Several cross-sectional studies and systemic analyses from various countries have reported that type 2 diabetes is associated with LST. A study from Australia reported that 43% of type 2 diabetes patients had TT levels <10 nmol/l.¹⁷ A study from Egypt reported 33.2% HG in type 2 diabetes patients.¹⁸ Another study from Brazil showed that FT and TT levels were subnormal in 46 and 34% of diabetics, respectively.¹⁹ In the United Kingdom, a cross-sectional study of 355 men with type 2 diabetic aged >30 showed that 17% had HG with TT <8 nmol/l, and a further 25% had symptoms of HG associated with a TT level between 8 and 12 nmol/l.¹⁴

The present study reports that of the LST subjects, 11.1% had primary HG and 88.9% had secondary HG, suggesting that hypogonadotropic HG is the predominant type of HG in our diabetic subjects. In a study Tenover et al.,²⁰ found that the majority of hypogonadal men over the age of 60 had low or inappropriately normal LH levels. On the other hand, Chandel et al.,²¹ found that LH and FSH concentrations in type 2 diabetic patients with low FT concentrations were in the normal range. Further, a recent study showed that high prevalence of HG and depressive symptoms were found in patients who had been newly diagnosed T2DM.²²

Some studies done on large population have indicated decreased testosterone levels in the older population compared to the younger.^{17,23} In our study, significant association was not found between TT and age. A higher prevalence of low TT was seen in men aged between 50 and 60 years, which is in agreement with the previous finding that HG was frequently associated with T2DM in the 6th decade of their life.¹⁶ In this study, there was a higher prevalence in age group 30-39 compared to age group more of 40-49. This high frequency of diabetes with HG in those aged less than 40 years could be due to the fact that most diabetic patients in this age group have by type I, and not T2DM.¹⁶

Many studies have addressed the relationship between BMI and LST of patients with T2DM. Some studies have shown a significant association between BMI and LST level.²⁴ In contrast, a study done by Tripathy D et al reported that there is no relationship between TT and BMI.¹⁰ However, the present study observed no significant association between BMI and LST levels. In a study done to find prevalence of LST in obese and diabetic men, found that obesity is associated with a

high prevalence of HG, and the presence of diabetes adds to that risk.²⁵ However, a study reported that the presence of LST was not entirely dependent upon obesity because 25% of nonobese patient also had HG.²⁶

DM is strongly associated with microvascular complications such as retinopathy and nephropathy resulting in organ and tissue damage in approximately one-third to one-half of people with the disease.^{27,28} Our study also found that more than one-third of the diabetes subjects had a microvascular complication. Significant differences were observed in the incidence of retinopathy and nephropathy among the patients with LST and normal testosterone. The prevalence of LST was higher in subjects with a longer duration of DM. But in a study done by Laaksonen DE et al, no association was found between duration of diabetes and LST.²⁹

In this present study, we found that diabetic patients with smoking have higher incidence of LST. Some cross-sectional studies have shown a positive association between smoking and total Testosterone levels.³¹ Study done by Fukui M et al showed no significant association between smoking and total or FT levels.³⁰

Serum testosterone levels have been reported to be lower in men with hypertension.³² the present study also found a higher prevalence of LST in the diabetic subjects with hypertension. These findings are consistent with those reached by others.³³

The present study reports no significant correlation among the subjects with dyslipidemia and subjects without dyslipidemia. This was agreement with the findings of several other investigators who reported no significant relationship between serum lipids and LST.^{30,34} In contrast, some other studies showed that lower HDL cholesterol and higher triglyceride levels were significantly correlated with LST in diabetics.^{17,33}

In the present study we did not find an association between the serum testosterone level and HbA1c concentration, which was correlating with the results obtained by some studies,¹⁷ while it was contradictory to Kapoor et al study.¹⁴

In conclusion, prevalence of hypogonadism is high in T2DM. All type 2 diabetics should be screened for hypogonadism and base line testosterone levels should be documented. Establishing a hormonal base line for patients with T2DM is also essential so that patient can be treated in the future. Low testosterone is a indicator of microvascular complications.

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