

Original Research Article

Testosterone levels in men with type 2 diabetes mellitus

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ABSTRACT

Background: To study testosterone levels in men with type 2 diabetes mellitus in age group of 30-50 years.

Methods: In this cross sectional study of 193 type 2 diabetes men aged between 30-50 years, total and free testosterone levels were calculated along with other relevant clinical variables like hypertension, BMI, dyslipidemia, peripheral neuropathy, retinopathy.

Results: The study group had study out of 193 patients 34.7% have low total testosterone levels, 29.53% have low free testosterone levels and 23.3% have both low and free testosterone levels. Maximum number of patients with low total testosterone levels were in the age group between 46-50 years (41.0%) and with low free total testosterone levels were in the age group between 36-40 years (41.8%).

Conclusions: Type 2 diabetes mellitus is associated with low levels of total and free testosterone. Obesity and dyslipidemia are also associated with low testosterone levels.

Keywords: Diabetes, Testosterone

INTRODUCTION

A Diabetes Mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Based on current trends, the International Diabetes Federation projects that 592 million individuals will have diabetes by the year 2035. In Asia, the prevalence of diabetes is increasing rapidly, and the diabetes phenotype appears to be somewhat different from that in the United States and Europe, with an onset at a lower body mass index (BMI) and younger age, greater visceral adiposity, and reduced insulin secretory capacity.¹ There are many diabetes related complications, one of which is low testosterone levels in men. Androgens play an important role not only in sex differentiation and development, but also in regulating the metabolism of glucose, proteins, lipids and some

inflammatory factors, all of which might have a great influence on insulin sensitivity. It is well known that reduced levels of total testosterone (TT) in middle-aged or older men may contribute to abdominal obesity, increased insulin resistance (IR) and diabetes mellitus. At least six large prospective clinical trials have suggested that reduction of TT predicted the increasing incidence of T2DM.^{2,3} Low concentrations of endogenous androgens have been linked with IR, which is an important upstream driver for metabolic abnormalities such as hyperglycemia, hypertension, or dyslipidemia, and increased cardiovascular risk. Type 2 Diabetes Mellitus (DM) associated hypogonadism might exacerbate sexual dysfunction by reducing libido and mood and further compromising penile vascular reactivity and lipid metabolism. Hence, testing circulating testosterone is strongly recommended in Type 2 DM patients with

erectile dysfunction.⁴ Testosterone levels are not only lower in men with type 2 DM, but also that the risk of developing type 2 DM is increased in men with low testosterone levels.^{5,6}

The prevalence rate of symptomatic hypogonadism in men with type 2 DM is high and documented rates range from 20-64% with higher prevalence rates reported in the elderly.⁷

The association between low serum testosterone (LST) and DM has recently received substantial attention. Studies have reported that men with type 2 DM (T2DM) have a high prevalence of LST. Further, reduced total testosterone (TT) levels have been associated with insulin resistance and subsequent risk for developing T2DM. 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.⁸ 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. Symptoms of HG have rarely been considered in combination with biochemical testosterone deficiency.⁹ There is a growing interest in understanding the concurrence of symptoms of low testosterone and a low testosterone level since the clinical significance of a low testosterone level alone is unclear.¹⁰

Screening and diagnosing

Assessment for low testosterone level and the diagnosis of male hypogonadism should include a thorough medical history, physical examination, presence of signs and symptoms, and confirmed laboratory values of at least two TT levels. Of the screening tools available, the androgen deficiency in aging male questionnaire (Annexure I) may be useful in identifying patients who have symptoms of low testosterone.¹¹ This simple 10-question survey can be completed by the patient or his partner and is used by the health care provider to initiate discussion with the patient.

METHODS

This observational, cross sectional study was performed in 193 male diabetic patient between 30 to 50 years of age who were registered with tertiary care IGMC hospital Shimla. Institutional ethical committee clearance was taken. Patients were excluded if they had history of secondary diabetes, (chronic pancreatitis, drugs, Cushing's, pituitary and thyroid disorder) and prior or present treatment for hypogonadism with testosterone replacement, with anti androgens, chronic diseases. (HIV infection, COPD, ESRD) critical illness hyperprolactinemia, medications (e.g. opiates, anabolic steroids).

All patients gave written informed consent. Detailed history was taken and detailed examination was done. Serum testosterone levels was measured. Total Testosterone Levels and Free Testosterone Levels were measured based on chemiluminescence on Beckman coulter access 2 immunoassay system (time for collection of sample was between 7am to 11am). Height and weight were measured and BMI was calculated. Blood pressure was recorded. Patients were asked to fill androgen deficiency in the aging male (ADAM) questionnaire. Table 1 and 2 shows reference ranges for total and free testosterone levels.

Table 1: Reference ranges for chemical variables testosterone levels in 30 to 40 years of age.

| Testosterone | Normal Range | Low |
|--------------|-----------------|------------|
| Total | 241 - 827ng/dl | <241ng/dl |
| Free | 9.1 - 32.7pg/ml | < 9.1pg/ml |

Table 2: Testosterone levels in 41 to 50 years of age.

| Testosterone | Normal Range | Low |
|--------------|----------------|-----------|
| Total | 241 - 827ng/dl | <241ng/dl |
| Free | 5.7- 30.7pg/dl | <5.7pg/ml |

Statistical analysis

Data was recorded on a Microsoft Excel spreadsheet. All discrete variables were expressed as percentages. Statistical analysis was performed using Epi Info2000 and SPS student version 16.0 (SPSS Inc, Chicago, USA).

RESULTS

Out of 193 patients who fulfilled the eligibility criteria, 67 (34.71%) patients were having low total testosterone levels and 57 (29.53%) were having low free testosterone levels and total of 45 (23.31%) patients were having low both total and free testosterone levels (Table 4). Baseline data are presented in Table 3.

The average age of study population was 43.32±5.10 years. Majority patients (79.80%) belonged to rural areas (Table 3). A total of 142 (73.57%) patients were known cases of type 2 diabetes mellitus and 51 (26.43%) patients were newly diagnosed type 2 diabetes mellitus (Table 3). Family history of diabetes was present in 133 (68.91%) patients (Table 3). Out of 193 patients, 95 (49.22%) were obese, among these 50 (52.63%) were having low total testosterone levels and 4 (42.10%) were having low free testosterone levels. Using the definition of hypogonadism as the combination of symptoms (positive ADAM score) in addition to a low testosterone level, 48 subjects (24.87%) had overt hypogonadism with total testosterone. Similarly, using bioavailable levels, 46 (23.83%) had overt hypogonadism with bioavailable testosterone (Table 5). Significant association between BMI and low total and free testosterone levels (p<0.0001) was found in

our study. Negative correlations were found between serum testosterone levels and serum lipid levels (p value <.0001), HbA1c levels (p value <.0001). In this study, a total of 72 (37.30%) patients were having peripheral neuropathy. A total of 27 (13.99%) patients were having retinopathy, a total of 20 (10.36%) patients were having Micro albuminuria (Table 6).

Table 3: Patient's clinical and biochemical demographics characteristics at baseline.

| Characteristics | N (%) | Mean (SD) | Median (IQR) |
|--|-------------|------------------|--------------|
| Total number of patients with type 2 diabetes mellitus | 193 (100) | | |
| Age: 30 to 35 years | 9 (4.66) | 32.5556 (1.0138) | 32 |
| 36 to 39 | 46 (23.83) | 37.4348 (1.0678) | 37 |
| 40 to 45 | 60 (30.93) | 42.9833 (1.7611) | 43 |
| 46 to 50 | 78 (40.41) | 48.3846 (1.3602) | 48 |
| Rural | 154 (79.80) | | |
| Urban | 39 (20.21) | | |
| Known cases of diabetes | 142 (73.57) | | |
| Duration of diabetes | | | |
| Not known | 70 (36.27) | | |
| 1 to 5 Years | 43 (22.28) | | |
| 6 to 10 Years | 67 (34.72) | | |
| 11 to 15 Years | 13 (6.74) | | |
| Newly diagnosed | 51 (26.42) | | |
| Family history of diabetes | 133 (68.91) | | |
| History of hypertension | 61 (31.60) | | |
| SBP | | 128.70 (13.9) | |
| DBP | | 82.72 (9.4) | |
| BMI | | 25.73 (3.33) | |
| Smoker | 112 (58.03) | | |
| Alcohol consumption | 84 (43.52) | | |
| Fasting blood glucose | | 183.72 (64.06) | |
| Post prandial blood glucose | | 242.32 (104.32) | |
| HbA1c | | 8.813 (1.72) | |
| TGs | | 214.35 (98.58) | |
| Total cholesterol | | 202.81 (50.68) | |
| HDL | | 36.46 (7.43) | |
| LDL | | 132 (40.40) | |
| Total testosterone levels | | 367.70 (208.44) | |
| Free testosterone levels | | 9.93 (6.83) | |

DISCUSSION

This prospective observational study included a total number of 193 patients of type 2 diabetes mellitus in age group between 30 to 50 years, who presented to Department of Medicine in Indira Gandhi Medical College, Shimla from 1st July 2015 to 30th June, 2016. The study has demonstrated that there is a high prevalence of low testosterone levels both total and free testosterone levels in men with type 2 diabetes mellitus

(Table 4). Of 193 patients 67 (34.71%) had low total testosterone levels and 57 (29.53%) had low free testosterone levels. A 45 (23.31%) patients had both low total and free testosterone levels. Previous studies showed that about one-third of type 2 diabetic men have low serum testosterone levels.¹²

Table 4: Prevalence of low testosterone levels in type 2 diabetes mellitus.

| Testosterone levels | Number of patients with normal levels | Number of patients with low levels | (%) |
|--------------------------------------|---------------------------------------|------------------------------------|--------|
| Total testosterone levels | 126 | 67 | 34.71% |
| Free testosterone levels | 136 | 57 | 29.53% |
| Low total & free testosterone levels | 148 | 45 | 23.31% |

In studies from diabetic clinics, total and free testosterone levels were low in men with T2DM.^{9,13} This study is limited by the absence of a non-diabetic group. Other recent cross-sectional studies included larger numbers of men with diabetes, between 100 and 580, but were limited by the absence of a non-diabetic control group. These studies from Australia, the United Kingdom, and the United States consistently showed that 30-50% of aging, obese men with diabetes, in the absence of known testicular or pituitary pathology, have low total or free testosterone, at least relative to reference ranges based on healthy young men.^{14,9,12} The degree of hypo testosteroneemia, however, was moderate, with mean total testosterone levels ranging from 10.5-12.7nmol/liter.^{14,9,12}

Prevalence of symptoms and low testosterone levels (hypogonadism)

In our study, using the definition of hypogonadism as the combination of symptoms (positive ADAM score) in addition to a low testosterone level, 24.87% (48 subjects) had overt hypogonadism with total testosterone. Similarly, using bioavailable levels, 23.83% (46 Men) had overt hypogonadism with bioavailable testosterone. Hypogonadism (HG) is a clinical condition consisting of both symptoms and biochemical signs of testosterone deficiency (Table 5).

However, many studies in men with diabetes have defined LST solely based on testosterone levels. Symptoms of HG have rarely been considered in combination with biochemical testosterone deficiency. Kapoor D et al, had shown a prevalence of 30-80% in men with type 2 diabetes.⁹ Kapoor D et al, in a cross sectional study of 355 type 2 DM male patients aged above 30 years, showed that low testosterone level is commoner in diabetic men and a significant portion had symptoms of hypogonadism. Overt hypogonadism was seen in 17% of men with low total testosterone and 14% of men with low bioavailable testosterone. BMI and

WHR negatively correlated with testosterone level with stronger association with WHR. Our study showed a

higher average BMI in men with low total and free testosterone levels (p value <0.0001).

Table 5: Total number of patients with low total and free testosterone levels full filling ADAM questionnaire.

| Total number of patient | Number of patients ADAM questionnaire "yes" | Number of patients ADAM questionnaire "yes" with low total testosterone levels | Number of patients ADAM questionnaire "yes" with low free testosterone levels | % of low total testosterone with ADAM questionnaire "yes" | % of low free testosterone with ADAM questionnaire "yes" |
|-------------------------|---|--|---|---|--|
| 193 | 81 | 48 | 46 | 24.87% | 23.83% |

Table 6: Baseline characteristics of patient: therapy and complication.

| Characteristics | Number of patients | (%) |
|---------------------------|--------------------|--------|
| Peripheral neuropathy | 72 | 37.30% |
| Retinopathy | 27 | 13.99% |
| Micro albuminuria present | 20 | 10.36% |
| ADAM Questionnaire (YES) | 81 | 41.97% |
| On OHA | 48 | 24.87% |
| ON OHA +Insulin | 74 | 38.34% |
| Insulin | 0 | 0% |

Table 7: Smoker and non-smokers with normal and low total testosterone levels.

| Smokers | Number of patients with normal total testosterone levels (n=126) | Number of patients with low total testosterone levels (n=67) | P value |
|-----------|--|--|---------|
| Yes (112) | 49 | 63 | <0.0001 |
| No (81) | 77 | 4 | |

Table 8: Smoker and Non-smoker with normal and low free testosterone levels.

| Smoker | Number of patients with normal total testosterone levels (n=136) | Number of patients with low total testosterone levels (n=57) | P value |
|-----------|--|--|---------|
| Yes (112) | 60 | 52 | <0.0001 |
| No (81) | 76 | 5 | |

The finding that testosterone levels are negatively correlated to BMI is in agreement with work done elsewhere.^{15,16} This study also showed an association between lipid profile and testosterone levels in men with type 2 diabetes. These finding is consistent with earlier research.^{17,18} Increased abdominal fat leads to increased aromatase activity. The resulting low testosterone increases lipoprotein lipase activity, the main enzymatic regulator of triglyceride uptake in adipose tissue. This results in inhibition of triglyceride uptake, increased lipid mobilization leading to increased visceral adiposity, and insulin resistance.

This, in turn, causes further hypogonadism and abdominal fat deposition.^{17,19} Low testosterone levels have been observed in association with dyslipidemia and hypertension.²⁰ Although the focus of this study was to determine testosterone levels in men with Type 2 diabetes mellitus, there are findings of lower testosterone levels in cigarette smokers (Table 7,8) in our study. There are differing reports on the impact of smoking on testosterone levels. Whilst some studies report a decline in testosterone levels with smoking, some have noted comparable androgen levels in smokers and non smokers and yet some others have documented higher testosterone levels in smokers compared to nonsmokers.²¹⁻²³ In this study, a total of 72 (37.30%) patients were having peripheral neuropathy. A total of 27 (13.99%) patients were having retinopathy, a total of 20 (10.36%) patients were having microalbuminuria (Table 6). DM is strongly associated with micro vascular complications such as retinopathy, nephropathy, and neuropathy resulting in organ and tissue damage in approximately one-third to one-half of people with the disease.^{24,25} Our study also found that more than one-third of the diabetes subjects had a micro vascular complication in the form of peripheral neuropathy ANDA significant association was found in diabetic neuropathy subjects. This is in agreement with other studies which found that a low total serum testosterone level was associated with diabetic neuropathic patients.^{14,26} In this context, it is important that the endocrine society now recommends the measurements of testosterone in patients with type 2 diabetes on routine basis.²⁷ Current U.S. endocrine society guidelines state that "information about the risks and benefits of testosterone therapy in men with diabetes is either limited or not available".²⁸

CONCLUSION

This study demonstrates that out of 193 patients 67 (34.71%) had low total testosterone levels and 57 (29.53%) had low free testosterone levels.45 (23.31%)patients had both low total and free testosterone levels in men with type 2 DM between 30 and 50 years of age. These patients have testosterone insufficiency and symptoms of hypogonadism. Also, diagnosis of hypogonadism is difficult in that the symptoms are nonspecific, especially in diabetic men, and this explains the importance of testosterone measurement to diagnose

hypogonadism in these patients. Further studies are required to establish the benefit of testosterone replacement therapy on the quality of life and the diabetic state in men with Type 2 DM aged between 30 and 50 years, as there are no definite guidelines regarding testosterone replacement therapy in men with type 2 diabetes mellitus.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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