Original Article

Frequency and Correlates of Hypogonadism in Adult Males with Type 2 Diabetes Mellitus

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Abstract

Background and Aims: There is increasing awareness about an association between type 2 diabetes mellitus (T2DM) and male hypogonadism. However, data are sparse and less uniform with respect to factors associated with hypogonadism in males with T2DM. This study aimed to assess the frequency and correlates of hypogonadism in these subjects. **Materials and Methods:** This cross-sectional study included 130 males with T2DM, age 25-60 years. Study subjects were screened for hypogonadal symptoms using androgen deficiency in aging male (ADAM) questionnaire. Serum total testosterone was measured in subjects with positive ADAM score. Hypogonadism was defined as the presence of positive ADAM score and low serum total testosterone (<3 ng/mL). Clinical and biochemical variables were compared between T2DM subjects with and without hypogonadism. **Results:** Hypogonadism was observed in 26.9% of the study subjects. Hypogonadal symptoms most frequently observed in patients with T2DM and hypogonadism were erectile dysfunction (96.4%), reduced libido (64.3%) and deterioration in work performance (53.6%). Group with T2DM and hypogonadism had higher (i) duration of T2DM (8.9 ± 5.03 vs. 4.8 ± 4.76 years; $P = .001$), (ii) frequency of diabetic retinopathy (58.3% vs. 27.3%; $P = .008$), (iii) frequency of diabetic neuropathy (42.9% vs. 19.7%; $P = .024$), (iv) proportion of subjects on insulin therapy (46.4% vs. 22.4%; $P = .027$), and (v) HbA1c (10.9 ± 2.63% vs. 9.3 ± 2.42%; $P = .006$), compared to group without hypogonadism. **Conclusion:** Hypogonadism was present in nearly one-fourth of the study subjects with T2DM. Compared to the subjects without hypogonadism, group with hypogonadism had longer duration of diabetes, higher HbA1c, greater frequencies of diabetic retinopathy and diabetic neuropathy, and more subjects on insulin therapy.

Keywords: Androgen deficiency in aging male (ADAM) questionnaire, hypogonadism, neuropathy, retinopathy, testosterone, Type 2 diabetes mellitus

Introduction

There is growing awareness and discussion surrounding an association between type 2 diabetes mellitus (T2DM) and hypogonadism.[1-4] Cross-sectional studies have consistently demonstrated higher prevalence of hypogonadism in males with T2DM.[5-12] However, the pathogenic mechanisms underlying co-occurrence of these two entities have not been precisely understood.

There appears to be a two-way relationship between T2DM and male hypogonadism with adiposity and insulin resistance being important connecting links.[2,4] Low serum testosterone promotes insulin resistance by dysregulation of fatty acid metabolism, alteration of body composition and impaired mitochondrial function in skeletal muscle.[2,13] In prospective study cohorts, low testosterone levels have been shown to herald the future occurrence of insulin resistance and diabetes.[14]

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On the other hand, the mechanisms by which diabetes leads to hypogonadism are not clear. Higher frequency of hypogonadotropic hypogonadism compared to primary hypogonadism in T2DM,[5,9] normal response of luteinizing hormone (LH) to injection of gonadotropin-releasing hormone (GnRH),[4] and impaired hypothalamic regulation of LH release in mice with brain-specific deletion of insulin receptor[15] suggest that hypothalamus may be the primary

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site of dysfunction. However, reduction in human chorionic gonadotropin mediated testosterone secretion from testicular Leydig cells in response to progressive insulin resistance has also been demonstrated.[16]

Evaluation of subjects with T2DM for presence of hypogonadism appears to have important health-related consequences. Male hypogonadism is associated with impairment in sexual and reproductive function, reduced bone mineral density, decreased energy levels, sadness of mood, visceral adiposity, reduced insulin sensitivity and enhanced cardiovascular risk.[4,17]

Patients with T2DM can be screened for hypogonadism using simple clinical and biochemical means. Clinical assessment for the symptoms of hypogonadism can be carried out using a validated questionnaire such as androgen deficiency in aging male (ADAM) questionnaire.[18] Morning serum total testosterone can then be measured in subjects with positive score on ADAM questionnaire to confirm the diagnosis of hypogonadism.[19]

A few studies from India have earlier investigated the patients with T2DM for the presence of hypogonadism.[20-23] There is paucity of information regarding clinical and biochemical factors associated with hypogonadism in these subjects. This study aimed to assess the frequency and correlates of hypogonadism in adult males with T2DM.

Materials and Methods

This was a cross-sectional observational study with convenient sampling design. The study was conducted from January 2019 to July 2020 in the Department of Medicine, at a tertiary care teaching hospital in Uttarakhand, India. The study protocol was approved by the Institutional Ethics Committee and written informed consent was obtained from all the study subjects.

All males with T2DM, age 25–60 years, attending the outpatient and inpatient departments were eligible for inclusion in the study. The exclusion criteria were patients suffering from decompensated chronic liver disease, end-stage chronic kidney disease, advanced malignancy, tuberculosis, acquired immunodeficiency syndrome, major psychiatric illness or those receiving testosterone replacement therapy.

Relevant demographic, anthropometric and clinical information were obtained from the study subjects. Patients were classified according to body mass index (BMI) in to underweight (BMI <18.5 kg/m^2), normal weight (BMI = 18.5 – 22.9 kg/m^2), overweight (BMI = 23.0 – 24.9 kg/m^2) and obese (BMI ≥25.0 kg/m^2) categories.[24] Abdominal obesity was defined as waist circumference ≥90 cm.[25] Dilated fundus examination was performed by Ophthalmologist to assess the presence of diabetic retinopathy. Estimated glomerular filtration rate (eGFR) was calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Reduced eGFR was defined as that less than 60 mL per minute per 1.73 square meter of body surface area. Patients were screened for peripheral neuropathy by assessing vibration sensation and ankle jerks in both feet.

Fasting plasma glucose (FPG), post-prandial plasma glucose (PPG), glycated hemoglobin (HbA1c), and serum creatinine were measured in NABL (National Accreditation Board for Testing and Calibration Laboratories) certified laboratory. HbA1c was measured using boronate affinity chromatography method. Plasma glucose and serum creatinine tests were performed using enzymatic hexokinase method and alkaline kinetic picrate method, respectively on UniCel DxC auto-analyzer.

Study subjects were screened for the presence of hypogonadal symptoms using ADAM questionnaire.[18] Briefly, ADAM questionnaire consists of 10 questions that elicit the presence of symptoms suggestive of hypogonadism. (Questions are listed in Table 3 of results). ADAM questionnaire has a sensitivity of 88% and specificity of 60% in detecting androgen deficiency in males over 40 years of age.[18] If a patient gives an affirmative answer to either question 1 or 7, or any three other questions, he is considered to have a positive ADAM score. Morning serum total testosterone was measured in study subjects with positive ADAM score. Serum total testosterone was measured using enzyme-linked fluorescent assay with a measurement range of 0.05 to 13.50 ng/mL (VIDAS® Testosterone, BioMerieux sa, France). Low serum testosterone level was defined as serum total testosterone <3 ng/ml.[9,19] Those study subjects with positive ADAM score and serum total testosterone <3 ng/ml were defined as having hypogonadism.

Statistical analysis

Study data were analyzed using 'IBM® SPSS® statistic version 20'. Qualitative variables were shown as frequency (percentage). Quantitative parameters were shown as mean ± standard deviation (SD). Study-related parameters were compared between T2DM subjects with and without hypogonadism using the Chi-square test for categorical data and independent *t*-test for continuous data, respectively.

Results

The study included 130 male subjects with T2DM. Table 1 shows demographic and anthropometric profile of study subjects. The mean age of the study cohort was 47.9 ± 8.80 years (range = 26-60 years). Mean BMI of study group was 25.2 ± 4.41 kg/m^2. Among study subjects, 16.2% were overweight and 48.5% were obese. Mean waist circumference of the study subjects was 93.4 ± 12.10 cm. Sixty percent of the study subjects had abdominal obesity.

Table 2 depicts clinical and biochemical parameters of the study cohort. About one-third of the study subjects had hypertension whereas 16% of them reported history of coronary artery disease. Diabetic retinopathy was the most commonly observed microvascular complication in the study group. Majority of the subjects had diabetes duration of less than 5 years.

Table 1: Demographic and anthropometric parameters of study subjects (*n*=130)

Parameter	Results
Age (years)	47.9±8.80
Age distribution (years)	
25-40	30 (23.1%)
41-50	41 (31.5%)
51-60	59 (45.4%)
Marital status (married: single)	123:7
Smoking (ever)	72 (55. 4%)
Height (cm)	164.7±6.69
Weight (kg)	68.6±13.19
BMI (kg/m^2)	25.2±4.41
BMI classification (kg/m^2)	
Low BMI (<18.5)	7 (5.4%)
Normal BMI (18.5-22.9)	35 (26.9%)
Overweight (23-24.9)	21 (16.2%)
Obese (≥25)	63 (48.5%)
Waist circumference (cm)	93.4±12.10
Abdominal obesity (waist circumference ≥90 cm)	72 (60%)
Present	48 (40%)
Absent	

Continuous variables are presented as mean±standard deviation and frequencies as percentage.

Table 2: Clinical and biochemical data of the study subjects (*n*=130)

Parameter	Results
Systolic blood pressure (SBP) (mm Hg)	126.7±19.96
Diastolic blood pressure (DBP) (mm Hg)	78.3±10.43
Hypertension	44 (33.8%)
CAD	21 (16.2%)
Diabetic retinopathy*	33 (34.0%)
Reduced eGFR (<60 mL/minute/1.73 m^2)	10 (7.7%)
Diabetic neuropathy	36 (27.7%)
Diabetes duration (years)	5.9±5.01
<5	72 (55%)
6-10	35 (27%)
>10	23 (18%)
Insulin therapy	36 (27.7%)
FPG (mg/dL)	197.5±73.71
PPG (mg/dL)	261.4±95.96
HbA1c (%)	9.8±2.69
<8	35 (28%)
8-10	32 (26%)
≥10	58 (46%)
Serum creatinine (mg/dL)	0.9±0.45

Continuous variables are presented as mean±standard deviation and frequencies as percentage. *Data on diabetic retinopathy were available for 97 study subjects.

Frequency of positive ADAM score and hypogonadism

Among 130 study subjects, 70 (53.8%) were found to have positive score on ADAM questionnaire. Morning serum total testosterone was available in 44 of these 70 subjects. Of these 44 study subjects, 28 were found to have low serum total testosterone (<3 ng/mL). These 28 subjects with positive ADAM score and low serum total testosterone were diagnosed to have hypogonadism. Serum total testosterone ranged from 0.34 ng/mL to 2.92 ng/mL in 28 subjects with hypogonadism. Seventy-six subjects, who either had negative ADAM score or had normal serum total testosterone with positive ADAM score, were classified as subjects without hypogonadism. Twenty-six subjects, who had positive symptoms on the ADAM questionnaire, but for whom serum testosterone values were not available, were not included in the calculation of frequency of hypogonadism. The frequency of hypogonadism in this study was thus 26.9% (28 of 104 subjects). Figure 1 shows frequency of study subjects with positive ADAM score and hypogonadism stratified by age and BMI.

Table 3 shows frequencies of affirmative answers given by study subjects with hypogonadism (n = 28) to individual questions listed in ADAM questionnaire. Erectile dysfunction was the most commonly reported symptom (96.4%) in subjects with hypogonadism, followed by reduced libido (64.3%) and deterioration in work performance (53.6%).

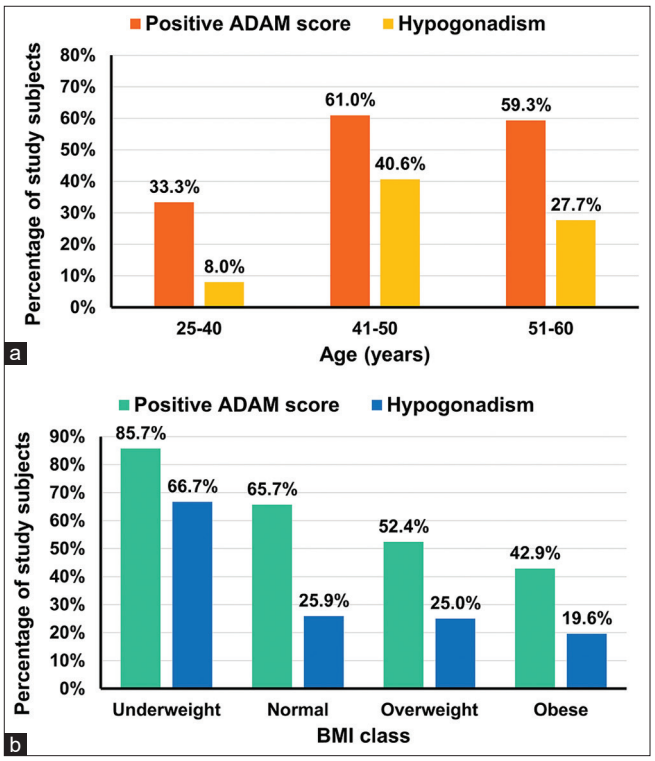

Figure 1: Frequency of study subjects with positive ADAM score and hypogonadism stratified by (a) age and (b) BMI

Demography, body composition and hypogonadism

Study subjects with hypogonadism (n = 28) had higher age compared to those without hypogonadism (n = 76); however, difference between two groups could reach only borderline statistical significance (49.8 ± 6.76 vs. 46.6 ± 9.25 years; P = .057). There was no significant difference between two groups with respect to marital status and frequency of smoking. Two groups had comparable BMI (23.9 ± 4.82 vs. 25.8 ± 4.15 kg/m^2; P = .081) and waist circumference (90.0 ± 14.68 vs. 93.9 ± 10.50 cm; P = .270).

Diabetes duration, glycemic control, diabetic complications and hypogonadism

Table 4 compares clinical and biochemical parameters between T2DM subjects with and without hypogonadism. Group with T2DM and hypogonadism had higher (i) duration of diabetes, (ii) HbA1c, (iii) frequency of diabetic retinopathy, (iv) frequency of diabetic neuropathy, and (v) proportion of subjects on insulin therapy compared to subjects with T2DM without hypogonadism.

Table 3: Frequency of affirmative answers to individual items in ADAM questionnaire in subjects with T2DM and hypogonadism (n=28)[18]

S. No.	Questions	Frequency (percentage)
Q1	Do you have a decrease in libido (sex drive)?	18 (64.3%)
Q2	Do you have a lack of energy?	9 (32.1%)
Q3	Do you have a decrease in strength and/or endurance?	9 (32.1%)
Q4	Have you lost height?	0 (0%)
Q5	Have you noticed a decreased "enjoyment of life"?	11 (39.3%)
Q6	Are you sad and/or grumpy?	4 (14.3%)
Q7	Are your erections less strong?	27 (96.4%)
Q8	Have you noticed a recent deterioration in your ability to play sports?	0 (0%)
Q9	Are you falling asleep after dinner?	4 (14.3%)
Q10	Has there been a recent deterioration in your work performance?	15 (53.6%)

Discussion

Male hypogonadism is a clinically important, though less commonly evaluated complication of diabetes. In this hospital-based, cross-sectional study, we examined frequency and factors associated with hypogonadism in 130 adult males with T2DM.

In present study cohort, the frequency of hypogonadism was 26.9%. Both lower and higher frequencies of hypogonadism have been reported in patients with T2DM from India. The first Indian study to have assessed prevalence of hypogonadism in T2DM was by Ganesh *et al*.[20] In this study from western India, authors detected hypogonadism in 15% of the patients with T2DM.[20] Agarwal *et al*.,[21] in a multicenter study, observed hypogonadism among 20.7% of patients with T2DM. Madhu *et al*.[22] from Delhi showed low serum testosterone in 32% of subjects with T2DM without coronary artery disease (CAD) and 40% in those with CAD. Bajaj *et al*.[23] detected low serum testosterone levels in 44.5% of the subjects who were recently diagnosed to have T2DM, in a study from north India. Studies from other parts of the world have also shown 7% to 51% prevalence of hypogonadism in T2DM.[5-12] The variation in prevalence of hypogonadism in patients with T2DM among these studies could be due to differences in genetic and environmental factors, criteria adopted to define hypogonadism as well as clinical characteristics of study population.

Erectile dysfunction and reduced libido were two most commonly reported symptoms by the subjects with hypogonadism in this study. These data are similar to that observed by Kapoor *et al*.[6] and Ugwu *et al*.[10] Interestingly,

Table 4: Clinical and biochemical parameters in T2DM study subjects with and without hypogonadism

Parameter	T2DM with hypogonadism (n=28)	T2DM without hypogonadism (n=76)	p value*
SBP (mm Hg)	124.2±18.33	127.82±21.34	0.399
DBP (mm Hg)	77.3±11.56	78.8±10.37	0.535
Hypertension	13 (46.4%)	22 (28.9%)	0.107
CAD	7 (25%)	10 (13.2%)	0.140
Diabetic retinopathy†	14 (58.3%)	15 (27.3%)	0.008
Reduced eGFR (<60 mL/minute/1.73 m^2)	3 (10.7%)	4 (5.3%)	0.389
Diabetic neuropathy	12 (42.9%)	15 (19.7%)	0.024
DM duration (years)	8.9±5.03	4.8±4.76	0.001
Insulin therapy	13 (46.4%)	17 (22.4%)	0.027
FPG (mg/dL)	214.2±97.04	194.6±60.65	0.340
PPG (mg/dL)	258.4±87.16	256.7±89.34	0.938
HbA1c (%)	10.9±2.63	9.3±2.42	0.006
Serum creatinine (mg/dL)	1.1±0.53	0.9±0.45	0.078

Continuous variables are presented as mean±standard deviation and frequencies as percentage. *P value less than 0.05 was considered as significant. †Data on diabetic retinopathy were available in 24 subjects with T2DM and hypogonadism, and 55 subjects with T2DM without hypogonadism.

the most common affirmative answer in the original ADAM questionnaire validation study was also in response to the question related to erectile dysfunction.[18]

In this study, subjects with T2DM and hypogonadism had higher duration of diabetes compared to subjects without hypogonadism. The similar association between duration of diabetes and hypogonadism was observed by Al Hayek *et al.*[9] Ganesh *et al.*[20] from India and Mirzaei *et al.*[8] from Iran however, did not find significant association between hypogonadism and duration of diabetes.

Subjects with T2DM and hypogonadism in this study were found to have higher HbA1c compared to the subjects without hypogonadism. Similar observation was also reported by Al Hayek *et al*.[9] Kapoor *et al*.[6] detected lower serum total testosterone in subjects with HbA1c >6.5% compared to controls. Understanding of pathogenic mechanisms responsible for low serum testosterone in diabetes is still evolving.[4,16] Contribution of hyperglycemia in causation of hypogonadism over and above the role of insulin resistance is not well understood. Using cell culture model, Morelli *et al*.[26] have reported deleterious effect of high glucose concentrations on expression of genes mediating function of GnRH neurons.

Higher duration of DM and HbA1c could have been responsible for disproportionately large frequency of hypogonadism in underweight subjects as shown in Figure 1. There were seven subjects in study cohort with BMI less than 18.5 kg/m^2. These subjects had average diabetes duration of 8.6 years and HbA1c of 13.4%.

In present study, subjects with T2DM and hypogonadism had higher frequency of diabetic retinopathy and neuropathy compared to study group without hypogonadism. Similarly, Al Hayek *et al*.[9] in their study observed significant relationship between low serum testosterone and presence of diabetic neuropathy. Bajaj *et al*.[23] also observed higher frequency of microvascular complications in patients with T2DM and low serum testosterone compared to those with normal serum testosterone. Higher HbA1c and duration of T2DM in patients with hypogonadism could explain the greater frequency of diabetic retinopathy and neuropathy in this group.[27]

In present study, more subjects with hypogonadism and T2DM were on the insulin therapy compared to the subjects without hypogonadism. This observation may also be a reflection of more advanced diabetes in former group.

Limitations

This is a cross-sectional study and thus could not establish causal relationship between occurrence of hypogonadism and associated risk factors. Being a hospital-based study with convenient sampling method, it is also susceptible to selection bias and the findings from this study cannot be generalized to the larger population. Compared to the serum total testosterone, free testosterone is considered as a more accurate marker of androgen status, particularly among patients with T2DM. However, in view of limited available resources, we could not measure free testosterone in study subjects. Another limitation of this study is nonavailability of serum testosterone in all the subjects with positive ADAM score.

Conclusion

Hypogonadism defined as the presence of hypogonadal symptoms and low serum total testosterone was observed in 26.9% of adult male subjects with T2DM. The subjects with hypogonadism were found to have longer duration of diabetes, higher HbA1c, higher frequencies of diabetic retinopathy and neuropathy, and more frequent use of insulin therapy compared to those without hypogonadism.

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Conflicts of interest

There are no conflicts of interest.

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