Original Article

A study to evaluate the prevalence of hypogonadism in Indian males with Type-2 diabetes mellitus

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ABSTRACT

Background: A high prevalence of hypogonadism in men with Type-2 diabetes mellitus (T2DM) has been reported worldwide. **Objectives:** To evaluate the prevalence of hypogonadism in Indian males with T2DM and assess the primary and secondary hypogonadism along with androgen deficiency. **Materials and Methods:** In this cross-sectional study, 900 men with T2DM were evaluated using androgen deficiency in aging male questionnaire. They were screened for demographic characteristics, gonadal hormone levels, lipid profile, and glycosylated hemoglobin. **Results:** The prevalence of hypogonadism in T2DM patients was found to be 20.7% (186 out of 900). Hypogonadism was of testicular origin (primary) in 48/186 (25.8%) patients, of pituitary or hypothalamic origin (secondary) in 14/186 (7.53%), and remaining 124/186 (66.67%) patients were found to have low testosterone with the inappropriate normal level of luteinizing hormone and Follicle-stimulating hormone. 451/900 (50.1%) patients were only symptomatic but had normal testosterone levels. Further 263 patients out 900 were asymptomatic, of which 51/900 (5.7%) patients had low levels of testosterone and 212/900 (23.5%) patients had normal testosterone level without symptoms. There were no deaths or other serious adverse events except mild pyrexia which was not related to the study. **Conclusion:** Hypogonadism diagnosis, at times, might not be validated with the help of androgen deficiency questionnaire or symptoms only. Given the large number of patients of T2DM in India, the incidence of hypogonadism is more in diabetic patients as compared to the general population. Hence, implementation of screening programs in diabetic patients is necessary to understand and detect individuals with low serum total testosterone at any early stage and to supplement testosterone accordingly.

Key words: Androgen, diabetes mellitus, hypogonadism, testosterone

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INTRODUCTION

Diabetes is fast becoming the epidemic of the 21st century. Type-2 diabetes mellitus (T2DM), which is more prevalent

Access this article online

Quick Response Code:

Website:
www.ijem.in

DOI:
10.4103/2230-8210.196008

and the main driver of the diabetes epidemic, now affects 5.9% of the world's population. In India, as per the 2011 estimates reported by the Indian Council of Medical Research, India diabetes study, 62.4 and 77.2 million people have diabetes and prediabetes, respectively.[1]

Hypogonadism is defined as a clinical syndrome which consists of clinical symptoms, with or without signs and associated with biochemical evidence of testosterone deficiency.[2] Male hypogonadism is a recognized medical condition that remains underdiagnosed by clinicians.[3] Several large studies over the last few years have reported a high prevalence of low testosterone levels in men (hypogonadism) with T2DM.[4] It has been demonstrated that free testosterone levels, which are independent of sex hormone-binding globulin (SHBG), are low in one-third of diabetic men.[5]

Visceral obesity is an important cause of insulin resistance which is an important feature of T2DM. Studies have shown that free testosterone levels are low in obese men and correlates inversely with the degree of obesity.[6,7] There is increased deposition of abdominal adipose tissue in hypogonadal patients, which in turn leads to a further decrease in testosterone concentrations, through conversion to estradiol by aromatase estradiol further favors abdominal fat deposition and perpetuates testosterone.[4]

Moreover, when combined with T2DM, obesity has been associated with a 50% prevalence of subnormal testosterone levels compared with 44% in normal weight men with T2DM, 40% in obese men without T2DM, and 26% in normal weight men without T2DM suggesting that both T2DM and obesity may be independent risk factors for hypogonadism and that the two conditions together may have an additive effect on the prevalence of hypogonadism.[8]

Interventional studies have shown a beneficial effect of testosterone replacement therapy (TRT) on insulin resistance.[9] A study in healthy men with low total testosterone reported an improvement in insulin sensitivity with testosterone treatment.[9] TRT has also been shown to reduce insulin resistance in men with obesity,[10,11] men with heart failure,[12] and T2DM patients.[13] Studies in Type-2 diabetic men have shown an improvement in glycemic control with TRT.[13,14]

These findings demonstrate the importance of investigating men with diabetes for testosterone deficiency. However, this data in India are scarce, and it is very important to understand the present disease burden in India. The present study was conducted to assess the prevalence of hypogonadism in Indian men with T2DM.

MATERIALS AND METHODS

Study design
This was a multicenter, prospective, epidemiological study which was conducted in10 centers of India, from five different geographical regions so as to represent the truly national data. The study recorded and evaluated the information of participating patients by means of a study pro forma and laboratory tests. This study involved recruitment of confirmed diagnosed T2DM patients with almost equal number of patients in three age groups (30–39, 40–49, and 50–59 years), and the program was carried out in routine clinical practices of participating health-care practitioners in five regions (Northern, Southern, Central, Eastern, and Western) of India.

The study was approved by the Institutional Review Board/Independent Ethics Committees and was conducted as per the International Conference on Harmonisation good clinical practice, the Declaration of Helsinki, and the Indian Council of Medical Research Ethical Guidelines. The study was registered under Clinical Trials Registry-India (CTRI) (www.ctri.nic.in) with the registration number as (REF/2013/09/005747).

Patients
All patients were provided information about the study, and informed consent was obtained before any screening procedure and enrollment into the study. Individuals were enrolled on the fulfillment of eligibility criteria, who were willing to provide informed consent. Patients with known causes of hypogonadism, T1DM, severe diseases such as chronic liver disease, renal disease, advanced malignancy, debilitating diseases such as tuberculosis, malabsorption, inflammatory bowel disease, pyrexia of unknown origin, acquired immunodeficiency syndrome, sickle cell disease, autoimmune diseases such as rheumatoid arthritis, ankylosing spondylitis, any inflammatory disease or infection, and already receiving hormone replacement therapy or with severe psychological symptoms were excluded from the study. Duration of participation of patient was from 1 to 7 days. Participation in the study did not interfere with the routine medical treatment of the patient. No trial medication was administered during the study.

Data collection
The patients'demographic characteristics were collected using a prestructured questionnaire. Smoking and alcohol habits were assessed by dividing men into categories

of smokers and nonsmokers and consumers and nonconsumers, respectively. Education status was also assessed by dividing men into categories of illiterate and literate individuals. The study participants were asked to complete the androgen deficiency in aging male (ADAM) questionnaire. 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. Blood was withdrawn and the serum was aliquoted to determine serumgonadal hormone levels (total testosterone, free testosterone, SHBG, luteinizing hormone (LH), Follicle-stimulating hormone (FSH), prolactin, and estradiol) These blood aliquotes from the patients were analyzed and summarized, using descriptive statistics, according to age ranges, body mass index (BMI) ranges and glycosylated hemoglobin (HbA1c) levels. All the above continuous parameters will be summarized using mean, standard deviation, median, and range. The primary (hypergonadotropic) androgen deficiency is defined as high levels of FSH or LH >10 IU/L, whereas the secondary (hypogonadotropic) androgen deficiency is defined as low levels of FSH or LH <2 IU/L. Similarly, patients in this study, who were positive on ADAM questionnaire and having deranged levels of FSH or LH as per the above statement, were classified as cases of primary and secondary hypogonadism. The prevalence rate of primary (hypergonadotropic) and secondary (hypogonadotropic) androgen deficiency in patients with T2DM according to age ranges, BMI ranges, and HbA1c levels were presented using proportion and 95% confidence interval (CI). The missing data will not be imputed. BMI was computed by dividing the weight in kilograms by the square of height in meters. Overweight was defined as BMI 23-24.9 kg/m², and obesity was defined as BMI ≥25 kg/m². Testosterone deficiency is defined as low free testosterone levels of <0.255 nmol/L with confirmation from a repeat test on separate occasion. In our study, hypogonadism was defined as patients showing as low free testosterone and who were symptomatic hypogonadal assessed through ADAM questionnaire.

Statistical analysis
All the statistical reports including summary tables and listings were generated using a customized reporting Statistical Analysis System (SAS®) Version 9.1.3 for windows (SAS Institute, Cary, North Carolina, USA).

RESULTS

Disposition
Overall 900 patients were enrolled and evaluated in the study excluding the six drop-out patients who were unavailable to provide their repeat free testosterone. All patients were included in the safety populations. In addition, all the patients aged between 30 and 59 years completed the study as per the protocol.

Demographics
The overall mean age (years) ± standard deviation (SD) was 45.2 ± 8.14, mean weight (kg) ±SD was 74.04 ± 13.843, mean height (cm) ±SD was 167.9 ± 6.83, and mean BMI (kg/m²) ±SD was 26.18 ± 4.212 [Table 1]. 199 (22.1%) patients were smokers, 98.2% were literate, and 28.6% patients were consumers of alcohol.

Primary efficacy
The percentage prevalence of hypogonadism (includes patients with positive symptoms evaluated by ADAM questionnaire and patients with low levels of testosterone evaluated by biochemical assay) was 20.7% (186 out of 900) [Table 2]. Hypogonadism was of testicular origin (primary) in 48/186 (25.8%) patients, of pituitary or hypothalamic origin (secondary) in 14/186 (7.53%) patients, and remaining 124/186 (66.67%) patients were found to have normal FSH/LH level with inappropriate low levels of

Table 1: Summary of demographic and baseline characteristics

Parameter/statistics	Overall (*n*=900)
Age (years)	
n	900
Mean (SD)	45.2 (8.14)
Range (minimum:maximum)	30:59
Weight (kg)	
n	900
Mean (SD)	74.05 (13.843)
Range (minimum:maximum)	40:131.4
Height (cm)	
n	900
Mean (SD)	167.9 (6.83)
Range (minimum:maximum)	147:190
BMI (kg/m²)	
n	900
Mean (SD)	26.18 (4.212)
Range (minimum:maximum)	15.3:50.0
Marital status (%)	
Married	880 (97.8)
Unmarried	20 (2.2)
Dietary habits (%)	
Vegetarian	365 (40.6)
Nonvegetarian	521 (57.9)
Other	14 (1.6)
Education (%)	
Literate	884 (98.2)
Illiterate	16 (1.8)
Smoking habit (%)	
Smokers	199 (22.1)
Nonsmoker	701 (77.9)
Alcohol consumption (%)	
Consumer	257 (28.6)
Nonconsumer	643 (71.4)

SD: Standard deviation, BMI: Body mass index

testosterone [Table 3]. Hypogonadism was most prevalent in the 5th and 6th decades ($P = 0.0128$ for 40–50 years age group and $P < 0.0001$ for 50–60 years age group). The prevalence was higher in underweight patients than those who weighed normal or were obese ($P = 0.0154$). 451 (50.1%) patients had symptoms but had normal testosterone levels. 451 (50.1%) patients were only symptomatic but had normal testosterone levels.

Secondary efficacy

Further, 263 patients out of 900 were asymptomatic, of which 51/900 (5.7%) patients had low levels of testosterone [Table 4] and 212/900 (23.5%) patients had normal testosterone level without symptoms. Out of these 51 patients, primary (hypergonadotropic) androgen deficiency was present in 13/51 (25.5%) patients while secondary (hypogonadotropic) androgen deficiency was present in 3/51 (5.9%) patients. Remaining 35/51 (68.6%) patients had no androgen deficiency meeting primary or secondary criteria, i.e. based on FSH and LH values [Table 5]. The age-wise distribution depicts that 18 (6.2%) testosterone-deficient patients belonged to age group 3039 years ($n = 291$), 15 (4.9%) testosterone deficient patients belonged to age group 40–49 years ($n = 305$), and 18 (5.9%) testosterone deficient patients belonged to age group 50–59 years ($n = 304$) [Table 6].

Safety results

Only one patient had one adverse event, i.e., pyrexia. This event was mild and not related to the study which resolved without sequelae. There were no deaths or other serious adverse events reported in this study.

DISCUSSION

Hypogonadism is defined as a clinical syndrome which consists of clinical symptoms, with or without signs and associated with biochemical evidence of testosterone deficiency.[2] Hypogonadism may result from testicular disease (primary hypogonadism) or dysfunction of the hypothalamic-pituitary unit (secondary hypogonadism).[15] Recently, the association between late-onset hypogonadism and T2DM[7,16-23] has been demonstrated in numerous studies (indicating that up to 40% of men with T2DM have testosterone deficiency, and up to 75% of them have sexual dysfunction, particularly erectile dysfunction,[24,25] which is higher than our study.

The prevalence of hypogonadism was around 20.7% in our study which is quite similar to another study by Ganesh *et al*.[26] This study was the first study to determine the prevalence of hypogonadism in Indian population. This was done in one center and quoted a prevalence of

Table 2: Prevalence of hypogonadism (androgen deficiency in aging male positive + low free testosterone) in patients with Type 2 diabetes mellitus-enrolled population

Statistics	Overall (*n*=900)
n (%)	186 (20.7)
95% CI	18.0, 23.3

CI: Confidence interval

Table 3: Prevalence of primary and secondary hypogonadism among hypogonadal patients

Prevalence	Overall (*n*=186)
Primary (hypergonadotropic) hypogonadism in patients with T2DM, *n* (%)	48 (25.8)
Secondary (hypogonadotropic) hypogonadism in patients with T2DM, *n* (%)	14 (7.53)
Low testosterone with inappropriate normal level of LH and FSH, *n* (%)	124 (66.67)

LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, T2DM: Type 2 diabetes mellitus

Table 4: Prevalence of testosterone deficiency (patients with testosterone deficiency+androgen deficiency in aging male negative) in patients with Type II diabetes mellitus-enrolled population

Statistics	Overall (*n*=900)
n (%)	51 (5.7)

Table 5: Prevalence of primary and secondary hypogonadism among testosterone deficient patients

Prevalence	Overall (*n*=51)
Primary (hypergonadotropic) androgen deficiency in patients with T2DM, *n* (%)	13 (25.5)
Secondary (hypogonadotropic) androgen deficiency in patients with T2DM, *n* (%)	3 (5.9)
Low testosterone with inappropriate normal level of LH and FSH, *n* (%)	35 (68.6)

LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, T2DM: Type 2 diabetes mellitus

Table 6: Prevalence of testosterone deficiency in patients with Type 2 diabetes mellitus (age-wise)

Prevalence	Statistics	Age group (years)			
		30-39 (*n*=291)	40-49 (*n*=305)	50-59 (*n*=304)	Overall (*n*=900)
Testosterone deficiency	*n* (%)	18 (6.2)	15 (4.9)	18 (5.9)	51 (5.7)
	95% CI	3.4, 9.0	2.5, 7.3	3.3, 8.6	4.2, 7.2

CI: Confidence interval

15% of hypogonadal patients. Albeit the definition of hypogonadism used in that study was that the patients with calculated free testosterone < 64.8 pg/mL were considered hypogonadal. Probably, the little higher prevalence was due to the higher age of our study cohort (30–59 years) which in the latter was 25–50 years. The higher prevalence can also be attributable to higher mean BMI of 26.18 kg/m², in our

study. Also, another study conducted by Dhindsa *et al*. was for levels of low testosterone involving 103 patients in the United States of America; the prevalence was around 33% as compared to our study where it was 26.3% (186 + 51).[4] In another study in Jordanian population, the prevalence was 18.5% which was also similar to our study.[27] Al Hayek *et al*., in another study (2011), in Jordanian males, found the prevalence to be 36.4% when hypogonadism was defined as total testosterone level of <3 ng/mL, in T2DM patients.[28]

Gray *et al*. (1991) reported that serum testosterone and calculated free testosterone levels showed a slight decrease with increasing age which was opposite in our study wherein it showed a little increase with the increasing age cohorts.[29] Although SHBG levels showed an increase in both our as well as the study conducted by Ganesh *et al*.[26] Also interestingly, the logistic regression analysis showed that hypogonadism was significantly related to age cohorts 40–49 years and 50–59 years than that of

30–39 years, in our study [Figure 1 and Table 7]. Further analysis showed that the number of patients was more in age group of 40–55 years as compared to other age groups for T2DM patients who were suffering from hypogonadism [Figure 2]. The odds ratio analysis suggests that the covariates age and BMI were statistically significant at 5% level of significance. For every 1 year increase age, there is 1.056 times more chance of getting hypogonadism in T2DM patients as compared to T2DM patients not suffering from hypogonadism. For every unit increase in BMI, there is 1.053 times more chance of getting hypogonadism in T2DM patients as compared to T2DM patients not suffering from hypogonadism [Figure 3]. There is 1.77 times more chance of getting hypogonadal patients with age group of 40–49 as compared to patients with age group of 30–39, which is statistically significant at 5% level of significance and there is 2.96 times more chance of getting hypogonadal patients with age group of 50–59 as compared to patients with age group of 30–39, which
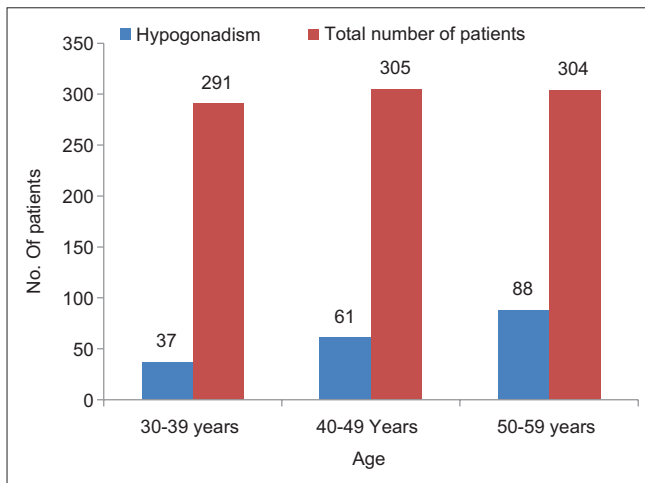

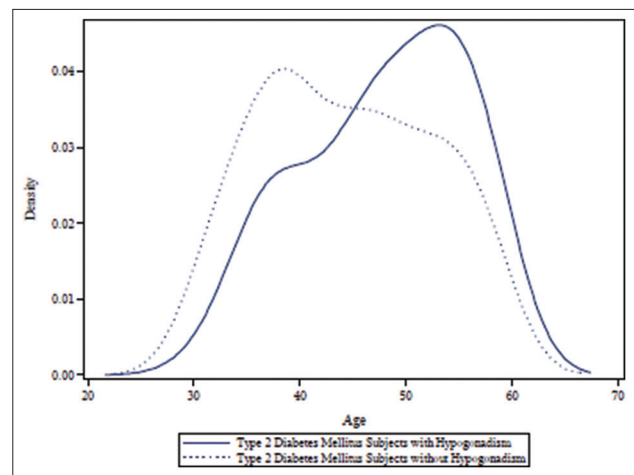**Figure 1:** Prevalence of hypogonadism stratified by age

Figure 2: Kernel density plots of Age by hypogonadism status

Table 7: Logistic regression-hypogonadism (all patients)				
Parameter	n (%)		OR (95% CI)	P
	T2DM patients with hypogonadism, *n*=186	T2DM patients without hypogonadism, *n*=714		
Age (years)				
30–39 (ref)	37 (12.7)	254 (87.3)	1.0	
40–49	61 (20.0)	244 (80.0)	1.77 (1.13, 2.77)	0.0128
50–59	88 (28.9)	216 (71.1)	2.96 (1.92, 4.56)	<0.0001
BMI				
Normal (ref)	29 (16.6)	146 (83.4)	1.0	
Underweight	5 (38.5)	8 (61.5)	4.51 (1.33, 15.23)	0.0154
Overweight	32 (16.2)	165 (83.8)	0.92 (0.53, 1.61)	0.7792
Obese	120 (23.3)	395 (76.7)	1.55 (0.98, 2.44)	0.0598
HbA1c (%)				
<7 (ref)	57 (22.7)	194 (77.3)	1.0	
7-<8	39 (21.0)	147 (79.0)	0.85 (0.53, 1.35)	0.4884
≥8	90 (19.4)	373 (80.6)	0.80 (0.54, 1.17)	0.2450

BMI - Normal: 18.5-22.9 (kg/m²), Overweight: 23-24.9 (kg/m²), Obese: ≥25 (kg/m²), Underweight: <18.5 (kg/m²). Age 30-39 years was considered as referenced category for age, normal category was considered as reference for BMI and <7% was considered reference category for HbA1c levels. Ref: Reference category, HbA1c: Glycosylated hemoglobin, BMI: Body mass index, OR: Odds ratio, CI: Confidence interval, T2DM: Type 2 diabetes mellitus

Parameter	n (%)		OR (95% CI)	P
	T2DM patients with testosterone deficiency + ADAM negative condition, *n*=51	**T2DM patients without testosterone deficiency + ADAM negative condition *n*=849**		
Age (years)				
30-39 (ref)	18 (6.2)	273 (93.8)	1.0	
40-49	15 (4.9)	290 (95.1)	0.79 (0.39, 1.59)	0.5055
50-59	18 (5.9)	286 (94.1)	0.95 (0.48, 1.88)	0.8850
BMI				
Normal (ref)	8 (4.6)	167 (95.4)	1.0	
Underweight	1 (7.7)	12 (92.3)	1.80 (0.20, 15.89)	0.5971
Overweight	9 (4.6)	188 (95.4)	0.92 (0.38, 2.65)	0.9966
Obese	33 (6.4)	482 (93.6)	1.55 (0.64, 3.16)	0.3803
HbA1c (%)				
<7 (ref)	13 (5.2)	238 (94.8)	1.0	
7-<8	13 (7.0)	173 (93.0)	1.37 (0.62, 3.04)	0.4369
≥8	25 (5.4)	438 (94.6)	1.02 (0.51, 2.03)	0.9613

Table 8: Logistic regression-testosterone deficiency (+ androgen deficiency in aging male negative)

BMI - Normal: 18.5-22.9 (kg/m²), Overweight: 23-24.9 (kg/m²), Obese: ≥25 (kg/m²), Underweight: <18.5 (kg/m²). Age 30-39 years was considered as referenced category for age, normal category was considered as reference for BMI and <7% was considered reference category for HbA1c levels. Ref: Reference category, HbA1c: Glycosylated hemoglobin, BMI: Body mass index, OR: Odds ratio, CI: Confidence interval, T2DM: Type 2 diabetes mellitus, ADAM: Androgen deficiency in aging male
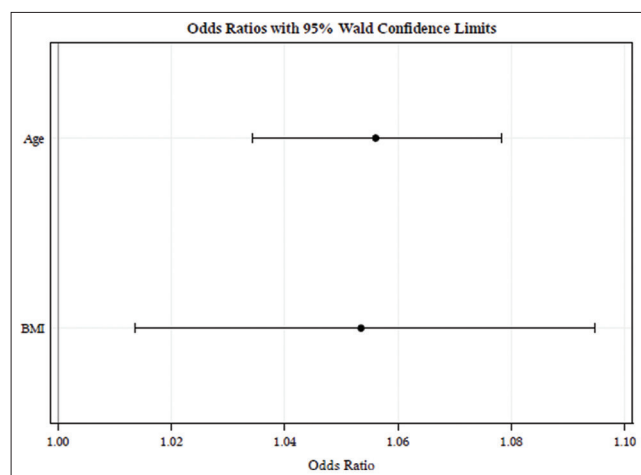

Figure 3: Odds ratio with 95% Wald confidence interval for variables age and body mass index

is statistically significant at 5% level of significance. In the Baltimore longitudinal study of aging,[30] the magnitude of the reduction in total testosterone averaged 0.03 ng/mL/year. The study found a prevalence of androgen deficiency of 4%, 2%, and 7% of men in their 20s, 30s, and 40s, respectively, using a cutoff of 3.25 ng/mL. Their findings clearly support the fact that effect of aging to lower circulating total and free testosterone levels at a fairly constant rate, independent of any other lifestyle factors. These findings corroborate the findings in our study wherein the age-wise prevalence suggests that 28.9% prevalence was found in age group 50–59 years, 20% prevalence was found in 40–49 years, and 12.7% in 30–39 years age cohorts, respectively.

Primary (hypergonadotropic) hypogonadism was defined as high levels of FSH or LH >10 IU/L whereas secondary (hypogonadotropic) hypogonadism is defined as low levels of FSH or LH <2 IU/L. Our finding was not consistent with the findings revealed in a Jordanian study[29] but was similar with the data reported by Kapoor *et al*.,[7] who found that 7% had hypogonadotropic hypogonadism and lower prevalence of primary hypogonadism (high LH and FSH) levels which was seen in 26% of patients with T2DM compared to 16.9% of those who were hypogonadal in our study who had a high level of LH.

The prevalence rate of testosterone deficiency in patients of T2DM, without any symptoms, was 5.7% [Table 8]. Out of this 51/900 (5.7%) patients, primary (hypergonadotropic) androgen deficiency was present in 13 (25.5%) patients while secondary (hypogonadotropic) androgen deficiency was present in 3 (5.9%) patients [Table 5]. This result was somewhat similar to the Taiwanese study where and 12% of the study participants had symptomatic androgen deficiency.[31]

CONCLUSION

The percentage prevalence of hypogonadism in patients with T2DM was moderate with highest number of patients belonging to age group 50–59 years. Significant correlation was found between age, BMI, and hypogonadism. Hypogonadism diagnosis, at times, might not be validated with the help of androgen deficiency questionnaire or symptoms only. Given the large number of patients of T2DM in India, the incidence of hypogonadism is more in diabetic patients as compared to the general population. Hence, implementation of screening programs in diabetic

patients is necessary to understand and detect individuals with low serum total testosterone at any early stage and to supplement testosterone accordingly. We recommend screening of all diabetic patients for testosterone evaluation and seeking an opinion from the experts in treating the disease accordingly and building a hormonal range for T2DM patients for future studies.

Financial support and sponsorship

Conflicts of interest

Raeesuddin Syed and Pradeep Shetty are employees of MSD Pharmaceuticals Private Limited.

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