Original Article

Association Between Type 2 Diabetes and Hypogonadism in India: An Observational Study

Ambika G. Unnikrishnan, Banshi D. Saboo[1], Anirban Majumdar[2], Ravi K. Saraogi[3], Shanmuga Sundar[4], Shriraam Mahadevan[5], Anantharaman Ramakrishnan[6], Indraneel Basu[7], Deep Dutta[8], Arpan D. Bhattacharya[9], Prakadeesh Bharathi[10], Kalpesh Gawand[10]

Department of Endocrinology, Chellaram Diabetes Institute, Pune, Maharashtra, [1]Department of Endocrinology, DiaCare Research, Ahmedabad, Gujarat, [2]Department of Endocrinology, Diabetes-Thyroid -Endocrine and Hormone Clinic, Kolkata, West Bengal, [3]Department of Endocrinology, Diabetes and Endocrine Clinic, Kolkata, West Bengal, [4]Department of Endocrinology, Magna Centre, Chennai, Tamil Nadu, [5]Department of Endocrinology, Sri Ramchandra Medical College and Research Institute, Chennai, Tamil Nadu, [6]Department of Endocrinology, Magna Clinic, Bengaluru, Karnataka, [7]Department of Endocrinology, iMED Clinic, Varanasi, Uttar Pradesh, [8]Department of Endocrinology, CEDAR Superspeciality Healthcare, Dwarka, New Delhi, [9]Department of Endocrinology, Shiva Jyothi Clinic, Bengaluru, Karnataka, [10]Department of Medical Affairs, Abbott Healthcare Pvt Ltd., Mumbai, Maharashtra, India

Abstract

Introduction: Hypogonadism is a common comorbidity associated with several metabolic disorders including type 2 diabetes (T2D) that can remain undetected without proper screening. Here, we evaluated the prevalence of hypogonadism in Indian male patients with T2D with or without obesity. **Methods:** In this prospective, observational study, male patients with T2D and hypogonadism were evaluated symptomatically using the androgen deficiency in ageing male (ADAM) questionnaire at baseline and confirmed on the basis of total testosterone (TT) levels (<300 ng/dL) at Days 5–7 (Visit 2) and 9–14 (Visit 4) assessed after 12 hours of fasting between 8 AM and 10 AM. Prevalence of hypogonadism was presented as proportion of patients. **Results:** Of 598 enrolled patients, 526 completed the study. Mean (standard deviation [SD]) age was 50.4 (9.12) years. The percentage of patients with TT <300 ng/dL at visit 2 was 18.4%, while upon repeat confirmation, it reduced to 8.6%. Thus, the prevalence of true hypogonadism was 8.6%. Prevalence of hypogonadism in patients with BMI range of >30 kg/m^2 (obese) was 11.1%. At screening, 81.4% (487 of 598) patients had positive ADAM questionnaire results. **Conclusions:** Prevalence of hypogonadism in Indian patients with T2D was found to be 8.6% upon repeat evaluation of testosterone. Symptomatic (ADAM questionnaire) as well as biochemical (total testosterone levels with repeat evaluation) confirmation is vital in the definite diagnosis of male hypogonadism.

Keywords: Androgen deficiency, androgen deficiency in ageing male questionnaire, hypogonadism, prevalence, testosterone, type 2 diabetes

Introduction

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] As per the International Diabetes Federation Atlas 2019, the number of diabetic patients aged between 20 and 79 years is estimated to increase from 77 million in 2019 to 101 million by 2030 and 134.2 million by 2045 in India.[2]

Androgen deficiency is a serious concern in the elderly and is thought to affect approximately 1 in 200 men.[3,4] A cross-sectional cohort study conducted in men aged 40–79 years showed a decline in testosterone and free testosterone levels by 0.4% and 1.3% with each advancing year, respectively.[4,5]

Hypogonadism can be either primary (hypergonadotropic hypogonadism wherein primarily testes are affected) or secondary (hypogonadotropic hypogonadism wherein the secretion of hypothalamic gonadotropin-releasing hormone or pituitary gonadotropins such as follicle stimulating hormone [FSH] and luteinizing hormone [LH] is impaired).

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Address for correspondence: Dr. Ambika G. Unnikrishnan, Department of Diabetology, Chellaram Diabetes Institute, Lalani Quantum, Chellaram Hospital, Pune-Bengaluru Highway, Bavdhan, Pune - 411 021, Maharashtra, India.
E-mail: ceo@cdi.org.in

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The major aetiology of secondary acquired hypogonadism is the physiological conditions that result in the alteration of hypothalamus-pituitary-gonadal axis. High levels of FSH or LH >10 IU/L are observed in patients with primary hypogonadism, and low levels of FSH or LH <2 IU/L or low-normal FSH or LH (2-10 IU/L) are observed in patients with secondary hypogonadism.[1,6]

Definite diagnosis of androgen deficiency is challenging because of the diurnal secretion and postprandial suppression of testosterone, inadequate characterization of individual testosterone levels in the absence of repeat screening,[7-9] limitations of symptom-based diagnostic questionnaires such as ADAM,[4,10] and impact of borderline low testosterone and other gonadal hormones' correlation with clinical symptoms. In addition, general screening of men above a certain age for testosterone deficiency is not feasible.[11]

T2D is a common comorbidity in patients with hypogonadism with prevalence ranging from 15.0% to 20.7%.[1,12] Moreover, the probability of hypogonadism in patients with T2D increases with age and body mass index (BMI).[1] Significantly lower serum testosterone levels have been reported in diabetic patients in comparison with non-diabetic patients,[13] and testosterone therapy has been found to cause substantial improvement in insulin sensitivity, indicating a strong association between T2D and hypogonadism.[14,15]

Considering the challenges associated with the diagnosis of hypogonadism and the alarming rise in the incidence of patients with T2D in India, the prevalence of hypogonadism in this population needs to be revisited. While careful clinical and biochemical assessment is essential prior to initiation of treatment,[7,4,10] very few Indian studies have focused on determining the prevalence of hypogonadism in patients with T2D based on concomitant symptom-based and biochemical screening with or without repeat testing of testosterone levels.[1,12,16] Here, we evaluate the prevalence of hypogonadism using questionnaire-based symptomatic evaluation and confirmatory biochemical evaluation of total testosterone levels in Indian men with T2D with or without obesity.

Materials and Methods

Study design

This was a prospective, multicentre, observational study in which male patients with T2D with or without obesity were enrolled at ten sites between July 2021 and April 2022 across India.

All assessments were conducted by the investigators or their qualified designees. Enrolled patients were observed up to 16 days, and each patient attended three to five visits depending on their testosterone level. At the screening/baseline visit on Day 1, patient demographic and baseline characteristics were recorded, and patients were asked to complete the ADAM questionnaire for symptom assessment. At visit 2 (Days 5–7), first evaluation samples were collected and analysed for total testosterone, FSH, LH and prolactin. Visit 3 (Days 6–8) was the end of study (EOS) visit for patients with total testosterone >300 ng/dL at visit 2. Patients with total testosterone <300 ng/dL at visit 2 were asked to return for additional follow-up visits 4 and 5. At visit 4 (Days 9–14), second evaluation samples were collected and analysed for evaluation of testosterone level. Visit 5 (Days 15–16) was the EOS visit for patients with total testosterone level <300 ng/dL at Visit 4. All samples were collected after 12 hours of fasting between 8 AM and 10 AM. Total testosterone was measured by electrochemiluminescence immunoassays (ECLIA) with intra-assay and inter-assay coefficient variance of 4.6%. All samples were processed by the same method in a central lab. No trial medication was administered during the study, and the routine medical treatment of the patients was not interfered.

Eligibility criteria

Male patients aged 30–65 years with a known history T2D for >5 years with or without obesity (defined as BMI >30 kg/m^2)[17] who were willing to avoid any major changes to their lifestyle during the entire duration of the study were included. Patients who were on androgen therapy or anabolic steroids within 12 weeks of entry into the study, patients with a history or current diagnosis of breast or prostate cancer, patients with known causes of hypogonadism (e.g., Klinefelter's syndrome, uncorrected cryptorchidism, surgical orchiectomy or prior infectious orchitis), type 1 diabetes, severe psychological symptoms, 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 patients receiving hormone replacement therapy were excluded from the study.

Study endpoints

The primary endpoint was the percentage of patients with T2D who had hypogonadism as defined by testosterone <300 ng/dL at visits 2 and 4. The secondary endpoints were 1) percentage of hypogonadal patients with T2D ± obesity; 2) percentage of hypogonadal patients with T2D ± obesity stratified by age groups; 3) percentage of patients with androgen deficiency as assessed by ADAM questionnaire with testosterone levels >300 ng/dL at visit 2 and <300 ng/dL at visits 2 and 4; and 5) percentage of patients with FSH or LH <2, 2-10, or >10 IU/L.

Study assessments

Baseline demographic and clinical profiles, clinical examination, history of T2D and obesity, significant medical and surgical history, any comorbidities, concomitant medications, laboratory tests, physical examination and vital parameters were recorded for all patients at screening visits. Enrolled patients were asked to complete the 10-item ADAM questionnaire. A patient was said to have androgen deficiency if he provided a positive response to the question on decrease in libido or the question on decrease in strength of erections, or any three of the other eight questions.[10]

Testosterone deficiency was defined as total testosterone level <300 ng/dL with confirmation from a repeat test at visit 4. In our study, hypogonadism was defined as TT levels <300 ng/dL at visits 2 and 4. At visit 4, primary and secondary hypogonadism were assessed as FSH or LH >10 IU/L, and <2 IU/L, respectively.[1]

Statistical analysis

No formal sample size calculation was performed for this study. This study planned to enrol approximately 600 male patients with T2D with or without obesity. The prevalence of hypogonadism was determined in the overall population and in patients stratified by age groups. All endpoint analyses were presented as number and percentage. The missing data were not imputed.

Ethical aspects

The study was conducted in accordance with the ethical principles laid down by the Declaration of Helsinki ICH-E6 R2 'Good Clinical Practice' guidelines, and New Drugs and Clinical Trials 2019. The trial was prospectively registered on the Clinical Trials Registry–India (CTRI/2021/04/032544) on 05 April 2021. Written informed consent was obtained from all patients before enrolment. Protocol was approved by the Royal Pune Independent Ethics Committee (DCGI Registration number: ECR/45/ lndt/MH/2013/RR-19).

Results

Patient disposition and baseline characteristics

A total of 598 patients were enrolled across 10 study sites in India, out of which 526 completed the study [Figure 1]. The mean (SD) age of the study population was 50.4 (9.12) years, and mean (SD) BMI was 26.5 (3.58) kg/m^2; majority of the patients (85.4%) were not obese and had BMI lesser than 30 kg/m^2. In all, 231 (38.6%) of the enrolled patients belonged to 50–59 years age group, while 26.1% belonged to the 40–49 years age group. Mean (SD) duration of diabetes was 9.2 (4.9) years. The most common comorbidity was hypertension (30.1%), followed by dyslipidemia [24.2%; Table 1].

Table 1: Demographics and baseline characteristics

Baseline characteristics	Overall (*N*=598)
Age (years), mean (SD)	50.4 (9.12)
BMI (kg/m^2), mean (SD)	26.5 (3.58)
Obesity status*, *n* (%)	87 (14.6%)
Age category, *n* (%)	
30-39 years	98 (16.4)
40-49 years	156 (26.1)
50-59 years	231 (38.6)
60-65 years	113 (18.9)
Education category	
Graduate	271 (45.3)
High school certificate	132 (22.1)
Middle school certificate	80 (13.4)
Others[#]	115 (19.2)
Occupation	
Professionals	179 (29.9)
Skilled workers/shop and market sales workers	125 (20.9)
Clerks, technicians/associate professionals	86 (14.4)
Others[†]	208 (34.8)
Smoking status	
Never	471 (78.8)
Former	62 (10.4)
Current	65 (10.9)
Alcohol consumption	
Never	494 (82.6)
Former	57 (9.5)
Current	47 (7.9)
Positive ADAM questionnaire score[‡], *n* (%)	487 (81.4)
Medical history, *n* (%)	
Dyslipidemia	145 (24.2)
Hypertension	180 (30.1)

*Patients with BMI ≥30 kg/m^2 were considered to be obese; [#]Others include professional or honours degree holders, illiterate, primary school certificate and intermediate or diploma holders; [†]Others include elementary occupation, plant and machine operators/assemblers, unemployed, craft and related trade workers, skilled agricultural/fishery workers, and legislators/senior officials/manager; [‡]A positive ADAM score was defined as positive response to the question on decrease in libido or the question on decrease in strength of erections, or any three of the other eight questions; ADAM: androgen deficiency in the ageing male; BMI: body mass index

Prevalence of hypogonadism in Indian real-world setting

Prevalence of hypogonadism by BMI category was 11.1% in patients with BMI >30 kg/m^2, 9.9% in patients with BMI 25–29.9 kg/m^2 and 6.8% in patients with BMI 23–24.9 kg/m^2. Prevalence of hypogonadism by age category was highest in 50–59 years with 33% followed by 28% in 30–39 years and 22% in 60–65 years' category [Table 2]. The percentage of patients with testosterone levels <300 ng/dL at initial testing (visit 2) was 18.4%, while upon repeat confirmation, this percentage reduced to 8.6%. Thus, the prevalence of true hypogonadism was 8.6%. Out of 45 patients with total testosterone <300 ng/dL at visits 2 and 4, 14 (31.1%) had primary hypogonadism, i.e., FSH or LH >10 IU/L and 31 (68.9%) had secondary hypogonadism (four patients with FSH or LH <2 IU/L and 27 patients with FSH or LH levels at 2–10 IU/L). In addition, 11 of 45 (24.4%) patients with hypogonadism had abnormal prolactin levels [Table 2].

Impact of variations in endogenous testosterone levels on diagnosis of hypogonadism

Considering the frequent variation in testosterone levels, we analysed the proportion of patients with adequate (total testosterone >300 ng/dL), borderline low (total testosterone 300–350 ng/dL) and low (total testosterone <300 ng/dL) levels [Table 3]. The incidence of borderline low testosterone at visits 2 and 4 was 10.8% (60 of 554 patients who completed visit 2) and 20.0% (15 of 75 patients who completed visit 4).

ADAM questionnaire assessment and prevalence of hypogonadism by biochemical testing

Androgen deficiency among the study population was assessed using the ADAM questionnaire. At screening, 81.4% (487 of 598) patients had positive ADAM questionnaire results. Of these, 363 (74.5%) patients had testosterone levels >300 ng/dL,

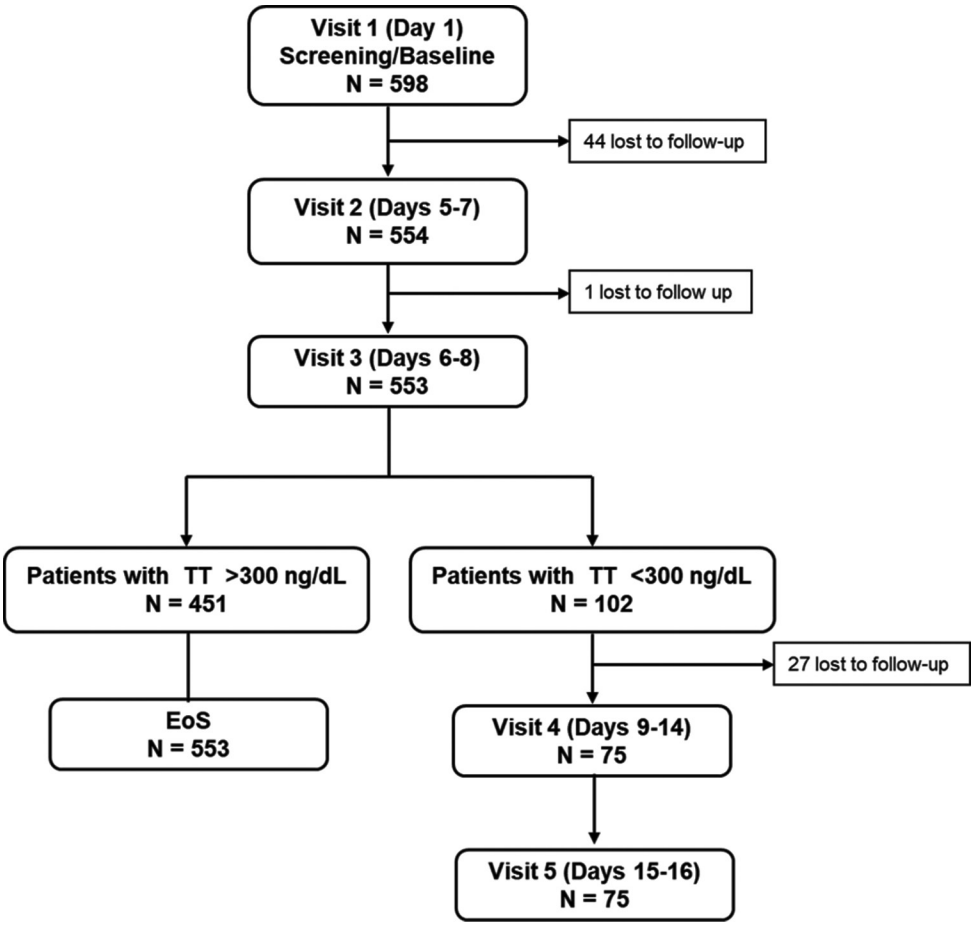

Figure 1: Patient disposition

based on biochemical testing at visit 2 indicating striking differences in the symptom-based assessment of ADAM questionnaire and biochemical testing. Of the 487 patients with positive results on ADAM questionnaire at baseline, 95 (19.5%) had total testosterone <300 ng/dL at visit 2 [Table 4].

Discussion

The objective of this observational study was to evaluate the prevalence of hypogonadism in Indian men with T2D with or without obesity.

In a study by Agarwal *et al.*,[1] the 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). In this study, prevalence of hypogonadism among men with T2D was 18.4% during initial assessment and 8.5% during repeated assessments. Even though there is a similarity with respect to prevalence during initial assessment, the same was significantly different after repeat assessment in comparison with prevalence reported in previous studies which have reported a prevalence ranging from 15% to 25.9%.[1,12] Prevalence from other parts of the world has been found to range from 2% to 29%.[18]

Wide variations in prevalence rates of hypogonadism in patients with T2D among various studies could be due to factors like differences in the criteria adopted to define hypogonadism, use of repeat evaluation method to confirm testosterone levels, sample collection time considering the diurnal variation of testosterone, environmental and seasonal factors,[19] as well as the clinical and metabolic characteristics of the study population. In our study, we have evaluated the prevalence of hypogonadism using a combination of ADAM questionnaire, estimation of total testosterone level at screening and confirmation with repeat testing at follow-up visits.

In a study by Mårin *et al.*,[20] low testosterone levels were found in patients with T2D and obesity, patients with T2D and normal weight and in obese patients without T2D. In our study, percentage of patients with low testosterone levels (<300 ng/dL) was 18.4% and that of patients with borderline low levels (300–<350 ng/dL) was 10.8%, while 45 of 75 patients had testosterone levels <300 ng/dL and 15 of 75) had borderline levels in repeat evaluation. The percentage variation in prevalence between the initial and repeated tests was probably due to the effect of borderline testosterone levels. Considering the fact that the dropout rate at repeat evaluation was 26.4% (27 of 102 eligible patients),

Table 2: Prevalence of hypogonadism in patients with T2D

Patient group	*N*	*n*	Prevalence* (%)
Overall	526	45	8.6
BMI category (kg/m^2)			
<18.5	5	0	0
18.5 to 22.9	67	3	4.4
23 to 24.9	132	9	6.8
25 to 29.9	241	24	9.9
>30	81	9	11.1
Age-wise categorization			
Aged 30-39 years	45	13	28.9
Aged 40-49 years	45	7	15.6
Aged 50-59 years	45	15	33.3
Aged 60-65 years	45	10	22.2
Biochemical markers			
FSH or LH <2 IU/L	45	4	8.9
FSH or LH 2-10 IU/L	45	27	60.0
FSH or LH >10 IU/L	45	14	31.1
Prolactin 4.04-15.2 ng/mL	45	34	75.6
Prolactin <4.04 ng/mL	45	0	0.0
Prolactin >15.2 ng/mL	45	11	24.4

*Prevalence was defined as total testosterone <300 ng/dL at visits 2 and 4 and calculated as (*n*/*N*)*100. BMI, body mass index; FSH, follicle stimulating hormone; LH, luteinizing hormone; T2D, type 2 diabetes

Table 3: Variations in total testosterone levels by visit

Total testosterone level (ng/dL), *n* (%)	Visit 2 *N*=554	Visit 4 *N*=75
>300 (normal)	448 (80.9)	30 (40.0)
<300 (low)	102 (18.4)	45 (60.0)
300	3 (0.5)	-
300-350 (borderline low)	60 (10.8)	15 (20.0)

Table 4: Assessment of androgen deficiency by ADAM questionnaire and prevalence of hypogonadism as confirmed by biochemical testing

Proportion, *n*/M (%)	Baseline (*N*=598)	Visit 2
Positive ADAM questionnaire	487 (81.4)	
Positive ADAM questionnaire + TT >300 ng/dL		363 (74.5)
Positive ADAM questionnaire + TT <300 ng/dL		95 (19.5)

ADAM, androgen deficiency in the ageing male

the chances of obtaining a higher prevalence rate than 8.6% at repeat evaluation cannot be ruled out.

Primary hypogonadism is testicular in origin and can be caused by ageing, infections, injury to the testes, undescended testicle, Klinefelter's syndrome, while secondary hypogonadism is caused by hypothalamic or pituitary disorders, HIV, medication, obesity and stress. In our study, the frequency of primary hypogonadism (31.1%) was lower than that of secondary hypogonadism (68.9%), which is consistent with previous studies.[21,22] The relationship between secondary hypogonadism and metabolic disorders such as T2D is considered to be bidirectional, wherein insulin resistance and subsequent increase in visceral adipose tissue triggers a proinflammatory cytokine-mediated decrease of sex hormone binding globulin, resulting in a temporary increase in free testosterone levels. This free testosterone is subsequently aromatized to estradiol in visceral adipose tissue, thereby causing testosterone deficiency. Furthermore, increased leptin levels in a proinflammatory set-up lead to leptin resistance at the hypothalamic-pituitary level, thereby reducing LH release and boosting testosterone suppression. All of these mechanisms contribute to substantial hypogonadotropic, i.e., secondary hypogonadism.[23]

The prevalence of hypogonadism is significantly greater in males with obesity than in normal-weight controls, and it ranges anywhere between 30% and 60% based on the criteria used for diagnosis and severity of obesity.[24] In the study by Agarwal *et al*.,[1] for every unit increase in BMI, there were 1.052-fold higher chances of the presence of hypogonadism in patients with T2D. In our study, the percentage of patients with hypogonadism was ~10.0% in patients with BMI >25.0 kg/m^2 (Asia-Pacific obesity classification) and >30 kg/m^2 (World Health Organization obesity classification).[25] A large study evaluating hypogonadism in 2162 males aged ≥45 years reported a prevalence of 38.7% based on the definition of total testosterone <300 ng/dL.[26] In obese patients, there is increased conversion of testosterone to estradiol due to the aromatase enzyme present in the adipose tissue. The consequent rise in serum estradiol exerts a negative feedback on the secretion of LH from the pituitary gland, resulting in overall decreased testosterone production.[27]

The Endocrine Society recommends to evaluate the causes of hypogonadism, like obesity which can be reversible without testosterone therapy, before considering testosterone replacement therapy as the primary treatment option.[28] If testosterone therapy is needed, goals of treatment are to improve symptoms associated with testosterone deficiency and maintain sex characteristics.[29] Hence, it is important to have proper screening and diagnosis for hypogonadism.

Strength and limitations

In the current study, screening was done symptomatically with ADAM questionnaire and biochemical evaluation of total testosterone levels was done twice to confirm the diagnosis. The study sites were equally distributed across the country to reduce the environmental and seasonal impact on testosterone values. Some of the limitations of this study included not categorizing the duration of diabetes as part of inclusion criteria and >25% dropout rate of patients with testosterone level <300 ng/dL after the first evaluation. Moreover, there was a potential for selection bias because this was a prevalence study where investigators included patients with a known history of diabetes, but without actual biochemical testing for level of glycaemic control. A study with defined diagnostic

criteria for controlled/uncontrolled diabetes, obesity and other metabolic abnormalities might provide deeper insights with regard to the impact of diabetes control and obesity on the prevalence of hypogonadism.

Conclusion

In this study, the prevalence of hypogonadism among patients with T2D was found to be 8.5% with the highest prevalence among patients aged >50 years as well as those with BMI >30 kg/m^2. The percentage of patients with primary hypogonadism was greater than secondary hypogonadism. Symptomatic as well as biochemical confirmation with repeat evaluation of testosterone is vital in the definite diagnosis of hypogonadism. Hence, it is important to have proper screening based on symptoms and correlate biochemically.

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Authors' contribution

UAG: Conceptualization, Data acquisition and analysis, Guarantor. SBD, MA, SRK, SS, MS, RA, BI, DD, BAD: Data acquisition. BP, GK: Conceptualization, Literature review, Data analysis. All authors contributed equally to manuscript editing and review.

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Conflicts of interest

Prakadeesh Bharathi and Kalpesh Gawand are employees of Abbott Healthcare Pvt. Ltd. All remaining authors received research grants from Abbott for participation in the study.

Data availability

Authors declare that data related to the study will be made available upon request.

Key messages

- Hypogonadism in adult men is often ignored and is recognized as a medical condition that remains underdiagnosed; hence, determining true prevalence of hypogonadism is challenging.
- In this prospective, multicentre, observational study, prevalence of hypogonadism was determined in Indian men with type 2 diabetes (T2D) who had a positive score for androgen deficiency in the ageing male (ADAM) questionnaire at baseline via multiple biochemical evaluations of testosterone levels.
- Overall prevalence of hypogonadism was found to be 18.4% at initial assessment and 8.6% after repeat assessment.
- Screening based on symptoms and biochemical confirmation with repeat evaluation of testosterone is vital in early diagnosis and could aid in optimal management of hypogonadism.

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