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Original Research Article

Clinical and Metabolic Correlates of Hypogonadism in Type 2 Diabetes

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Conflict of interest: Nil

Abstract:

Background: Hypogonadism is a widespread comorbidity in men with Type 2 Diabetes Mellitus (T2DM), significantly impacting their metabolic health and quality of life. Understanding the clinical and metabolic associates of hypogonadism in T2DM individuals is crucial for improving management and outcomes. The study aims to examine the associations among hypogonadism and various clinical and metabolic parameters in male individuals with T2DM.

Methods: The study comprised 173 male T2DM individuals aged 35-65 years. Data were gathered on demographic details, BMI, waist circumference, duration of diabetes, FBS, PPBS, HbA1C, lipid profiles, and testosterone levels. Hypogonadism was termed by low total testosterone levels (<300 ng/dl) and a positive ADAM questionnaire. Statistical analysis involved correlation and regression analyses to explore associations between hypogonadism and clinical/metabolic parameters.

Results: The incidence of hypogonadism was 27.2%. Participants with hypogonadism had higher mean age (53.79 ± 7.37 years vs. 49.11 ± 8.01 years, $p < 0.001$), BMI (26.55 ± 2.27 kg/m² vs. 24.81 ± 2.20 kg/m², $p < 0.001$), and waist circumference (94.05 ± 4.21 cm vs. 90.88 ± 4.07 cm, $p < 0.001$). They also had longer diabetes duration (9.53 ± 4.44 years vs. 6.15 ± 4.31 years, $p < 0.001$), higher FBS (151.81 ± 23.05 mg/dl vs. 136.97 ± 22.67 mg/dl, $p < 0.001$), PPBS (231.74 ± 67.55 mg/dl vs. 203.25 ± 57.26 mg/dl, $p = 0.008$), and HbA1C (8.74 ± 2.18% vs. 7.88 ± 1.74%, $p = 0.005$). Substantial negative correlations were seen among testosterone levels and age, waist circumference, BMI, diabetes duration, FBS, PPBS, and HbA1C.

Conclusion: Hypogonadism is prevalent among male T2DM patients and is significantly associated with adverse clinical and metabolic parameters. Aging, obesity, central obesity, and poor glycemic control are key factors linked to reduced testosterone levels.

Recommendations: Regular screening for hypogonadism in men with T2DM is recommended. Addressing hypogonadism through lifestyle modifications, weight management, and possibly testosterone replacement therapy could improve metabolic health and quality of life in these patients.

Keywords: Hypogonadism, Type 2 Diabetes Mellitus, BMI, Waist Circumference, Testosterone.

Introduction

Type 2 Diabetes Mellitus (T2DM) is a worldwide health concern, with its incidence steadily increasing due to lifestyle changes, obesity, and aging populations. T2DM is characterized by insulin resistance and chronic hyperglycemia, which contribute to various complications, including cardiovascular disease, neuropathy, and nephropathy [1]. Emerging evidence suggests that T2DM also significantly impacts endocrine function, particularly gonadal function in men. Hypogonadism, defined by low serum testosterone levels, is increasingly recognized as a common comorbidity in men with T2DM.

The incidence of hypogonadism in males with T2DM differs widely, with estimates ranging from 25% to 50% in different populations [2]. This condition not only affects quality of life by contributing to symptoms like fatigue, decreased libido, and erectile dysfunction but also exacerbates the metabolic dysregulation inherent in diabetes. Hypogonadism in men with T2DM has been related with elevated visceral adiposity, dyslipidemia, and poor glycemic control, creating a vicious cycle that further complicates diabetes management [3].

Recent studies have highlighted the complex interplay between metabolic health and testosterone levels. Obesity, particularly central obesity, is a significant risk factor for both T2DM and hypogonadism [4, 5]. Excess adipose tissue, notably visceral fat, contributes to insulin resistance and alters sex hormone metabolism, leading to reduced testosterone levels. Conversely, low testosterone levels can promote the accumulation of visceral fat, thereby worsening insulin resistance and metabolic control [6]. This bidirectional relationship underscores the importance of understanding the

clinical and metabolic correlates of hypogonadism in T2DM individuals.

In addition to obesity, aging and the duration of diabetes are critical factors influencing hypogonadism. Testosterone levels naturally decline with age, and this decline is often accelerated in men with T2DM. Longer duration of diabetes is also related with a higher incidence of hypogonadism, likely due to the cumulative effects of chronic hyperglycemia on endocrine function. Poor glycemic control, reflected by elevated fasting and postprandial blood sugar levels and higher HbA1C, is another important correlate of hypogonadism in this population [7].

Given the significant overlap between T2DM and hypogonadism, it is crucial for clinicians to recognize and address this comorbidity to improve patient outcomes. Regular screening for hypogonadism in men with T2DM, along with appropriate therapeutic interventions such as lifestyle modifications, weight management, and possibly testosterone replacement therapy (TRT), could potentially mitigate the adverse effects of hypogonadism and enhance overall metabolic health.

The study goal was to evaluate the associations between hypogonadism and various clinical and metabolic parameters in male individuals with Type 2 Diabetes Mellitus.

Methodology

Study Design: A cross-sectional observational study.

Study Setting: The study was conducted at Apollo Hospital, Bhubaneswar, Odisha, in the Department of General Medicine and Endocrinology, conducted over 16 months, from November 2020 to February 2022.

Participants: The study included 173 male patients with T2DM.

Inclusion Criteria:

- Adult male patients with T2DM, aged 35-65 years.
- Both newly diagnosed T2DM patients as per the recent American Diabetes Association (ADA) guidelines and already confirmed T2DM patients undergoing treatment with oral hypoglycemic agents (OHA) and/or parenteral insulin.

Exclusion Criteria:

- Patients with a known case of hypogonadism already obtaining hormone replacement therapy.
- Patients with severe conditions, including chronic liver and renal diseases, advanced cancer, debilitating illnesses like tuberculosis, malabsorption syndromes, and autoimmune disorders, as well as those experiencing severe psychological symptoms.

Bias: To minimize selection bias, almost equal numbers of participants were selected from each of the three age groups. Detailed history taking and physical examination ensured the collection of comprehensive data, reducing information bias.

Variables: Variables included prevalence of hypogonadism in male T2DM patients, age, BMI, waist circumference, duration of T2DM, FBS, PPBS, HbA1C, lipid profiles (total cholesterol, triglycerides, LDL, HDL), total testosterone (TT) levels and response to the Androgen Deficiency in the Aging Male (ADAM) questionnaire.

Data Collection: Data were collected using a pre-structured study proforma. This included detailed history regarding present illness, past illnesses, co-morbidities, substance abuse, and medication use. Physical examination involved measuring height, weight, and waist circumference. Each participant completed the ADAM questionnaire to evaluate androgen deficiency.

Procedure

- **Physical measurements:** Participants' height and weight were taken while they were wearing lightweight clothing and no shoes. BMI was determined using the formula weight (kg)/height (m)^2. Waist circumference was measured at the midpoint between the iliac crest and the lower rib.
- **Blood samples:** Blood samples were assembled between 8 AM and 10 AM after fasting to measure fasting blood sugar (FBS), HbA1C, lipid profiles, and gonadal hormone levels. A second blood sample was collected two hours later for postprandial blood sugar (PPBS) measurement.
- **Laboratory analyses:** Plasma glucose levels were measured using the Hexokinase method with spectrophotometry. HbA1C levels were determined via high-performance liquid chromatography (HPLC). Lipid profiles were analyzed using spectrophotometry, while total testosterone, LH, and FSH levels were measured using the chemiluminescence immunoassay (CLIA) method.

Statistical Analysis: A Microsoft Excel spreadsheet containing the data was created, and IBM SPSS Statistics version 23.0 was used for analysis. Values were reported as mean ± standard deviation (SD) or median; and percentages. At $p < 0.05$, statistical significance was established.

Ethical consideration: Ethical approval was obtained from the Institutional Ethical Committee

and Scientific Committee before the study began. All participants provided written informed consent.

Result

The study included 173 male patients with T2DM aged between 35 and 65 years. The participants were allocated into three age groups: 35-45 years (31.2%), 46-55 years (34.7%), and 56-65 years (34.1%). Out of these patients, 47 (27.2%) were diagnosed with hypogonadism, defined by both low total testosterone (TT) levels (<300 ng/dl) and a positive response to the ADAM questionnaire.

Table 1: Key Findings of Clinical and Metabolic Correlates of Hypogonadism

Parameter	Hypogonadism, Mean ± SD		p-value
	Yes	No	
Age (Years)	53.79 ± 7.37	49.11 ± 8.01	<0.001
BMI (Kg/m²)	26.55 ± 2.27	24.81 ± 2.20	<0.001
Waist Circumference (cm)	94.05 ± 4.21	90.88 ± 4.07	<0.001
Duration of Diabetes (Years)	9.53 ± 4.44	6.15 ± 4.31	<0.001
Fasting Blood Sugar (mg/dl)	151.81 ± 23.05	136.97 ± 22.67	<0.001
Postprandial Blood Sugar (mg/dl)	231.74 ± 67.55	203.25 ± 57.26	0.008
HbA1C (%)	8.74 ± 2.18	7.88 ± 1.74	0.005

Participants with hypogonadism had a higher mean age in contrast to those without hypogonadism (53.79 ± 7.37 years vs. 49.11 ± 8.01 years, $p < 0.001$). The incidence of hypogonadism increased with age, with 13% in the 35-45 years group, 31.7% in the 46-55 years group, and 35.6% in the 56-65 years group. This indicates that aging is a significant factor in the development of hypogonadism in T2DM individuals. The moderate negative correlation (NC) between age and testosterone levels ($r = -0.45$, $p < 0.001$) further supports this observation, showing that testosterone levels decrease with age.

Mean BMI was higher in patients with hypogonadism (26.55 ± 2.27 kg/m²) compared to those without hypogonadism (24.81 ± 2.20 kg/m², $p < 0.001$). The risk of hypogonadism was 3.25 times higher in obese individuals (BMI ≥ 25 kg/m²) compared to non-obese patients. The moderate NC between BMI and testosterone levels ($r = -0.5$, $p < 0.001$) suggests that higher BMI is related with lower testosterone levels, highlighting obesity as a critical factor in the pathogenesis of hypogonadism in T2DM patients.

Mean WC was higher in patients with hypogonadism (94.05 ± 4.21 cm) compared to those without hypogonadism (90.88 ± 4.07 cm, $p < 0.001$). The risk of hypogonadism was 4.8 times higher in participants with central obesity (WC ≥ 90 cm) compared to those without, indicating a strong association between visceral fat and reduced testosterone levels. The moderate NC between WC and testosterone levels ($r = -0.44$, $p < 0.001$) underscores the impact of central obesity on hypogonadism.

The average diabetes duration was longer in people with hypogonadism (9.53 ± 4.44 years) compared to those without hypogonadism (6.15 ± 4.31 years, $p < 0.001$). The risk of hypogonadism was 8.67 times higher in individuals with a diabetes duration > 5 years. The moderate NC between the duration of diabetes and testosterone levels ($r = -0.46$, $p < 0.001$) emphasizes that longer exposure to hyperglycemia may lead to greater disruption of gonadal function.

Mean fasting blood sugar (FBS) was higher in patients with hypogonadism (151.81 ± 23.05 mg/dl) compared to those without hypogonadism (136.97 ± 22.67 mg/dl, $p < 0.001$). Similarly, mean postprandial blood sugar (PPBS) was higher in patients with hypogonadism (231.74 ± 67.55 mg/dl) compared to those without hypogonadism (203.25 ± 57.26 mg/dl, $p = 0.008$). Mean HbA1C was also higher in patients with hypogonadism (8.74 ± 2.18%) compared to those without hypogonadism (7.88 ± 1.74%, $p = 0.005$). The risk of hypogonadism was considerably higher in people with poor glycemic control, as indicated by higher FBS, PPBS, and HbA1C levels. Moderate NC between testosterone levels and FBS ($r = -0.31$, $p < 0.001$), PPBS ($r = -0.23$, $p = 0.002$), and HbA1C ($r = -0.3$, $p < 0.001$) underscore the link between hyperglycemia and testosterone deficiency.

Discussion

The study included 173 male participants with T2DM aged 35-65 years, with a hypogonadism prevalence of 27.2%, defined by low TT levels and a positive ADAM questionnaire. Patients with hypogonadism were generally older (mean age 53.79 ± 7.37 vs. 49.11 ± 8.01 years, $p < 0.001$), showing a NC among age and testosterone levels ($r = -0.45$, $p < 0.001$), highlighting aging's impact on gonadal function.

Hypogonadal participants had a greater mean BMI (26.55 ± 2.27 kg/m² vs. 24.81 ± 2.20 kg/m², $p < 0.001$), with a NC between BMI and testosterone ($r = -0.5$, $p < 0.001$), indicating obesity as a critical factor. They also had higher mean WC (94.05 ± 4.21 cm vs. 90.88 ± 4.07 cm, $p < 0.001$), with a NC ($r = -$

0.44, $p < 0.001$), suggesting visceral fat's strong association with reduced testosterone levels

Table 2: Correlation Analysis of Testosterone Levels with Clinical and Metabolic Parameters

Parameter	Correlation Coefficient (r)	p-value
Age (Years)	-0.45	<0.001
BMI (Kg/m²)	-0.5	<0.001
WC (cm)	-0.44	<0.001
Diabetes Duration (Years)	-0.46	<0.001
FBS (mg/dl)	-0.31	<0.001
PPBS (mg/dl)	-0.23	0.002
HbA1C (%)	-0.3	<0.001

The mean diabetes duration was longer in hypogonadal participants (9.53 ± 4.44 years vs. 6.15 ± 4.31 years, $p < 0.001$), with a NC ($r = -0.46$, $p < 0.001$), indicating prolonged hyperglycemia's impact on gonadal function. Hypogonadal patients exhibited poorer glycemic control, with higher mean FBS (151.81 ± 23.05 mg/dl vs. 136.97 ± 22.67 mg/dl, $p < 0.001$), PPBS (231.74 ± 67.55 mg/dl vs. 203.25 ± 57.26 mg/dl, $p = 0.008$), and HbA1C (8.74 ± 2.18% vs. 7.88 ± 1.74%, $p = 0.005$), with NC between testosterone and FBS ($r = -0.31$, $p < 0.001$), PPBS ($r = -0.23$, $p = 0.002$), and HbA1C ($r = -0.3$, $p < 0.001$), linking poor glycemic control to lower testosterone levels.

The results highlight the substantial associations between hypogonadism and various clinical and metabolic parameters in male T2DM patients. Older age, higher BMI, larger waist circumference, longer duration of diabetes, and poor glycemic control were all strongly associated with lower testosterone levels. These findings suggest that aging, obesity, visceral fat, and chronic hyperglycemia are critical factors in the development of hypogonadism among diabetic patients.

Addressing hypogonadism in diabetes management could potentially improve metabolic health and overall quality-of-life in these people. The strong correlations between these clinical and metabolic parameters and testosterone levels underscore the importance of regular screening for hypogonadism in male T2DM patients, as well as the potential benefits of interventions such as testosterone replacement therapy (TRT) to manage this condition effectively. Further research is needed to explore the therapeutic benefits of TRT and other interventions in this population.

According to a study, 17.2% of 267 men diagnosed with T2DM had hypogonadism. Men classified as hypogonadal had glomerular filtration rates that were significantly lower, as well as a higher prevalence of abnormal liver function tests, chronic kidney disease, and psychiatric treatment. Age >60 years (OR = 3.58, $p = 0.005$), hypertriglyceridemia (OR = 2.16, $p = 0.035$), BMI >27 kg/m² (OR = 2.85, $p = 0.025$), and abnormal hepatic function tests (OR = 3.57, $p = 0.005$) were among the major risk variables [8].

257 males with T2DM were found to have a hypogonadism prevalence of 11.67% in another investigation. Testosterone levels and fasting insulin, HOMA-IR, and BMI showed a strong inverse connection. Even after controlling for age, BMI, HBA1c, and lipid levels, HOMA-IR was found to be independently correlated with testosterone levels (OR = -5.185, 95% CI = -8.29 to -2.075). Hypogonadism and diabetic retinopathy were also substantially correlated [9].

In 213 males with T2DM, a study found that BMI, HOMA-IR, LH levels, and metabolic syndrome were independently significant risk factors for hypogonadism. TT showed a NC ($r = -0.142, -0.154$, $p < 0.05$) with fasting insulin and HOMA-IR, and a positive correlation ($r = 0.157, 0.138$, $p < 0.05$) with LH and FSH. Patients suffering from metabolic syndrome had significantly lower TT levels ($p < 0.05$) [10].

A cross-sectional study that included 200 male T2DM discovered that 26% of them had hypogonadism. Total testosterone was notably inversely correlated with FBS, sex hormone-binding globulin (SHBG), and BMI. The study made clear that males with low serum levels of testosterone should be screened early and should take supplements [11].

In Nigerian males with T2DM, central obesity, systolic hypertension, hyperglycemia, and hypercholesterolemia were identified to be major risk factors for hypogonadism. Total testosterone was found to significantly negatively correlate with both HDL cholesterol ($r = -1.25$, 95% CI = -5.95 to -3.45, $p = 0.02$) and triglycerides ($r = -1.85$, 95% CI = -3.58 to -0.12, $p = 0.04$) [12].

In a different study, the corrected volumetric bone mineral density (vBMD) at the tibia was greater in men with than in men without T2DM (857.3±69.0 mg/cm³ vs. 828.7±96.7 mg/cm³, $p = 0.02$). On the other hand, their serum levels of osteocalcin and C-telopeptide (CTX) were lower, indicating that they had inferior bone geometry and decreased bone turnover [13].

Additionally, a study found that among males with T2DM, overt hypogonadism is a significant cardiovascular risk factor, associated with greater incidence of macrovascular problems (42.6% vs. 31.3%, p = 0.042). In hypogonadal patients, poor glycaemic control, as demonstrated by higher HbA1c values, was substantially more prevalent (20.8% vs. 31.3%, p = 0.043) [14].

In men with T2DM, a considerable correlation was noted between low testosterone levels and non-fatal cardiovascular events. Additionally, the study found that hypogonadism worsens insulin resistance, which leads to weight gain and poorer metabolism of carbohydrates [15].

Conclusion

Hypogonadism is prevalent among male T2DM patients and is significantly associated with adverse clinical and metabolic parameters. Addressing hypogonadism in diabetes management could potentially improve metabolic health and overall quality of life in these patients. Further research is warranted to explore the therapeutic benefits of testosterone replacement therapy (TRT) in this population.

Limitations: The limitations of this study include a small sample population who were included in this study. Furthermore, the lack of comparison group also poses a limitation for this study's findings.

Recommendation: Regular screening for hypogonadism in men with T2DM is recommended. Addressing hypogonadism through lifestyle modifications, weight management, and possibly testosterone replacement therapy could improve metabolic health and quality of life in these patients.

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List of abbreviations:

T2DM: Type 2 Diabetes Mellitus

BMI: Body Mass Index

WC: Waist Circumference

FBS: Fasting Blood Sugar

PPBS: Postprandial Blood Sugar

HbA1C: Hemoglobin A1c

TT: Total Testosterone

ADA: American Diabetes Association

OHA: Oral Hypoglycemic Agents

ADAM: Androgen Deficiency in the Aging Male

LH: Luteinizing Hormone

FSH: Follicle-Stimulating Hormone

CLIA: Chemiluminescence Immunoassay

NC: Negative Correlation

SHBG: Sex Hormone-Binding Globulin

HOMA-IR: Homeostasis Model Assessment of Insulin Resistance

vBMD: Volumetric Bone Mineral Density

CTX: C-telopeptide

TRT: Testosterone Replacement Therapy

SD: Standard Deviation

SPSS: Statistical Package for the Social Sciences

OR: Odds Ratio

CI: Confidence Interval

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