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The prevalence of hypogonadism in male patients with type 2 diabetes mellitus and clinically relevant factors

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ABSTRACT

Aims: Hypogonadism has been reported at high rates in male patients with type 2 diabetes mellitus (T2DM). However, the origin of male hypogonadism in patients with T2DM is poorly known. The aim of this study was to determine the prevalence of hypogonadism and to investigate the potential impact of certain clinical and biochemical variables on hypogonadism in patients with T2DM.

Methods: The study included a total of 513 consecutive males (aged 30 - 60 years) with T2DM who presented at the endocrinology outpatient clinic. The demographic and clinical characteristics of the patients were recorded. Biochemical parameters, total testosterone (TT), gonadotrophins, prolactin, serum lipids, and hemoglobin A1c (HbA1c) were measured. Correlations between metabolic and clinical conditions and T levels were analyzed.

Results: The mean age of the study population was 45.5±12.6 years. Hypogonadism was present in 122 (23.7%) patients, of which 24 (23.3%) were determined with primary hypogonadism. Compared with participants with normal testosterone, those with hypogonadism had lower estimated glomerular filtration rate (eGFR), and the liver function test results, HbA1c and triglycerides levels, and duration of diabetes were higher. Correlation analyses showed that TT was negatively correlated with body mass index (BMI), waist circumference, age, fasting blood glucose, HbA1c, uric acid and triglycerides, and positively correlated with eGFR and high density lipoprotein cholesterol (HDL-C). Multivariate logistic regression analysis revealed that BMI, age, diabetes course, hypertrglyceridemia, hyperuricemia and eGFR <60 ml/min/1.73 m² are independent risk factors for hypogonadism in male patients with type 2 diabetes.

Conclusion: The current study results demonstrated that the prevalence of hypogonadism is higher in men with type 2 diabetes than in the general population and age, diabetes duration, BMI, triglycerides and uric elevation are independent risk factors.

Keywords: Diabetes, male hypogonadism, testosterone

INTRODUCTION

Approximately 537 million people worldwide are affected by diabetes mellitus (DM), which is a chronic, progressive, metabolic disease that can cause complications in several organ systems.[1,2] Male hypogonadism is one of these complications and the frequency of this has been reported to vary between 20% and 40% in previous studies.[3-5] Male hypogonadism is a disorder in which testosterone (T) deficiency is clinically characterized and biochemically confirmed.[5] The Endocrine Society recommends routine T measurement in males with Type 2 DM (T2DM).[6] However, despite being frequently seen, it can be said that male hypogonadism is often overlooked.[7] Diseases such as dyslipidemia, obesity, and metabolic syndrome, which often accompany T2DM, can also cause hypogonadism.[5,8] The fact that hypogonadism in T2DM is mostly in the form of hypogonadotropic hypogonadism suggests that disruption of the hypothalamic-pituitary axis plays a fundamental role in the pathogenesis.[9] However, the underlying mechanism of hypogonadism that develops associated with diabetes, and which correlations of diabetes are associated with hypogonadism are not clear. When it is considered that the incidence of diabetes is continously increasing and a significant proportion of patients are of reproductive age, there can be seen to be a significant problem. The aim of this study was to determine the frequency of hypogonadism in males with T2DM, and to evaluate the risk factors by examining the correlations of biochemical and clinical conditions with serum T levels.

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METHODS

Approval for this retrospective study was granted by the Clinical Researches Ethics Committee of Health Sciences University Dışkapı Yıldırım Beyazıt Training and Research Hospital (Date: 17.05.2021, Decision No: 111/11). The study was conducted in Kilis Prof. Dr. Alâeddin Yavaşça State Hospital and in accordance with the Declaration of Helsinki. The study included 513 consecutive male patients, aged 30-60 years, who presented at the Endocrinology Outpatient Clinic between January 2023 and July 2023 with a diagnosis of T2DM. Patients were excluded from the study if they had Type 1 DM, hypopituitarism, end-stage renal failure, cirrhosis of the liver, chronic alcoholism, or malignancy.

All the patients included in the study met the diagnostic criteria for diabetes defined by the World Health Organisation (WHO) in 1999.[10,11] The diagnosis of hypogonadism was defined as total testosterone (TT) level <240 ng/dl or a TT level of <300 ng/dl in the presence of signs or symptoms.6 TT measurements were taken before 10.00 a.m. in a fasting condition. Low T levels were confirmed with a second measurement, in accordance with the recommendation of the Endocrine Society.[6] The body mass index (BMI) values of the patient, waist circumference, duration of diabetes, smoking status, the presence of retinopathy, neuropathy, or nephropathy, and macrovascular complications related to diabetes were recorded from the medical records. Blood samples were taken in the morning after overnight fasting, and the values were recorded of fasting blood glucose, glycosylated hemoglobin (HbA1c), serum lipids, follicle-stimulating hormone (FSH), luteinising hormone (LH), prolactin, liver transaminases, creatinine, estimated glomerular filtration rate (eGFR), and serum uric acid. FSH or LH ≥10 IU/L was defined as primary hypogonadism, and FSH or LH <10 IU/L as secondary (central) hypogonadism. The normal reference range for uric acid is 2.6-6 mg/dl, and values >6 mg/dl are considered hyperuricemia. The normal reference ranges for liver transaminases AST (Aspartate transaminase): 5-34 U/L and ALT (alanine aminotransferase): 0-55 U/L. Values above this range were considered as elevated liver transaminases.

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS 28.0 software. Continuous data were reported as mean±standard deviation values, and categorical data as number and percentage. Normality of distribution of the data was tested with the Kolmogorov-Smirnov test. Categorical variables were analyzed using the Chi-square test or Fisher's Exact test. The Student's t-test was applied to continuous variables showing normal distribution, and the Mann Whitney U-test was used when distribution was not normal. Correlations between the data were examined using Pearson and Spearman correlation analyses. Multivariate logistic regression analysis was performed to determine the risk factors associated with hypogonadism. Results were shown as odds ratio (OR) and 95% confidence interval (CI). A value of $p<0.05$ was accepted as statistically significant.

RESULTS

Hypogonadism was determined in 122 (23.7%) of the 513 patients evaluated. Secondary hypogonadism was seen in 98 (80.3%) of the patients with hypogonadism. When the patients with and without hypogonadism were compared, higher values were determined in the patient group with hypogonadism (Group 1) than in the patient group without hypogonadism (Group 2) in respect of age (51.2±8.9 vs. 44.3±11.2 years, $p<0.001$), duration of diabetes (11.4±4.5 vs. 7.6±4.2 years, $p<0.001$), BMI (31.5±3.8 vs. 26.4±4.1, $p<0.001$), fasting blood glucose (198±21.3 vs. 143±17.6, $p=0.014$), HbA1c (9.4±1.3 vs. 8.2±1.1, $p=0.027$), and triglycerides (291±71.7 vs. 216±53.3, $p=0.02$). The levels of high-density lipoprotein (HDL) cholesterol (38.9±4.5 vs. 47.1±5.6, $p=0.043$) and eGFR (66.1±22.3 vs. 75±21.2, $p=0.002$) were determined to be lower in Group 1 (Table 1). Elevations in hypertension, hyperuricemia, and liver tests were seen at a higher rate in the patients with hypogonadism ($p=0.03$, $p<0.001$, $p=0.002$, respectively). The gonadal hormone levels in the study population are shown in Table 2. In addition to TT, the LH (3.5±0.8 vs. 5.1±1.1, $p=0.034$) and FSH (2.7±0.9 vs. 5.9±1.6, $p=0.014$) levels were significantly lower in the patients with hypogonadism compared to those without.

Table 1. Comparisons of general data in the two groups

	Low TT group (n=102)	Normal TT group (n=411)	p value
Age (years)	51.2±8.9	44.3±11.2	<.001
Duration of diabetes (years)	11.4±4.5	7.6±4.2	<.001
Waist circumference (cm)	106.7±9.1	101.2±10	0.569
Body mass index (kg/m²)	31.5±3.8	26.4±4.1	0.034
Fasting blood glucose (mg/dl)	198±21.3	143±17.6	0.014
HbA1c (%)	9.4±1.3	8.2±1.8	0.027
Triglycerides (mg/dl)	291±71.7	216±53.3	0.02
Total cholesterol (mg/dl)	256±66.3	234±56.2	0.78
LDL-C (mg/dl)	153±31.1	137±24.3	0.11
HDL-C (mg/dl)	38.9±4.5	47.1±5.6	0.043
eGFR (ml/min/1.73 m²)	66.1±22.3	75±21.2	0.002
Elevated liver transaminases (%)	22	14.5	0.07
Hyperuricemia (%)	31.3	19.8	<.001
Microalbuminuria (%)	14.5	12.9	0.65
Diabetic retinopathy (%)	21.2	19.3	0.73
Diabetic neuropathy (%)	36.7	31.4	0.69
Hypertension (%)	41.6	33.8	0.03
Ischemic heart disease (%)	21.7	18.8	0.16
Smokers	25.5	27.6	0.89

Results are expressed as mean±SD values or prevalence (%).

Table 2. Comparisons of sex hormones in two groups

	Low TT group (n=102)	Normal TT group (n=411)	p value
Total testosteron (ng/dl)	251.2±38.9	444.3±56.2	<.001
Prolactin (ng/ml)	24.7±3.1	21.8±1.6	0.569
Luteinizing hormone (IU/ml)	3.5±0.8	5.1±1.1	0.034
Follicle-stimulating hormone (IU/ml)	2.7±0.9	5.9±1.6	0.014

Data are presented as mean±SD values in each group

The results of the correlation analyses showed a negative correlation of the TT levels with age (r=-0.223, p<.001), BMI (r=-0.209, p=0.004), fasting blood glucose (r=-0.063, p=0.242), HbA1c (r=-0.286, p=0.013), uric acid (r=-0.291, p=<0.001), and triglycerides (r=-0.086, p=0.506), and a positive correlation with eGFR (r=0.156, p=0.02) and HDL cholesterol (r=0.071, p=0.061) (Table 3).

Table 3. The correlations of serum TT with the clinical and biochemical parameters

	r	p
Age (years)	-0.223	<.001
Duration of diabetes (years)	-0.211	<.001
Waist circumference (cm)	-0.071	0.177
Body mass index (kg/m²)	-0.209	0.04
Fasting blood glucose (mg/dl)	-0.063	0.242
HbA1c (%)	-0.286	0.013
Triglycerides (mg/dl)	-0.086	0.506
HDL-C (mg/dl)	0.071	0.061
GFR (mL/min/1.73 m²)	0.156	0.02
Uric acid (mg/dl)	-0.291	<.001

According to the results of the multivariate logistic regression analyses, the variables of age (ref: <50 years) (OR:2.83, CI 95%: 1.838-3.611, p<0.001), duration of diabetes (ref: <10 years) (OR:2.79, CI 95%: 2.131-3.237, p<0.001), BMI (ref: <30 kg/m²) (OR:1.427, CI 95%: 1.119-2.011, p=0.034), HbA1c (ref: <10%) (OR:2.122, CI 95%: 1.875-2.651, p=0.010), eGFR (ref: >60 ml/min/1.73 m²) (OR: 3.455, CI 95%: 2.887-4.011, p<0.001), hypertriglyceridemia (OR: 1.643, CI 95%: 1.111-2.430, p=0.018), and hyperuricemia (OR:3.182, CI 95%:2.981-4.211, p<0.001) were determined to be independent risk factors for hypogonadism (Table 4).

Table 4. Multivariate logistic regression analysis of the relationship between hypogonadism and clinical and biochemical variables

Variables	Odds ratio (95% CI)	p value
Age (ref:<50 years)	2.83 (1.838-3.611)	<.001
Duration of diabetes (ref: <10 years)	2.79 (2.131-3.237)	<.001
Body mass index (ref: < 30 kg/m²)	1.427 (1.119-2.011)	0.034
Hba1c (ref: <10%)	2.122 (1.875-2.651)	0.010
Hypertriglyceridemia	1.643 (1.111-2.430)	0.018
Hyperuricemia	3.182 (2.981-4.211)	<.001
eGFR (ref: >60 ml/min/1.73 m²)	3.455 (2.887-4.011)	<.001

CI: Confidence interval

DISCUSSION

In this study, which examined the frequency and risk factors of hypogonadism in males with T2DM, the frequency of hypogonadism was seen to be consistent with the literature.[4,5,10] Males with T2DM are known to be at greater risk of hypogonadism than those without diabetes, regardless of the metabolic status.[13] The results of the current study showed that age, duration of diabetes, BMI, poor glycemic control, eGFR <60 ml/min/1.73 m², hypertriglyceridemia, and hyperuricemia were independent risk factors for hypogonadism.

A decrease in T levels is associated with ageing, even in healthy males.[14,15] The effect of ageing on T is due to increased visceral obesity, drug use, and an unhealthy lifestyle.[16,17] In a study of diabetic patients aged >60 years, Harman SM et al.[18] reported that no increase was seen in the frequency of hypogonadism compared to those without diabetes, and there was an increase in the frequency of hypogonadism at an earlier age. Al Hayek AA et al.[5] reached similar results. In the current study, the inclusion of diabetic patients aged 30-60 years seemed rational, and a negative correlation was determined between TT levels and age. This result showed that increasing age up to 60 years was associated with the development of hypogonadism in males with T2DM. This correlation was confirmed by the 2.83-fold increased risk of hypogonadism in males with T2DM aged >45 years.

Type 2 DM, which is traditionally known as a disease of middle age and old age, is increasingly occurring at younger ages.[1,19] This means that patients are living with diabetes for a longer period. In literature, there has been shown to be an increase in both microvascular and macrovascular complications as the duration of diabetes becomes prolonged.[20,21] In a study conducted in 2004, it was reported that hypogonadotropic hypogonadism was frequently seen in males with diabetes, and this was independent of glycemic control and the duration of diabetes.[22] However, the current study results showed a 2.79-fold increase in the risk of hypogonadism when the duration of diabetes exceeded 10 years. This could be a natural result of a longer disease duration as age increases. In the current study, no correlation was determined between hypogonadism and microvascular and macrovascular complications associated with diabetes. This situation is an indirect sign that insulin resistance, increased adipose tissue, and metabolic syndrome are at the forefront rather than vascular problems in the pathogenesis of hypogonadism in males with T2DM.

Insufficient glycemic control is a significant risk factor for the progression of diabetes and complications in T2DM patients.[23] In the current study, there was a negative correlation between HbA1c and TT, and the risk of

hypogonadism was seen to be increased 2.12-fold in patients with HbA1c >10%. Advanced age, the duration of diabetes and dyslipidemia are known to play a role in poor glycemic control.[9] At the same time, these variables are independent risk factors for male hypogonadism.[24] Even so, hypogonadotropic hypogonadism is seen comparatively less in Type 1 DM than in T2DM, which basically shows that the underlying condition is due to insulin resistance.[25] In one way, poor glycemic control in patients with T2DM reflects the severity of insulin resistance, and in this respect, it is expected that poor glycemic control is a risk factor for hypogonadism in T2DM.

Hypertriglyceridemia, which is a component of metabolic syndrome, is known to be associated with hypogonadism.[26] By impairing intracellular signalling of insulin, the fat mass and excess triglycerides cause insulin resistance.[27] This also causes hypogonadism by decreasing LH expression with mechanisms such as an increase in estradiol, leptin, and cytokines.[28-31] In the current study, hypertriglyceridemia and BMI >30 kg/m² were seen to be independent risk factors for hypogonadism. A possible explanation of the significant effect of BMI on hypogonadism in males with T2DM is that the conversion of testosterone to oestrogen by aromatase can lead to a decrease in testosterone levels.[32]

Another important result of the current study was the increased risk of hypogonadism in males with T2DM with chronic renal disease (eGFR <60 nl/min/1.73m²). This finding was similar to the results shown for the first time by Herrero A et al.[33] but in contrast, no correlation was determined between hypogonadism and the presence of microalbuminuria, which is a microvascular complication of diabetes. There are similar results in previous studies.[5]

Another noticeable result of the current study was the determination of a negative correlation between T and serum uric acid level, and in males with T2DM, hyperuricemia is an independent risk factor for hypogonadism. T2DM may have a direct effect on the oxidisation of purine nucleotides and this causes an increase in uric acid levels.[34] Hyperinsulinemia can lead to hyperuricemia by increasing the xanthine oxidase synthesis rate.[34] Previous studies have shown a strong correlation of hyperuricemia with insulin resistance, metabolic syndrome, increased BMI, and increased visceral adipose tissue.[35,36] That the complex and multidirectional correlation of uric acid with other risk factors of hypogonadism is a risk factor for hypogonadism was seen to be in parallel with previous studies.

Limitations

There were some limitations to this study, primarily the retrospective design. A second limitation was that the results were the data from single centre, and as they had a regional characteristic do not have sufficient power for definitive clinical recommendations. Therefore, the findings should be confirmed with further, prospective, multicentre studies. Another limitation was the absence of free testosterone and sex hormone binding globulin (SHBG) results. Finally hypogonadism in this study was based only on the testosterone level, and a validated international scale was not used to question symptoms.

CONCLUSION

The prevalence of hypogonadism is higher in males with T2DM than in the general population. There was determined to be a significant correlation between hypogonadism and age, duration of diabetes, BMI, chronic kidney disease, hypertriglyceridemia and hyperuricemia. Just as for other typical complications of diabetes, screening for hypogonadism, which is often seen and is associated with many variable risk factors, can be recommended while patients are still at the asymptomatic stage and the measurement of T levels should be performed in all males with T2DM.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Clinical Researches Ethics Committee of Health Sciences University Dışkapı Yıldırım Beyazıt Training and Research Hospital (Date: 17.05.2021, Decision no: 111/11).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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