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RESEARCH

Hypogonadism and associated risk factors in male patients with type 2 diabetes mellitus attending the diabetic clinic of Tikur Anbessa Specialized Teaching Hospital, Addis Ababa, Ethiopia

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Background: A high prevalence of hypogonadism among men with type 2 diabetes mellitus (T2DM) has been reported worldwide. This in turn creates a substantial public health burden in terms of inadequate sexual function and potential infertility. However, the status of this health problem is not well established in Ethiopia. Therefore, this study was aimed to assess hypogonadism and its associated risk factors among men with T2DM.
Methods: This cross-sectional study was conducted at Tikur Anbesa Specialized Teaching Hospital in Addis Ababa, Ethiopia from February to May 2017 on 115 male patients with T2DM aged 40–80 years. Symptoms of hypogonadism were assessed using the Androgen Deficiency in Aging Men (ADAM) questionnaire. Total testosterone (TT), luteinising hormone (LH) and follicle stimulating hormone (FSH), fasting blood glucose (FBG) and lipid profiles were measured at the clinical chemistry laboratory of Ethiopian Public Health Institute. Hypogonadism was defined as the presence of clinical symptoms and low TT [TT < 12.1 nmol/l] according to International Society for the Study of the Aging Male.
Results: Of the total 115 study subjects, hypogonadism was seen in 23.5%, of whom 74.1% and 25.9% had secondary and primary hypogonadism, respectively. TT showed a significant negative correlation with waist circumference (WC) ($r = -0.465$, $p < 0.001$), BMI ($r = -0.363$; $p < 0.001$), FBG ($rho = -0.328$, $p < 0.001$) and TG ($rho = -0.357$, $p < 0.001$) respectively but a significant positive correlation with HDL-C ($r = 0.339$, $p < 0.001$)]. WC and FBG were independently associated with hypogonadism.
Conclusion: According to our study, visceral obesity and hyperglycaemia were found to be independent risk factors associated with hypogonadism.

Keywords: Ethiopia, hypogonadism, risk factors, type 2 diabetes mellitus, total testosterone

Introduction

Hypogonadism has been defined as the presence of low serum testosterone levels and clinical symptoms such as erectile dysfunction (ED), diminished frequency of morning erections, decrease in sexual thoughts (low libido), difficulty in achieving orgasm, reduced intensity of orgasm, fatigue, impotence, impaired concentration, depression and decreased sense of well-being.[1–3] The total testosterone (TT) or free testosterone cut-off values used in the definition varies according to different guidelines. For instance, an Endocrine Society Clinical Practice guideline recommended 10.4 nmol/l[1] and the International Society for the Study of the Aging Male recently recommended 12.1 nmol/l as a lower TT cut-off value.[3]

The linkage between hypogonadism and type 2 diabetes (T2DM) has recently been drawing public health attention.[4] This is because male patients with T2DM are significantly more likely to develop hypogonadism.[1,4,5] As a result of this and the rise in the prevalence of T2DM, a high prevalence (20–64%) of hypogonadism has been reported worldwide.[5] Consequently, sexual function problems, infertility and poor quality of life are becoming prevalent among these patients.[4]

Hypogonadism was classified as primary (hypergonadotropic) and secondary (hypogonadotropic) hypogonadism. Primary hypogonadism, which is caused by testicular failure, is characterised by high luteinising (LH) and follicle stimulating hormone (FSH) concentrations whereas secondary hypogonadism, which is caused by the defect in the hypothalamus or pituitary gland, is characterised by low or low-normal FSH and LH. Both types of hypogonadism were observed in men with T2DM. However, secondary hypogonadism was the most prevalent among these men with a prevalence range of 25–40%.[2,4]

The exact mechanism of the occurrence of hypogonadism in men with T2DM remains unclear, but insulin resistance, an important feature of T2DM, appears to be a common denominator. This can be supported by the fact that testosterone replacement therapy (TRT) for hypogonadal men with T2DM was found to improve insulin sensitivity.[6] More importantly, obesity appears to play an important synergistic role in this pathogenesis.[4,6]

Because an increase in fat mass in adipose tissue can cause an increase in the activity of the aromatase enzyme, this can convert serum testosterone to oestradiol, which directly reduces the level of serum testosterone. The resulting oestradiol provides negative feedback on the hypothalamic–pituitary–gonadal axis, and further reduces the level of serum testosterone.[2]

Different studies have identified that waist circumference (WC), body mass index (BMI), hyperglycaemia and dyslipidaemia in

male patients with T2DM were found to be major risk factor correlates of T2DM associated closely with hypogonadism.[7,8] The association of some of these correlates with TT can be indirectly explained as testosterone replacement therapy (TRT) was found to alter them. It was confirmed that a significant decrease in WC was observed in men with new onset T2DM treated with transdermal testosterone, diet and exercise compared with those prescribed only diet and exercise. TRT was also found to decrease triglycerides (TG), total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) and improved glycaemic controls but its action on high-density lipoprotein cholesterol (HDL-C) was inconsistent.[4,6]

As the incidence of T2DM is steadily rising in men worldwide, T2DM related hypogonadism has also been rising at an alarming rate. This, in turn, creates a substantial public health burden in terms of inadequate sexual function and potential infertility in men.[9] However, this condition is often under-diagnosed and under-discussed in developing countries. Different reasons were suggested to explain this fact. First, patients make such conversation personal and feel uncomfortable about initiating it due to taboo or stigma.[10] Second, the target-based management of T2DM is already creating a workload for clinicians and as a result they do not usually engage in diagnosing and treating hypogonadism in these patients.[11] Third, a testosterone test, which is used to identify those who can benefit from TRT and treated with phosphodiesterase inhibitors to improve ED, is not routinely done in resource-limited countries like Ethiopia.[11,12] Fourth, even though the Endocrine Society task force and the International Society for the Study of Aging Male recommended physicians order a testosterone test for all men with T2DM, physicians do not usually order the test to diagnose this condition.[1,3]

Moreover, despite the continent having a high burden of T2DM, hypogonadism is rarely studied in sub-Saharan African countries and Ethiopia is no exception. Therefore, we aimed to determine the prevalence and associated factors of male hypogonadism in men with T2DM.

Study design and methods

This cross-sectional study was conducted in the Diabetic Clinic of Tikur Anbessa Specialized Teaching Hospital in Addis Ababa, Ethiopia from February to May 2017. A total of 115 with T2DM whose age was between 40 and 80 years were selected using a convenience sampling method among consecutive male patients who were already diagnosed with T2DM and waiting for treatment during the study period. Their diagnosis of T2DM was obtained from their medical records. With the help of a physician, any subjects with a history of chronic diseases including end-stage renal failure, hypopituitarism, acquired immunodeficiency syndrome, and malignancy were excluded from the study as these conditions are known to decrease testosterone level.

The study protocol was approved by the Departmental Research and Ethics Review Committee of the Department of Medical Laboratory Sciences and that of Internal Medicine of the College of Health Sciences of Addis Ababa University. All the selected subjects gave written informed consent.

Demographic and clinical assessment

Demographic characteristics such as age, marital status and smoking history were collected using a structured questionnaire. Duration of diabetes and current diabetic medication were collected from medical records using checklists.

Data for body mass index (BMI) and waist circumference (WC) were collected and interpreted according to the consensus statement from the International Diabetes Federation and the blood pressure of each subject was measured by an experienced nurse after the patient was allowed to rest for about 10 minutes. Subjects whose BP readings were ≥ 140/90 mmHg were considered hypertensive.[13]

Symptoms of hypogonadism were assessed using the ADAM[14] questionnaire, which is the most widely accepted screening questionnaire consisting of 10 questions. Subjects who can read and write completed the ADAM questionnaire on their own, and those who could not were assisted by an experienced nurse. A diagnosis of ADAM was suspected if a 'yes' answer was provided to questions 1 (presence of loss of libido) and 7 (presence of erectile dysfunction), or to any other three questions. To make the questionnaire understood, it was translated into Amharic (the local working language).

Laboratory evaluation

Five millilitres of overnight fasting venous blood sample was collected via sterile venepuncture from each study subject before 10 am in a serum separator tube (BD_{TM}). Then, each sample of blood was allowed to clot for 30 minutes and centrifuged at 3000 revolutions per minutes for 5 minutes to separate the serum. The separated serum samples were stored at −20°C until analysis. Analysis was done at the Ethiopian public health clinical chemistry laboratory using an automated analyser (Elecsys® 2010 analyzer-Cobas e 411, Roche Diagnostics GmbH, Indianapolis, IN, USA), which uses electrochemiluminescence (ECL) technology to determine hormones (TT, LH and FSH). To measure TT using this analyser, the competitive immunoassay principle with analyte liberation was used and to measure both LH and FSH the sandwich immunoassay principle was used. To determine lipid profiles (using Cobas 6000 module-501, Roche Diagnostics GmbH, Indianapolis, IN, USA), the enzymatic method was used. To determine fasting blood glucose (FBG) level using glucose oxidase method, an automated analyser (Mindray 200E, Guandog, China) was used.

Hypogonadism was defined as the presence of symptoms of hypogonadism and TT (≤ 12.1 nmol/l). Though a different TT cut-off value was recommended by different guidelines, the indicated cut-off value used is a recent recommendation in 2015 by the International Society for the Study of the Aging Male.[3] Hypogonadal subjects were further classified. Subjects who had hypogonadism with either low or normal FSH (≤ 14 mIU/ml), LH (≤ 7.8 mIU/ml) or both were diagnosed as having secondary hypogonadism whereas those with higher serum FSH (> 14 mIU/ml), LH (> 7.8 mIU/ml) or both were diagnosed as having primary hypogonadism.[15]

Hypercholesterolemia was indicated by a total cholesterol level ≥ 200 mg/dl. HDL-C was considered low when the level was < 40 mg/dl. LDL-C was considered high when the level was ≥1 00 mg/dl. Hypertriglyceridemia was considered high when the TG level was ≥ 150 mg/dl. Dyslipidaemia was considered present when one or more of the previous abnormalities were found in serum lipids.[13]

Statistical analysis

Data obtained were entered into Microsoft Excel (Microsoft Corp, Redmond, WA, USA) and exported to SPSS version 20 (IBM Corp, Armonk, NY, USA) for analysis. Descriptive statistics were used to summarise qualitative variables. All parametric

values were expressed as mean ± SD but for non-parametric values median was reported with interquartile range. Pearson's and Spearman's correlation for parametric and non-parametric data were used to establish correlations between dependent and independent variables respectively. The Mann–Whitney *U*-test was used for comparing non-parametric data and an independent samples t-test for parametric data. Simple logistic regression was used to identify potential predictors of hypogonadism and those with a *p*-value < 0.25 were entered into a multivariate model with automatic backward and forward likelihood ratio method of elimination, based on the *p*-values in the model to identify independent risk factors for hypogonadism. A *p*-value < 0.05 was considered statistically significant.

Results

Sociodemographic and clinical characteristics of study participants

As demonstrated in Table 1, of the total of 115 study subjects, more than half of them were in the age range greater than 60 years (range 40–80 years). The median age of the study subjects was 60 years (IQR 40–78.2). The mean ± SD of BMI and WC were 25.30 ± 3.26 kg/m^2 and 98.56 ± 8.70 cm respectively. The median (IQR) systolic and diastolic blood pressure were 130 mmHg (IQR 100–180) and 80 mmHg (IQR 60–100).

Regarding the current medication of diabetes, 54 (46.8%), 35 (30.4%), 21 (18.3%), and 4 (3.5%) were on insulin or on metformin, a combination of metformin and glibenclamide, a combination of insulin and metformin, and glibenclamide alone respectively. Moreover, 72 (62.7%) of the subjects were found to be hypertensive and 91(79%) had dyslipidaemia. The majority of the subjects (111; 96.5%) were married and only 3 (2.6%) of them were divorced. About 27% of the subjects were current or past smokers.

Laboratory measurements

As demonstrated in Table 2, the mean ± SD of TT, LH and FSH was 19.15 ± 6.99 nmol/l, 7.56 ± 3.30 mIU/l and 7.67 ± 4.94 mIU/l respectively. The mean ± SD of HDL-C, LDL-C and TC was 35.19 ± 10.44 mg/dl, 90.53 ± 32.46 mg/dl, and 72.2 ± 253.2 mg/dl respectively. The median values of TG and FBG were 141.9 mg/dl (IQR 71.07–656.65 mg/dl) and 168 mg/dl (IQR 82.9–307.2 mg/dl) within 2.5th and 97.5th percentile values respectively.

Prevalence of androgen deficiency symptoms, low testosterone level and secondary hypogonadism among the study subjects

The Androgen Deficiency in the Aging Male (ADAM) questionnaire was used to assess symptoms of hypogonadism among the study subjects. As summarised in Table 3, 104 (90.4%) were ADAM positive whereas the remaining 11 (9.6%) were ADAM negative. Only 27 (23. 5%) of ADAM positive subjects had a low TT level (TT ≤ 12.1 nmol) and hence were hypogonadal. It is important to note that about 66.9% of ADAM positive patients had normal TT levels and this speaks to the low sensitivity of the questionnaire.

Comparison of some clinical and laboratory measurements between subjects with and without hypogonadism

Paired *t*-test results are summarised in Table 4. Mean BMI was significantly higher in the hypogonadal group (26.9 ±

Table 1: Sociodemographic and clinical characteristics of the study subjects (*n* = 115)

Variables	Categories	*n* (%)	Mean ± SD	Range	Median (IQR)
Age (years)			59.6 ± 10.2	40–80	60 (40–78.2)
Marital status	Married	111 (96.5)			
	Divorced	3 (2.6)			
	Widowed	1 (0.9)			
Smoking history	Current	5 (4.3)			
	Past	26 (22.6)			
	Never	84 (73)			
Duration of DM			9 ± 6.9	1–30	7 (1–30)
Diabetes medication	Insulin	27 (23.4)			
	Metformin	27 (23.4)			
	Glibenclamide	4 (3.5)			
	Insulin and metformin	21 (18.3)			
	Metformin and glibenclamide	35 (30.4)			
Dyslipidaemia	Yes	91 (79.1)			
	No	24 (20.9)			
Hypertension	Yes	72 (62.9)			
	No	43 (37.4)			
BMI (kg/m^2)	Normal	59 (51.3)	25.30 ± 3.3	18.7–34.8	
	Overweight	46 (40.0)			
	Obese	10 (8.7)			
WC (cm)	Normal	30 (26.1)	98.56 ± 8.7	80–118	
	Obese	85 (73.9)			
SBP (mmHg)				100–190	130 (100–180)
DBP (mmHg)				60–110	80 (60–100)

Note: BMI = body mass index; WC = waist circumference; SBP = systolic blood pressure; DBP = diastolic blood pressure; IQR = interquartile range.

Table 2: Laboratory measurement values of some parameters of men with T2DM attending for treatment at the diabetic clinic of TASTH February–March 2017 ($n = 115$)

Variables	Categories	*n* (%)	Mean ± SD	Range	Median (IQR)
TT (nmol/l)	≤ 12.1	29 (25.2)	19.15 ± 6.99	6.97–37.13	
	> 12.1	86 (74.8)			
LH (mIU/ml)	> 7.8	43 (37. 4)	7.56 ± 3.30	2.71–18.7	7.07 (3.37–16.01)
	< 7.8	72 (62.6)			
FSH (mIU/ml)	≤ 14	102 (88.7)	7.68 ± 4.94	1.39–26.25	
	> 14	13 (11.3)			
FBG (mg/dl)				82–313	168 (82.9–307.2)
TC (mg/dl)	< 200	98 (85.2)		72.2–253.2	148 (84.1–244.8)
	≥ 200	17 (14.8)			
TG (mg/dl)	< 150	64 (55.7)		59.4–776.4	142 (71.1–656.7)
	≥ 150	51 (44.3)			
LDH-C (mg/dl)	< 100	70 (60.9)	90.53 ± 32.5	28.5–170.6	
	≥ 100	45 (39.1)			
HDL-C (mg/dl)	< 40	83 (72.2)	35.5 ± 10.4	13.3–71	
	≥ 40	32 (27.8)			

Note: TT = total testosterone; LH = luteinising hormone; FSH = follicle stimulating hormone; TC = total cholesterol; FBG = fasting blood glucose; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides.

3.5 kg/m^2) than in eugonadal individuals (24.86 ± 3.02 kg/m^2), t (113) = 3.035, $p = 0.003$. The mean WC was significantly higher in the hypogonadal group (104.85 ± 8.77 cm) than in eugonadal individuals (96.62 ± 7.75 cm), t (113) = 4.676, $p < 0.001$. Similarly, the mean FSH level was significantly lower in the hypogonadal group (6.28 ± 2.75 mIU/ml) than in eugonadal individuals (8.10 ± 5.38 mIU/ml), t (113) = −2.34, $p = 0.022$. However, the mean HDL-C level was lower in the hypogonadal group (31.08 ± 8.57 mg.57 mg/dl) than in the eugonadal group (36.83 ± 10.63 mg.63 mg/dl) t (113) = −2.563, $p = 0.012$

Table 3: Frequency of low and normal total testosterone groups in ADAM positive and negative study subjects ($n = 115$)

	Testosterone groups		
Symptoms of hypogonadism	Low TT (TT ≤ 12.1 nmol/l)	Normal TT (TT > 12.1 nmol/l)	Total TT
ADAM positive	27 (23.5%)	77 (66.9%)	104 (90.4%)
ADAM negative	2 (1.7%)	9 (7.8%)	11 (9.6%)
Total	29 (25.2%)	86 (74.8%)	115 (100%)

A Mann–Whitney *U*-test indicated that the FBG level was significantly higher in the hypogonadal group with a median of 235 mg/dl than in the eugonadal group with a median of 161 mg/dl, U = 711.5, $p = 0.002$. Similarly, TG was significantly elevated among the hypogonadal group with a median of 174 mg/dl than in the eugonadal ones with a median of 136 mg/dl.

Table 4: Comparison of some clinical and laboratory measurement values of study participants between hypogonadal and eugonadal groups ($n = 115$)

		Testosterone level		
		Hypogonadal group ($n = 27$)	Eugonadal group ($n = 88$)	*t* test
No.	Parametric values	(mean ± SD)	(mean ± SD)	*p*-value
1	BMI (kg/m^2)	26.90 ± 3.54	24.80 ± 3.02	0.003
2	WC (cm)	104.85 ± 8.77	96.62 ± 7.75	< 0.001
3	LH (mIU/ml)	7.06 ± 3.09	7.72 ± 3.36	0.365
4	FSH (mIU/ml)	6.28 ± 2.75	8.10 ± 5.38	0.022
5	TC (mg/dl)	159.37 ± 42.35	154.20 ± 38.28	0.549
6	LDL-C (mg/dl)	86.45 ± 36.09	91.78 ± 31.38	0.458
7	HDL-C (mg/dl)	31.08 ± 8.57	36.83 ± 10.63	0.012
No.	**Non-parametric values**	**Median**	**Median**	***p*-value**
8	Age (years)	60.0	60.0	0.721
9	Duration of DM (years)	6.0	7.0	0.629
10	SBP (mmHg)	130.0	130.0	0.293
11	DBP (mmHg)	80.0	80.0	0.583
12	FBG (mg/dl)	235.0	161.0	0.002
13	TG (mg/dl)	174.0	136.0	0.047

Note: BMI = body mass index; WC = waist circumference; LH = luteinising hormone; FSH = follicle stimulating hormone; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; SBP = systolic blood pressure; DSP = diastolic blood pressure.

Table 5: Correlation of independent continuous variables with total testosterone

No.	Parameters	Pearson correlation coefficient (*r*)	*p*-value
1	BMI (kg/m^2)	−0.363	* < 0.001
2	WC (cm)	−0.465	* < 0.001
3	LH (mIU/ml)	0.131	0.164
4	FSH (mIU/ml)	0.100	0.289
5	TC (mg/dl)	−0.085	0.364
6	LDL (mg/dl)	0.051	0.488
7	HDL (mg/dl)	0.339	* < 0.001
No	**Parameters**	**Spearman correlation coefficient (*rho*)**	***p*-value**
8	Age (years)	−0.015	0.874
9	Duration of DM (years)	0.047	0.616
10	SBP (mmHg)	−0.154	0.100
11	DBP (mmHg)	−0.124	0.185
12	FBG (mg/dl	−0.328	***< 0.001**
13	TG (mg/dl)	−0.357	***< 0.001**

Note: * = indicates significant correlation; *rho* = is used for non-parametric values; *r* is used for parametric values; BMI = body mass index; WC = waist circumference; LH = luteinising hormone; FSH = follicle stimulating hormone; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; SBP = systolic blood pressure; DSP = diastolic blood pressure.

Correlation of total testosterone with independent variables

As depicted in Table 5, TT showed significant negative correlation with WC ($r = -0.465$, $p < 0.001$) and BMI ($r = 0.363$; $p < 0.001$) respectively. TT also showed a significant negative correlation with FBG ($rho = -0.328$, $p < 0.001$) and TG ($rho = -0.357$, $p < 0.001$) respectively. However, it showed a significant positive correlation with HDL-C ($r = 0.339$, $p < 0.001$). However, age, duration of diabetes, LH, FSH, TC, LDL, SBP and DBP did not show any correlation with TT.

Table 6 indicated that a 1 cm increase in WC increases the odds of developing hypogonadism by 1.14 times, while controlling for FBG. Similarly, an increase in FBG of 1 mg/dl increases the odds of developing hypogonadism by 1.02 times while controlling for WC.

Discussion

Prevalence of hypogonadism among the study subjects

In this study, the prevalence of symptoms of hypogonadism was 90.4% using the ADAM questionnaire and this was unexpectedly high. However, only 23.5% of these individuals were truly hypogonadal (TT ≤ 12.1 nmol/l). This discrepancy may be partly due to the presentation of some testosterone deficiency symptoms even when TT levels are as high as 15 nmol/l, which is different from the TT cut-off value (12.1 nmol/l) used in our study.[3] Additionally, the non-specific nature of the ADAM questionnaire may also contribute to this discrepancy because of the universal presence of these symptoms, even in patients with normal testosterone levels.

The prevalence of hypogonadism in this study was lower than that of similar studies conducted in different countries[11,16–22] but a study conducted in Iran reported a lower prevalence.[23] Possible explanations for these variations in the prevalence of hypogonadism in this population group may be a variation in the type of testosterone measured, whether TT or free testosterone, the cut-off value of TT or free testosterone, age categories of the study subjects, the prevalence of obesity, diabetic duration, study design and laboratory methods used.[5,24]

In this study, 74.10% of hypogonadal subjects presented with secondary hypogonadism and the remaining 25.9% presented with primary hypogonadism. In line with our study, studies in Nigeria and Jordan reported a similar higher prevalence of these conditions.[15,25] This finding confirmed the fact that secondary hypogonadism was more prevalent than primary hypogonadism in men with T2DM. This was supported by the evidence that insensitivity to insulin at the hypothalamic level may contribute to a decrease in gonadotrophin releasing hormone, which in turn decreases the level of gonadotropins.[26]

Correlation of serum total testosterone level with independent variables

In this study, age was not significantly correlated with TT. This variable also did not correlate with TT in similar studies conducted in South Africa and New York.[16,17] In contrast to this study, a study conducted in Jordan reported a significant positive correlation of age with TT.[25] Studies in England and Nigeria reported the presence of a significant negative correlation between age and TT level.[12,15] The most plausible explanation for these inconsistencies is that serum hormone binding globulin (SHBG), which accounts for 60–80% of testosterone binding, increases with age. Yet low levels of SHBG may occur in the presence of insulin resistance, thus resulting in a decrease in TT levels. Therefore, in the absence of the assessment of bioavailable testosterone levels, the degree to which this confounder (SHBG) affected our results if at all is difficult to speculate on.[27]

This study also identified that BMI, WC, FBG and TG showed a significant negative correlation with TT whereas HDL-C showed a significant positive correlation with it. A case-control study in Ghana reported a similar result.[28] However, the level of serum TT was not correlated with LH and FSH in our study. This might be due to the slight rise in these hormones with age, as observed in our study and others suggesting an age-related alteration in this feedback mechanism.[17]

Table 6. Multiple logistic regression analyses: results of predictors of hypogonadism in males with T2DM ($n = 115$)

Variables	B	SE	Wald	*p*-value	Odds ratio	95% CI for EXP (B)	
						Lower	Upper
WC	0.154	0.038	16.484	0.000	1.20	1.08	1.256
FBG	0.015	0.004	11.774	0.001	1.02	1.01	1.024
Constant	−19.614	4.294	20.863	0.000	0.000		

Note: WC = waist circumference; FBG = fasting blood glucose.

Comparison of independent variables in hypogonadal and eugonadal groups of study subjects

In this study, age, DM duration, LH, FSH, LDL-C and TC did not differ significantly between hypogonadal and eugonadal groups. A similar study conducted in Egypt also reported that there is no significant mean difference in these variables between the two groups except for the mean of lipid profiles, which showed a significant difference between the two groups.[22] It was unexpected to see a lack of significant mean difference in LH and FSH between the groups. This might be due to the high prevalence of primary hypogonadism (25.9%) in our study, which is related to testicular problems rather than to gonadotropins.

This study also identified that the means of WC, BMI, FBG or TG were significantly higher in hypogonadal group but HDL-C was significantly lower in this group. A similar study conducted in Italy reported the same finding.[28] However, the means of FBG, TG or HDL-C did not show any statistically significant difference between the two groups in a study conducted in China.[7]

Risk factors associated with hypogonadism

Though not to a great extent, WC and FBG were identified as risk factors associated with hypogonadism in T2DM patients. Similar studies also reported the same finding with regard to WC.[7,8] The finding of WC as a risk factor for hypogonadism was explained in certain literature. First, it was suggested that visceral adiposity, which is measured by WC, induces aromatisation of testosterone to oestradiol and causes elevation of oestradiol primarily in adipose tissue by aromatase, which has increased activity as visceral adiposity increases.[13] Oestradiol directly feeds back and inhibits the hypothalamic–pituitary–testicular (HPG) axis through kisspeptin.[29] An increase in oestradiol levels would also lead to the suppression of gonadotrophin-releasing hormone and impaired secretion of gonadotropin by the pituitary gland, which results in the reduction of testosterone secretions.[5,9] Second, an increase in adipocytokines due to obesity, including the pro-inflammatory cytokines such as tumour necrosis factor α (TNF-α), interleukin-1β, and interleukin-6, inhibits the secretion of testosterone, both at the hypothalamic–pituitary and the testicular level.[30] Third, leptin usually stimulates the release of gonadotropin-releasing hormone; however, in obesity, where excess leptin is produced from adipocytes, the hypothalamic–pituitary axis becomes resistant to leptin. In addition, leptin inhibits the stimulatory action of gonadotropin on the Leydig cells of testes, thereby further decreasing testosterone production.[31] Visceral adiposity also enhances delivery of free fatty acids, which in turn decreases peripheral glucose disposal primarily in skeletal muscle and this results in hyperglycaemia.[22] Hyperglycaemia in turn has an effect on testicular microvasculature and results in a decrease in TT level.[32] Our finding regarding FBG as a risk factor was not supported by much of the literature but is in line with studies conducted in Ghana and Korea. This can be justified based on the fact that hyperglycaemia has an effect on testicular microvasculature by altering Leydig cell function, directly causing primary hypogonadism. Moreover, if glucose is not reaching the cells because of insulin insensitivity, there will not be enough energy generated for the various metabolic processes involved in maintaining testosterone levels.[23,32]

The present study has several limitations. One of these was the use of a small, non-probability sampling method and the selection of study subjects from tertiary referral outpatient services, where most of the patients had many complications and numerous comorbidities. The absence of a control group (non-diabetic subjects) to compare the prevalence of hypogonadism and other variables in men with T2DM and cross-sectional nature of this study was another limitation. Moreover, free testosterone (FT) or bioavailable testosterone, which is the gold standard, and preferable tests to diagnose hypogonadism in T2DM subjects were not determined due to unavailability of these assays in our practice. Additionally, failure to measure haemoglobin A1C, which is a better glycaemic control indicator, because of financial problems was a further limitation of this study. These limitations made this study difficult to generalise to the majority of men with T2DM.

Conclusion

In conclusion, this study demonstrated that hypogonadism is a common occurrence among men with type 2 diabetes and the most prevalent type of hypogonadism is hypogonadotropic hypogonadism (secondary hypogonadism) in a tertiary healthcare setting in Addis Ababa, Ethiopia. Symptoms of hypogonadism are, however, non-specific and occur in a significant proportion of eugonadal subjects with normal testosterone. This study also identified that visceral obesity and hyperglycaemia are independent risk factors for hypogonadism for Ethiopian men with T2DM in a tertiary setting.

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References

1. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2006;91: 1995–2010.
2. Dandona P, Rosenberg MTA. Practical guide to male hypogonadism in the primary care setting. Int J Clin Pract. 2010; 64: 682–96.
3. Lunenfeld B, Mskhalaya G, Kalinchenko SY, et al. Recommendations on the diagnosis, treatment and monitoring of late-onset hypogonadism in men—a suggested update. Aging Male. 2013;16(4): 143–50.
4. Dandona P, Dhindsa S. Update: hypogonadotropic hypogonadism in type 2 diabetes and obesity. J Clin Endocrinol Metab. 2011;96 (9):2643–51.
5. Al Hayek AA, Khawaja NM, Khader YS, et al. The prevalence of hypogonadism among diabetic and non-diabetic men in Jordan. J Diabetes Complications. 2014; 28(2):135–40.
6. Kapoor D, Goodwin E, Channer KS, Jones TH. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. Eur J Endocrinol. 2006;154(6):899–906.
7. Zheng R, Cao L, Cao W, et al. Risk factors for hypogonadism in male patients with type 2 diabetes. J Diabetes Res. 2016;2016:1–8.
8. Kaufman JM, Vermeulen A. The decline of androgen levels in elderly men and its clinical and therapeutic implications. Endocrinol Rev. 2005;26:833–76.
9. Dandona P, Dhindsa S, Chandel A, et al. Low testosterone in men with type 2 diabetes – a growing public health concern. Diabetes Voice. 2009;54(2):27–9.
10. Mutagaywa R. Prevalence of erectile dysfunction and associated risk factors among diabetic men attending diabetic clinic at Muhimbill National Hospital in Dar Es Salaam. 2012.

11. Hackett G. The clinical importance of testosterone in men with type 2 diabetes. Trends in urology and men's health.2010. Accessed on Nov 25, 2017 from: bwww.trendsinurology.com.
12. Kapoor D, Aldred H, Clark RS, et al. Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes. Diabetes Care. 2007;30(4):911–17.
13. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome – a new worldwide definition. A consensus statement from the international diabetes federation. Diabetes Med. 2006;23:469–80.
14. Ugwu TE, Ikem RT. Performance of the Androgen Deficiency in Aging Male questionnaire for the clinical detection of androgen deficiency in black sub-Saharan African men with Type-2 diabetes mellitus. J Endocrinol Metab Diabetes S Afr. 2017;22(1):1–4.
15. Ugwu TE, Ikem RT, Kolawole BA, et al. Clinicopathologic assessment of hypogonadism in men with type 2 diabetes mellitus. Indian J Endocrinol Metab. 2016; 20(5):667.
16. Kempa T, Rheedera P. The prevalence and association of low testosterone levels in a South African male, diabetic, urban population. J Endocrinol Metab Diabetes S Afr. 2015;20(2):92–97.
17. Dhindsa S, Prabhakar S, Sethi M, et al. Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. J Clin Endocrinol Metab. 2004;89(11):5462–8.
18. El Saghier EO, Shebl SE, Fawzy OA, et al. Androgen deficiency and erectile dysfunction in patients with type 2 diabetes. Clin Med Insights Endocrinol Diabetes. 2015;8:55.
19. Afkhamizadeh M, Ghaderian SB, Rajabian R, et al. Prevalence of hypogonadotropic hypogonadism in type 2 diabetes male patients. Open J Endocrine Metabolic Dis. 2015;5(03):29–36.
20. Kim JS, Kim BS, Jeon JY, et al. Testosterone deficiency associated with poor glycemic control in Korean male diabetics. Endocrinol Metab. 2014;29(3):300–6.
21. Diaz-Arjonilla M, Schwarcz M, Swerdloff RS, et al. Obesity, low testosterone levels and erectile dysfunction. Int J Impot Res. 2009;21:89–98.
22. Mohieldin JM, Elabeid BEH, Abdalla OM. Assessment of hypogonadism in sudanese males with type 2 diabetes and its association with obesity. J Glob Diabetes Clin Metab. 2016;1 (1):1–4.
23. Aboelnaga MM, Elshahawy H. Prevalence and predictors for low total testosterone levels among male type 2 diabetic patients: an Egyptian experience. Int J Res Med Sci. 2017;4 (8):3381–7.
24. Rabijewski M, Papierska L, Zgliczyński W, et al. The incidence of hypogonadotropic hypogonadism in type 2 diabetic men in Polish population. BioMed Res Int. 2013;2013:1–6.
25. Ogbera OA, Sonny C, Olufemi F, et al. Hypogonadism and subnormal total testosterone levels in men with type 2 diabetes mellitus. J Coll Physicians Surg Pak. 2011;21:517–21.
26. Rao PM, Kelly DM, Jones TH. Testosterone and insulin resistance in the metabolic syndrome and T2DM in men. Nat Rev Endocrinol. 2013;9:479–93.
27. Corona G, Mannucci E, Petrone L, et al. Association of hypogonadism and type II diabetes in men attending an outpatient erectile dysfunction clinic. Int J Impot Res. 2006;18:190–7.
28. Asare-Anane H, Ofori EK, Yeboah FA, et al. Primary hypogonadism in Ghanaian men with type 2 diabetes mellitus. Cell. 2013;2 (5):310–315.
29. Jones TH, Kennedy RL. Cytokines and hypothalamic-pituitary function. Cytokine. 1993(5): 531–8.
30. Mantzoros CS. The role of Leptin in human obesity and disease: a review of current evidence. Ann Int Med. 1999;130:671.
31. Isidori AM. Leptin and androgens in male obesity: evidence for leptin contribution to reduced androgen levels. J Clin Endocrinol Metab. 1999;84:3673–80.
32. Allan CA. Sex steroids and glucose metabolism. Asian J Androl. 2014;16:232.

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