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Research Article

Prevalence and predictors for low total testosterone levels among male type 2 diabetic patients: an Egyptian experience

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ABSTRACT

Background: Diabetes mellitus (DM) affects an estimated 285 million people worldwide. This number is expected to reach 438 million by the year 2030. The aim of this study was to determine the prevalence of male hypogonadism among Egyptian patients with type 2 diabetes and to identify the risk factors may be associated with low serum testosterone concentrations in men with type 2 diabetes.
Methods: 140 male patients with type 2 diabetes were recruited in this cross-sectional study. This study WAS conducted from January 2012 to January 2016 in the endocrinology and metabolism unit, Mansoura University, Egypt.
Results: We found 48 (34.2%) patients with hypogonadism (defined as TT ≤300 ng/dl) among 140 male patients with type 2 diabetes. 7 out of 48 (14.5%) patients with TT ≤300 ng/dl had high abnormal gondotrophins hormones levels while 41 patients out of 48 (85.5%) had normal gondotrophins hormones levels. We found BMI, WC, Hba1c, UACR, retinopathy ratio, nephropathy ratio, smoker ratio and patient on insulin therapy ratio were increased in the low TT group with statistically significance, but non statistically significant difference in age, diabetic duration, FSH, LH, Prolactin and lipid profile. In this study by using Pearson correlation, we found a statistically significant correlation between TT levels with BMI, WC, FSH, LH, Hba1c, and UACR (P value<0.05). Also by using stepwise multiple regression analysis, we found BMI, WC, LH, Hba1c, and UACR were statistically significant predictors of TT levels. In logistic regression analysis, we found Hba1c, UACR, and WC were statistically significant risk factors for MHG.
Conclusions: Visceral obesity, higher Hba1c, and degree of albuminuria are independent risk factors for hypogonadism in Egyptian male patients with type 2 diabetes.

Keywords: Type 2 DM, Male hypogonadism, Total testosterone, Egyptian

INTRODUCTION

Diabetes mellitus (DM) affects an estimated 285 million people worldwide. This number is expected to reach 438 million by the year 2030.[1] On the other hand, Male hypogonadism (MHG) is a clinical syndrome that results from failure to produce physiological concentrations of testosterone.[2]

MHG is significantly associated with various comorbidities reduced libido, erectile dysfunction, increased adiposity, low energy and fatigue.[3] Muscle weakness and low bone mass, Depression, anxiety loss of libido, and erectile dysfunction and decreased quality, abnormal lipid profile, CVS pathophysiologic change.[4-7] The association between low serum testosterone (LST) and diabetes (DM) has recently received substantial attention; studies have reported that male patients with

type 2 diabetes are significantly more likely to develop hypogonadism.[8]

Thus, it is unclear which the risk factors correlates in DM are associated with MHG, Therefore, it is especially important to explore the risk factors for hypogonadism to facilitate prevention, early diagnosis, and early treatment. The aim of this study was to determine the prevalence of male hypogonadism among Egyptian patients with type 2 diabetes and to identify the risk factors may be associated with low serum testosterone concentrations in men with type 2 diabetes.

METHODS

One hundred and forty male patients with type 2 diabetes were recruited in this study from January 2012 to January 2016 in the endocrinology and metabolism unit, Mansoura University, Egypt. Informed consent was obtained from all patients. Patients were divided according total testosterone (TT) levels into either a low testosterone group (TT≤300 ng/dl) or a normal testosterone group (TT>300ng/dl).

Inclusion criteria were patients with type 2 diabetes, age between 18 and 65, male sex while exclusion criteria were: acute or chronic renal disease, acute or chronic hepatic disease, heart failure, drugs affecting testosterone levels, a history of gonadal disease, malignancy and endocrinal disease apart from Type 2 DM. Thought clinical examination with respect height, weight, body mass index (BMI calculated as: weight (kg)/height $(m)^2$), blood pressure, and waist circumference (WC) were done for all participant. In the laboratory evaluation, the patients were tested in the morning after 8h fasting, including glycosylated hemoglobin (HbA1c), liver and kidney function, cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c) and urine albuminto-creatinine ratio (UACR). Total testosterone (TT), prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH), were measured by ELISA assay (Roche Diagnostics, Mannheim, Germany). Statistical Analysis was conducted using SPSS 22.

All values are expressed as the mean±SD for the quantitative variables and as a percentage for the qualitative variables. Chi-square tests or independent t-test were done to find out associations. Multiple and multivariate logistic regression was carried out to assess the factors associated with TT≤300 ng/dl. P values<0.05 were considered statistically significant.

RESULTS

A total one hundred forty (140) males type 2 DM patients enrolled in this study from from January 2012 to January 2016 with age ranged 31-63 years (mean age 50.5±7.7 years), diagnosed with type 2 DM. Details of patient characteristics were presented in Table 1.

Table 1: Patients' characteristics.

	Mean (n = 140)	Standard deviation
Age (year)	50.50	7.775
Diabetic duration(year)	9.66	4.046
Smoker ratio	66 (47.1%)	-
Insulin therapy	52 (37.1%)	-
Body weight (kg)	97.74	13.642
Height (m)	1.7297	0.06335
BMI (Kg/m^2)	32.8702	5.64836
Waist circumference(cm)	113.96	18.247
Systolic BP (mmHg)	140.43	13.078
Diastolic BP (mmHg)	86.54	9.594
Total cholesterol mg/dl	246.45	41.208
LDL-C mg/dl	151.1029	43.35641
HDL-C mg/dl	43.99	6.868
Triglycerides mg/dl	256.77	80.336
UACR mg/gm	156.21	201.757
Retinopathy	58 (41.4%)	-
Nephropathy	25 (17.9%)	-
Hba_1c %	8.0000	1.39851
FSH mIU/L	7.0821	1.71968
LH mIU/L	5.4207	1.42836
Prolactin ng/ml	18.8643	2.98080
Total testosterone ng/dl	403.5071	129.75763

We found 48 (34.2%) patients with hypogonadism (defined as TT≤300 ng/dl) among 140 male patients with type 2 diabetes. 7 out of 48 patients with TT≤300 ng/dl (27.08%) had high abnormal gondotrophins hormones levels (hypergonadotrophic hypogonadism) while 41 patients out of 48 had normal gondotrophins hormones levels (hypogonadotrophic hypogonadism).

Table 2: Comparison of clinical and laboratory characteristics of male type 2 DM patients with TT>300 VS ng/dl those with TT≤300 ng/dl.

	TT > 300 ng/dl (n=92)	TT ≤ 300 ng/dl (n=48)	P value
Age (year)	50.86±8.2	49.81±6.87	0.1385
BMI (Kg/m^2)	32.07±5.82	34.41±4.99	0.019
Waist circumference(cm)	109.66±18.02	122.19±15.83	<0.001
Hba$_1$c %	7.64±1.1	8.69±1.89	<0.001
Diabetic duration(year)	9.24±3.66	10.48±4.62	0.111
Insulin therapy	27 (29.3%)	25 (52.1%)	0.007
FSH mIU/L	6.85±1.19	7.42±2.41	0.169
LH mIU/L	5.24±0.84	5.76±2.11	0.108
Prolactin ng/ml	18.77±2.8	19.03+3.3	0.647
Total cholesterol mg/dl	248.3±41.62	242.9±40.59	0.463
LDL-c mg/dl	154.16±42.75	145.24±44.34	0.249
HDL-c mg/dl	44.36±7.23	43.29±6.41	0.385
Triglycerides mg/dl	248.92±79.33	271.81±80.94	0.110
Retinopathy ratio	28 (30.4%)	30 (62.5%)	<0.001
Nephropathy ratio	6 (6.5%)	19 (39.6%)	<0.001
UACR mg/gm	97.58±110.85	268.58±277.43	<0.001
Smoker ratio	37(40.2%)	29 (60.4%)	0.023

Table 3: Pearson correlation and stepwise multiple regression analysis between total testosterone levels with other statistically significant correlated independent factor.

	r	P value	B	β	P value
BMI	-0.175	0.038	7.81	0.34	0.005
Waist circumference	-0.411	<0.001	-4.309	-0.606	<0.001
FSH	-0.209	0.013	-0.022	-0.236	0.814
LH	-0.257	0.003	-17.377	-0.191	0.006
Hba1c	-0.240	0.004	-15.888	-0.171	0.016
UACR	-0.361	<0.001	-0.181	-0.283	<0.001

Constant =887.194

Table 4: Logistic analyses by enter method for predictors of hypogonadism in type 2 patients.

	B	S.E.	Wald	P value	OR	95% CI for OR	
						Lower	Upper
smoking	-0.925	0.480	3.708	0.054	0.397	0.155	1.017
LH	0.250	0.154	2.629	0.105	1.284	0.949	1.738
Hba$_1$c	0.566	0.170	11.111	0.001	1.761	1.263	2.456
WC	0.046	0.021	4.642	0.031	1.047	1.004	1.092
UACR	0.004	0.002	5.452	0.020	1.004	1.001	1.007
retinopathy	-0.728	0.666	1.197	0.274	0.483	0.131	1.779
BMI	-0.035	0.067	0.277	0.599	0.966	0.848	1.100
Insulin therapy	0.149	0.552	0.073	0.787	1.161	0.393	3.424

In comparison between low testosterone group (TT≤300 ng/dl) with normal testosterone group (TT>300 ng/dl), we found BMI, WC, Hba1c, UACR, retinopathy ratio, nephropathy ratio, smoker ratio and patient on insulin

therapy ratio were increased in the low TT group with statistically significance (p<0.05), but non statistically significant (p>0.05) difference in Age, Diabetic duration, FSH, LH, Prolactin and lipid profile (TC, LDL-c, HDL-c and TG) were found between the two groups as shown in Table 2.

In this study by using Pearson correlation, we found a statistically significant correlation between TT levels with BMI, WC, FSH, LH, Hba1c, and UACR (P value< 0.05). Also by using stepwise multiple regression analysis, we found BMI, WC, LH, Hba1c, and UACR were statistically significant predictors of TT levels (P value>0.05) as described in Table 3.

In multivariate logistic regression analysis for identification of risk factors for MHG, we found Hba1c, UACR, and WC were statistically significant risk factors for MHG (P value>0.05), but smoking , retinopathy, LH and insulin therapy were non-significant risk factors (P value<0.05) as described in Table 4.

DISCUSSION

MHG is characterized by abnormally low serum testosterone levels associated MHG is significantly associated with various comorbidities. In this study, we found MHG prevalence among Egyptian patients with type 2 diabetes (defined as TT≤300ng/dl) was 34.2%.

Studies reported differences in testosterone levels with the varying ages of participants; cut-off points used to define MHG, method of analysis, duration, and complication of diabetes are dissimilar.[8] A Australia study reported that MHG prevalence 43% of type 2 diabetes patients with TT levels <288 ng/dl, while in the United Kingdom, MHG prevalence 17% with TT<231 ng/dl and 34% in Brazilian study by using free testosterone.[9-11] In Arabic world, MHG defined as TT less than 300 ng/dl was estimated to be 36.5% in patient with type 2 DM.[8] A recent study from Egypt reported 33.2% HG in type 2 diabetes patients.[12]

Thus, identification of risk factors and predictors of hypogonadism is essential because of high prevalence and associated co morbidity. The main finding in this result that Hba1c, degree of albuminuria and waist circumference were significant risk factors for MHG in Type 2 DM patients. In this study, 14.5 % of type 2 DM patient with MHG had hypergonadotrophic HG and 85.5% had hypogondotrophic HG, Also we found no statistically significant difference in LH and FSH between type 2 diabetic patient with MHG and those without MHG. These results are in concordance with previous study suggesting that hypogondotrophic HG is the predominant type of HG as in our diabetic patients.[8,14,15]

These findings pointed to the possibility of a failure at central level, which may be owing to hypothalamic defect and/or to an absence of pituitary response to the gonadotropin-releasing factor.[15] Hyperglycemia and/or IR appear to play a role in the activity of the GnRH pulse generator which might be a marker of potential development of hypogonadism.[15] In addition, TNF, IL-1 beta and other inflammatory factors can suppress the release of pituitary gondotrophins in states of hyperglycemia.[16]

In this study we found MHG associated with higher BMI and waist circumference also BMI and waist circumference were significant predictors for TT levels in T 2 DM. These result confirmed that visceral obesity rather than generalized obesity is the responsible for this suppressive effect on TT levels. Previous studies linked obesity and MHG prevalence in diabetic and non-diabetic.[8,13,17,18]

In contrast, there was a study denies this relationship between TT and BMI.[19] Obesity can promote estrogen secretion and suppress hypothalamic GnRH production.[20] Possible mechanisms found in obesity are proposed by some authors, including decreased SHBG, increased aromatization of testosterone to estradiol in fat cells and cytokine-mediated inhibition of testicular steroid production.[21] On the one hand, increasing body fat suppresses the hypothalamic axis by multiple mechanisms via increased secretion of pro-inflammatory cytokines, insulin resistance and diabetes [1x] Overall or abdominal obesity increases glucocorticoid turnover and production which may disturb regulation of the hypothalamic-pituitary-adrenal also was suggested.[22]

In the present study, we found MHG associated with higher HbA1c and negatively correlated with its levels. Also HbA1c was a significant predictors for TT levels in T 2 DM and risk factor for MHG. These findings are consistent with the results obtained by some studies while it contrast other studies analysis did not find an association between the serum testosterone level and HbA1c concentration, or found positive correlation with HbA1c concentrations.[23-26]

As regard microvascular complications, we found T2DM hypogonadism patients have higher incidence of nephropathy and retinopathy. Also we found degree of albuminuria negatively correlated with TT levels and predict its level. Degree of albuminuria in our regression analysis result was one of risk factor for male hypogonadism in T2DM. Lower testosterone levels in in type 1 DM patients exhibiting nephropathy neuropathy had been reported.[27]

Also old study in type 2 DM reported low testosterone levels in DM microvascular complication.[28] By contrast these results are inconsistent with other study found non-significant association between microvascular complication and testosterone levels.[29] But up to our Knowledge it's the first study correlate the MHG with degree of albuminuria in type 2 DM.

Microalbuminuria is a renal marker of generalized vascular endothelial damage and early atherosclerosis.[30] We hypothesis that albuminuria is a marker for microvascular affection of hypothalamus in diabetic patient leads to disturbed gonadotrophic hormones. It is intriguing that TT was not correlated with age in current study, there is a progressive reduction in HPG axis activity and testosterone levels decline in aging men.[31] But in diabetic patients, studies were controversial. Some studies reported decline with age while other deny this association.[8,17,32]

A longer duration of DM not correlated with TT levels nor MHG prevalence as this result is inconsistent with other research.[8] while in agreement with other studies.[17,33] Different patients selection and study design may be responsible for this contrast.

In the current study, we found none of lipids (TC, LDL-c, HDL-c and triglyceride) were significantly associated with low TT, which is in agreement with the result of other studies denied significant relationship between serum lipids and hypogonadism.[17,34,35] In contrast, other studies correlated lower HDL-c and higher triglyceride levels were significantly with LST in T2DMs.[9,36]

In the present study, smoker ratio was significantly higher in MHG patient but regression analysis showed no significant correlation between smoking and MHG, The relation of smoking with testosterone was controversial, some studies had shown a positive association between smoking and total or FT levels, also smoking cessation decreased testosterone levels in men followed for idiopathic infertility, while some studies found no association.[8,37-40] but on contrast other study show decreased testosterone levels with smoking, also in a prospective, baseline smoking predicted larger declines in testosterone during a 13-yr follow-up.[41,42]

The mechanisms by which cigarette smoking affect TT levels are uncertain.[43] Nicotine-mediated inhibition of aromatase was suggested but some authors on contrast, others suggested that the products of cigarette smokng, nicotine and cotinine, inhibit testosterone synthesis in Leydig cells, possibly by inhibiting the steroidogenic enzymes, 17a-hydroxylase and 17, 20-lyase.[44-46]

Also association of smoking is with increased insulin resistance.[47] The decrease in testosterone and increase in hypogonadism as a result of decreased smoking could also be secondary to weight gain and increased abdominal obesity, but adjustment for waist girth and its changes did not attenuate the relationship.[43] The difference of type and index of smoking may be the cause a we included in this study cigarette and Gaza smoking. In conclusion, WC, higher Hba1c, and degree of albuminuria are independent risk factors for hypogonadism in Egyptian male patients with type 2 diabetes. Our results will direct attention of physician and endocrinologists to early assessment of testosterone levels in all type 2 diabetics for early diagnosis especially those with risk factors in order to detect early those with MHG.

CONCLUSION

Visceral obesity, higher Hba1c, and degree of albuminuria are independent risk factors for hypogonadism in Egyptian male patients with type 2 diabetes.

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