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ORIGINAL PAPER

Testosterone deficiency in non-obese type 2 diabetic male patients

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Summary ***Background and aims: it is unclear whether male hypogonadism is ascribable to the diabetic state per se, or because of other factors, such as obesity or age. We aimed to investigate the prevalence and identify the predictors for testosterone deficiency among non-obese type 2 diabetic males.***

Methods: This cross-sectional study was conducted on 95 non-obese type 2 diabetic males with BMI below 30. We evaluated the total testosterone (TT) levels to determine prevalence and risk factors of testosterone deficiency. Serum TT ≤ 300 ng/dl defined testosterone deficiency.

Results: The prevalence of testosterone deficiency was 29.1%. Testosterone deficient patients had statistically significantly higher visceral adiposity index (VAI), waist, and triglyceride in comparison with normal testosterone patients. TT level correlated with VAI, waist, BMI, LH, and age. VAI was the only significant predictor of TT levels even after adjustment for age and BMI in regression analysis. Furthermore, VAI was a statistically significant risk factor for testosterone deficiency in binary logistic analysis.

Conclusions: testosterone deficient non-obese type 2 diabetic male patients had elevated VAI, waist, and triglyceride. Moreover, elevated VAI was a risk factor for testosterone deficiency. VAI could be an easily applicable and reliable index for the evaluation and prediction in type 2 non-obese diabetic males.

KEY WORDS: *Non-obese; T2DM; Visceral obesity; Testosterone; VAI; Males.*

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INTRODUCTION

Diabetes mellitus (DM) is a major cause of health concern due to its increasing prevalence rate worldwide. By the turn of the last decade, the *International Diabetes Federation* (IDF) estimated that 404.7 million people worldwide had *type 2 diabetes mellitus* (T2DM), with the total number of diabetic patients expected to rise to 679.7 million by 2045 (1). One complication of *type 2 diabetes* (T2DM) is *hypothalamic-pituitary-testicular axis* (HPT axis) dysfunction. The hallmark of HPT axis dysfunction is characterized by subnormal testosterone levels in association with non-elevated luteinizing hormone concentrations. These abnormalities were not affected by the duration or severity of diabetes (2). Testosterone deficiency is associated with many comorbidities such as chronic fatigue, loss of libido, erectile dysfunction, low haematocrit level, cardiovascular events, and decreased bone density (3).

Several studies consistently show significant relationships between serum testosterone and T2DM (4). Many studies reported that 25% to 50% of type 2 diabetic males have lowered testosterone levels (5). Hence, testosterone deficiency in T2DM has high clinical importance. Although male hypogonadism (MHG) in T2DM has been investigated in many researches, the mechanism underlying the pathogenesis of testosterone deficiency in diabetes is still not fully understood yet (6). The majority of previous studies have assessed testosterone levels in elderly, obese males with T2DM (7).

On other hand, it is well established that obesity is a major risk factor for type 2 diabetes and cardiovascular disease (8). Several studies have linked male hypogonadism with being overweight or obese (9). Large population-based studies have confirmed that obesity is the single most important factor associated with low testosterone, overriding the effects of age and comorbidities (10). Therefore, it is unclear whether this is ascribable to the diabetic state per se, or because of other factors, such as obesity or age. Hence, the role of the diabetic state in relation to the effects of obesity and comorbidities on testosterone levels in diabetic men is debatable (11).

In this study, we tried to limit the confounding factor that affects the testosterone levels in diabetic males such as obesity. Therefore, we aimed to investigate the prevalence and identify the predictors for testosterone deficiency among non-obese type 2 male diabetic patients.

PATIENTS AND METHODS

Study population

This cross-sectional study was conducted at *Mansoura University's Endocrinology*, Diabetes, and *Metabolism Unit, Specialized Medical Hospital*, between March 2021 and August 2021. The *Mansoura Faculty of Medicine's Institutional Research Board* approved the study design. All study participants provided written informed consent. We enrolled 95 patients aged 25 to 65 who had been diagnosed with T2DM using the *American Diabetes Association's* diabetes diagnosis criteria.

Inclusion criteria were set as follows: males with type 2

No conflict of interest declared.

diabetes; body mass index below 30; history of normal pubertal development; a normal sense of smell for exclusion of Kallman syndrome; age between 18 and 65. In contrast, patients were excluded from this study in case of: female sex; abnormal renal function; abnormal albumin levels; diabetes with macro albuminuria; liver disorders; heart failure; usea of drugs that may affect testosterone levels, such as replacement therapy and anabolic steroids; patients with known causes of hypogonadism; history of malignancy; autoimmune diseases; diseases of the endocrine system other than Type 2 DM, including Type 1 DM, pituitary disorders, and abnormal thyroid functions. All patients were divided into either a low testosterone group (TT ≤ 300 ng/dl) or a normal testosterone group (TT > 300 ng/dl).

Clinical assessment and anthropometric measurements

All subjects underwent a comprehensive medical evaluation including medical history with special emphasis on diabetes duration, medication, smoking history, and diabetic complications history; physical examination and measurement of anthropometric parameters. The patient's height and weight were measured while they were dressed casually and were not wearing shoes. BMI was calculated by dividing weight (kg) by height square (m^2).

Waist circumference (WC) was measured halfway between the inferior border of the last rib and the crest of the ilium at the end of expiration. Following standard procedure, blood pressure was measured with a sphygmomanometer. VAI was calculated for all participants using the following formula for males (12):

VAI: WC / [39:68 + (1.88 × BMI)] × TG/1:03 × 1:31/HDL.

Biochemical parameters

After a 12-hour overnight fast, venous blood samples were collected from all patients between 8 A.M. and 10 A.M. including: *complete blood count* (CBC), fasting lipid profile that included *triglycerides* (TG), *total cholesterol* (TC), *low-density lipoprotein* (LDL), and *high-density lipoprotein* (HDL); serum creatinine; *glycosylated haemoglobin* (HbA_1C)*; fasting blood sugar; albumin; luteinizing hormone* (LH); serum total testosterone. LDL-cholesterol was estimated according to the Friedewald formula (TC minus HDL-cholesterol minus TGs/5 in mg/dl). *Visceral adiposity index* (VAI) was calculated for women and men according to the formulas.

Definition

Diabetes was defined as a fasting plasma glucose of 100 mg/dl or higher, HbA_1c of 6.5% or higher, or a previous diagnosis of type 2 diabetes. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, current use of the antihypertensive drug. Overweight was defined by a body mass index of at least 25 kg/m^2. Testosterone deficiency was defined as serum TT less than 300 ng/dl that is the lower limit of the normal range according to the American urological association guidelines (13).

LH level above 9.4 IU/L was defined as hypergonadotropic hypogonadism, while LH levels below 9.4 IU/L were defined as hypogonadotropic hypogonadism (14).

Statistical analysis

The *Statistical Package for the Social Sciences* (SPSS), Version 23 was used to analyze the statistical data. Continuous variables were presented as the mean ±standard deviation, and categorical variables were expressed as a proportion (%) whereas non-normally distributed data are expressed as the median (interquartile range). Differences between groups of patients were compared by the Mann-Whitney U or Student T-test for continuous variables and the Chi-square test for categorical variables. The relationship between testosterone (the dependent variable) and other statistically significant correlated parameters in Pearson correlation (the independent variables) was investigated using linear regression. The risk factors associated with Testosterone deficiency were assessed using binary logistic regression, and the *odds ratio* (OR) and 95 per cent *confidence interval* (CI) were calculated. P values less than 0.05 were considered statistically significant.

RESULTS

We enrolled ninety-six non-obese patients with type 2 DM in this cross-sectional study. Among those diabetic patients, 27 (28.4%) were of normal weight, while 68 (71.6%) were overweight. Their age ranged between 34 and 65 years. We observed that the prevalence of testosterone deficiency was 29.1% (28 patients). We observed high abnormal level of LH in 14 patients with low testosterone levels. The prevalence of hypergonadotropic hypogonadism was 50% of testosterone deficient patients. Other clinical, anthropometric, and laboratory details of the patient were presented in Table 1.

Table 1.
General characteristics of the study population.

	N = 96
Age (year)	51.41 ± 7.17
Diabetic duration(year)	9.59 ± 4.18
Smoker ratio	66 (47.1%)
Insulin therapy	52 (37.1%)
Body weight (kg)	86.69 ± 7.96
Height (m)	1.78 ± .058
BMI (Kg/m^2)	28.245 (3.05)
Waist circumference(cm)	99.48 ± 9.68
Systolic BP (mmHg)	135.00 (15)
Diastolic BP (mmHg)	85.00 (15)
Total cholesterol mg/dl	248.54 ± 43.29
LDL-C mg/dl	155.88 ± 47.98
HDL-C mg/dl	43.83 ± 6.85
Triglycerides mg/dl	244.14±74.48
UACR mg/gm	28 (62)
Retinopathy	29 (30.2%)
Hba_1c %	8.5 ± 1.613
Total testosterone ng/dl	405.71 ± 133.78
Testosterone deficiency	28 (29.1%)
LH mIU/L	7.44 ± 2.67
VAI	3.25 (1.58)

Data expressed as mean (interquartile range) according normality of distribution, Data expressed as mean ± standard deviation or Data expressed in parenthesis are percentage.
BM: Body mass index; WC: Waist circumference; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; uACR: Urinary albumin creatinine ratio; Hba_1c: Glycated hemoglobin; LH: luteinizing hormone; VAI: Visceral adiposity index.

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 = 68)	TT ≤ 300 ng/dl (n = 28)	P value
Age (year)	52.1 ± 7.29	49.71 ± 6.69	0.139
DM duration (year)	9.34 ± 4.27	10.21 ± 3.98	0.354
Smoker ratio	30 (44.1%)	11 (39.2%)	0.821
Height (m)	1.78 ± .06	1.7675 ± .05	0.290
Body weight (kg)	86.54 ± 8.39	87.04 ± 6.96	0.785
BMI (Kg/m^2)	27.75 (3.44)	28.73 (2.13)	0.197
WC (cm)	98.24 ± 9.35	102.50 ± 9.95	0.049
Systolic BP (mmHg)	135.00 (15)	137.50 (14)	0.218
Diastolic BP (mmHg)	85 (15)	85 (13)	0.09
microalbumiric	24 (35.5%)	12 (42.8%)	0.497
Retinopathy ratio	16 (23.5%)	13 (46.4%)	0.049
TV mg/dl	249.96 ± 41.94	245.11 ± 47.02	0.620
LDL-c mg/dl	158.51 ± 45.48	149.49 ± 53.93	0.405
HDL-c mg/dl	44.56 ± 7.53	42.07 ± 4.44	0106
TG mg/dl	234.43 ± 76	267.71 ± 66.14	0.046
Hba_1c %	8.36 ± 1.53	8.93 ± 1.7	0.111
LH mIU/L	7.2 ± 1.85	8.02 ± 4.01	0.173
UACR mg/gm	28 (62.53)	28 (74)	0.812
VAI	3.03 (1.54)	3.86 (1.77)	0.006

Data are presented as the mean ± SD. median (IQ range) or the number of patients in each group with percentages. BM: Body mass index; WC: Waist circumference; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglyceride;; Hba_1c: Glycated hemoglobin; LH: Luteinizing hormone; uACR: Urinary albumin creatinine ratio; VAI: Visceral adiposity index.

In the comparison between 28 patients in the low testosterone group (TT ≤ 300 ng/dl) and 68 patients in the normal testosterone group (TT > 300 ng/dl), we found that the low testosterone group had a statistically significant higher mean or median of VAI, WC, and triglyceride in comparison with normal testosterone group. Moreover, a higher percentage of patients complicated with retinopathy was observed in low testosterone groups. Other differences between the two groups were shown in Table 2. According to Pearson correlations, TT was negatively correlated with VAI (log), WC, BMI (log), and LH. On the other hand, TT was positively correlated to age. However, TT was not correlated with duration of diabetes, Hba1c, or lipid parameters. We conducted a regression analysis to determine predictors of total testosterone levels as the dependent variable and age, BMI (log), LH, and VAI (log) as the independent variables in our study patients. We observed that VAI was the only significant predictor of TT levels (p-value = 0.41). Furthermore, VAI was a statistically significant predictor of TT levels even after adjustment for age and BMI as shown in Tables 3, 4.

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
Age	.218	.033	2.723	.146	.145
Log BMI	.213	.037	25.488	.040	.760
WC	-.255	.012	-1.723	-.125	.352
LH	-.222	.030	-8.630	-.172	.082
Log VAI	-.278	.006	-164.284	-.208	.041

BM: Body mass index; WC: Waist circumference; LH: Luteinizing hormone; VAI: Visceral adiposity index.

Table 4.
Association between total testosterone levels and other statistically significant correlated independent factors in regression analysis after adjustment for BMI and age.

	Model 1			Model 2		
	B	β	P value	B	β	P value
Age	2.723	.146	.145	2.721	.146	.147
WC	-1.723	-.125	.352	-1.638	.118	.397
BMI (log)	25.488	-.208	.760	4.984	.008	974
LH	-8.630	-.172	.082	-8.654	-.173	.083
VAI (log)	-164.284	040	.041	-165.076	-.209	.041

Model 1 adjusted for age and model 2 adjusted for BMI and age.
BM: Body mass index; WC: Waist circumference; LH: Luteinizing hormone; VAI: Visceral adiposity index.

The binary logistic regression was performed with hypogonadism as the dependent variable and age, overweight (defined by BMI more than 30), WC, LH, retinopathy, and VAI (log) as the independent variables. We observed that the Visceral adiposity index was a statistically significant risk factor for testosterone deficiency among non-obese type 2 diabetic males (p-value = 0.46). More data are available in Table 5.

Table 5.
Logistic regression analysis for risk factor of testosterone deficiency.

	B	S.E	Wald	P value	OR	95% C.I. for Odds ratio	
						Lower	Upper
Age	-.046	.037	1.563	.218	.956	.891	1.027
Overweight	-.802	.878	.834	.367	2.373	.363	15.536
Waist	.045	.033	1.891	.207	.344	.066	1.806
Log VAI	3.629	1.629	4.965	.046	1.436	1.007	2.048
Retinopathy	-1.138	.514	4.901	.060	.382	.140	1.043
LH	.049	0.84	.308	.579	1.050	.883	1.249

B: Estimated coefficient; S.E: Standard error; CI: Confidence interval; WC, waist circumference; VAI: Visceral adiposity index; LH: Luteinizing hormone.

Discussion

Despite the high prevalence of male hypogonadism in type 2 diabetic, regardless of diabetic control status, the underlying mechanisms of hypogonadism pathogenesis in type 2 diabetes mellitus have not been fully clarified yet (15). In the same consent, the contribution of the diabetic status or hyperglycaemia on androgen levels in males is still debated. The strong association between type 2 diabetes with obesity, insulin resistance status, and aging may be the significant contributory factor in testosterone deficiency in type 2 DM patients rather than diabetes itself (16).

The main result in this cross-sectional study is that visceral adiposity functional activity evaluated by VAI is the main risk factor in type 2 diabetic males with BMI below 30. Moreover, VAI was the only predictor for testosterone levels in non-obese type 2 diabetic males even after adjustment for age and BMI, although testosterone levels

in our study correlated with anthropometric parameters such as BMI and waist circumference. VAI as a index for visceral fat dysfunction is more reliable than other obesity parameters in predicting testosterone deficiency. Low TT levels were strongly associated with increased VAI in our cross-sectional study regardless of age, or diabetes status control.

Although many studies evaluated hypogonadism in diabetic patients, only a few studies evaluated obesity by VAI. A recent population-based study among diabetic and non-diabetic observed that VAI was the best predictor of male hypogonadism among different obesity indices (17, 18). Likewise, VAI is more reliable than other metabolic or anthropometric parameters in the evaluation of visceral adiposity effect on erectile dysfunction (19, 20).

In this cross-sectional study, the prevalence of testosterone deficiency was 29.1 per cent. This prevalence of testosterone deficiency in type 2 diabetic males was lower than that reported in previous studies in Egypt (21) and the Middle East region (22). The difference is expected by the selection of our patients with BMI below 30. Surprisingly, we have a high prevalence of hypergonadotropic hypogonadism. We observed high abnormal level of LH in 14 patients (50%) with low testosterone levels. In our study, we observed that other obesity parameters such as BMI or waist diameters correlated with testosterone levels in Pearson correlation. However, BMI and WC were not a significant predictor for testosterone levels in regression analysis. Several studies consistently reported a negative impact for obesity on testosterone levels (18, 19, 23). These results in non-obese type 2 diabetic male patients could point to the role of abdominal obesity in the pathogenesis of male hypogonadism in T2DM. The results in this study may indicate that adipose fat function may be important than fat mass.

In this study, age correlated with testosterone levels. This result was in concordance with many previous studies that observed decreased levels of testosterone with aging in diabetic patients (11, 24, 25) and the general population (26). However few studies did not observe this link in type 2 diabetic patients (27, 28).

In this study, we observed significantly higher triglyceride levels in testosterone deficient diabetics. However, HDLc levels were insignificantly different between the two groups. This may be attributed to the effect of patients' selection and lifestyle such as exercise and diet that could affect HDL levels. Many studies linked hypogonadism and dyslipidaemia (21, 22, 27). Moreover, controlled trials on testosterone replacement observed favourable effects for testosterone on lipid profile in diabetics (29). However, the effect of dyslipidaemias on testosterone levels is still unexplored. VAI includes anthropometric and metabolic parameters as TG or HDL-c. Hence, the correlation between testosterone and TG or HDL-c cannot be excluded.

Surprisingly, testosterone deficiency was not related to diabetic status. Testosterone deficiency in this study did not correlate with glycated haemoglobin or the duration of diabetes. These results are in agreement with many studies in diabetics in general (28). However, our findings contradict another large study which correlated testosterone levels with diabetic status control (30).

In this study, we found that non-obese diabetics with testosterone deficiency had higher significant retinopathy prevalence. However, we found non-significant different urinary albumin excretion between both groups. The effect of nephropathy was not assessed in this study as we excluded macro-albuminuria patients. Micro-vascular complications were reported in many studies to correlate with low testosterone levels in males (21, 22, 31).

Although the pathophysiological mechanism of testosterone deficiency in Type 2 DM is still not fully revealed, few mechanisms have been hypothesized. The role of inflammatory mediators such as tumour necrosis factor-alpha and Interleukin-1 beta was postulated. Obesity is considered as a state of chronic inflammation (33). These mediators have been reported to suppress hypothalamic *gonadotropin-releasing hormone* (GnRH) at the hypothalamic level (34). Insulin resistance is another mechanism that could be involved in hypogonadism pathogenesis. Insulin resistance and brain insulin resistance, which was defined as impaired insulin action in the neuron (34). Normal insulin response is required for the HPG axis's functional integrity to be maintained (35). According to one study, hyperinsulinemia caused by neuronal insulin receptor knockout can result in a 60-90% decrease in LH concentrations (33). Another mechanism could be related to adipokines such as leptin and adiponectin which have been reported to have a permissive role in the regulation of the *hypothalamic-pituitary-gonadal* (HPG) axis. Leptin resistance in the hypothalamus or other neurons may play a role in the pathogenesis of hypogonadism seen in obesity, insulin resistance, and T2DM (29). Furthermore, leptin directly suppresses the stimulatory action of gonadotropins on the testicular Leydig cells, reducing testosterone formation (28). Furthermore, testosterone has a direct correlation with circulating adiponectin (36). Finally, the aromatase enzyme converts testosterone to oestrogen in adipose tissue, resulting in hypothalamic-pituitary-gonadal axis inhibition and subsequent hypogonadism (37).

In the light of those postulated mechanisms for male hypogonadism in diabetic patients, VAI could be a valuable index for predicting male hypogonadism and is linked with these postulated mechanisms. VAI by involving the metabolic parameters could reflect chronic inflammatory status. Decreases in serum HDL and increases in triglycerides were reported to be linked with inflammatory status and mediators (38). Likewise, VAI was reported to be strongly correlated with insulin resistance estimated by HOMA-IR and metabolic syndrome (39, 40). Furthermore, among the most commonly used adiposity assessment indices, VAI has the strongest correlation with the most well-known adipocytokines in diabetic patients (41) and non-diabetic (42). Finally, a population-based study observed that VAI correlates with estradiol levels in males which reflect aromatase enzyme activity (43). Hence, the VAI value could better reveal the effects of WC, BMI, HDL, and TG on testosterone levels.

This cross-sectional study cannot inform whether low testosterone is the cause or the result of visceral obesity. Current evidence, however, suggests that this relationship is bidirectional (11). A two-way relationship between low testosterone levels and abdominal obesity

was reported (44). Weight loss could increase testosterone levels, indicating that testosterone deficiency is functional (45). Weight loss bariatric surgery-induced resulted in a significant increase in Testosterone levels (46). In contrast, lower testosterone level after androgen deprivation therapy is associated with weight gain (45). In our study, a higher prevalence of hypergonadtropic hypogonadism could point to an increased risk of T2DM with testosterone deficiency.

This study is not devoid of some limitations, firstly the cross-sectional design. The second limitation was the relatively small case number that might limit the power to detect a difference. Thirdly, because free testosterone levels can reflect the extent of testosterone's biological activities, free testosterone concentration should be used to assess hypogonadism. However, free testosterone determination is difficult, so free testosterone is frequently calculated with a formula in practical activity. Finally, this study is a single-centre study in a tertiary hospital. Therefore, patient selection bias might exist.

This research highlights the value of an easily applicable tool such as the visceral adiposity index in predicting testosterone deficiency in non-obese diabetics. VAI could be more reliable than other parameters in predicting testosterone deficiency in diabetics.

In conclusion, the elevated VAI index is associated with higher risks of testosterone deficiency in non-obese diabetic males. VAI is an easily applicable reliable index for the prediction of male hypogonadism in non-obese type 2 diabetic male patients.

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