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Total Serum Testosterone Level in Obese Patients with Type -2 Diabetes Mellitus

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Abstract: Both obesity and type 2 diabetes mellitus (T2DM) are independently associated with reduced serum testosterone. The additive effect of obesity and T2DM on reducing testosterone levels need to be investigated. Their combined additive effects may place obese T2DM patients at higher risk of decreased testosterone and the associated increased morbidity and mortality. The aim of this study was to screen obese T2DM patients for biochemical hypogonadism regardless of the presence of overt clinical symptoms to consider testosterone replacement therapy. 152 adult male aged 40 to 68 years with T2DM were recruited through simple random sampling. The study participants were grouped based on their BMI into lean (n=48); overweight (n=57), obese (n=37) and morbidly obese (n=11). Total serum testosterone (TST), BMI and waist circumference (WC) were measured in all patients and luteinizing hormone (LH) was measured in 103 of them. Low TST was defined as TST<9nmol/L and the normal range for LH was 1.7-11.2mIU/ml. Mean TST in lean T2DM patients was 15.61± 6.0 nmol/l. TST levels were significantly lower in obese and morbidly obese groups compared with the lean group (P=0.003 and 0.015 respectively). TST negatively correlated with BMI (r= -0.29, P<0.001) and WC (r= -0.21, P<0.009). Overall, 19.7% of T2DM patients had low TST. The prevalence of low TST increased from 14.9% in lean, to 21.1% in overweight, to 21.6% in obese, to 27.3% in morbidly obese T2DM patients, (P=0.74). LH was inappropriately normal in 95% (19/20) of patients with low TST. Obese T2DM patients had reduced TST levels and a higher prevalence of reduced TST compared to lean patients. TST negatively correlated with BMI and WC. Therefore, screening obese T2DM patients for testosterone deficiency should be considered.

Keywords: Testosterone, Luteinizing hormone, Type2 diabetes mellitus, Obesity, Hypogonadism

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1. INTRODUCTION

World prevalence of diabetes mellitus among adults aged 20 to 79 years is expected to increase to 7.7% by 2030[1]. The prevalence in Sudan has been reported to increase since 1996 to reach 18.7%. [2] Type 2 diabetes mellitus (T2DM) is the commonest form of diabetes, accounting for more than 90% of diabetic patients in Africa.[3] Studies have shown that men with T2DM, have significantly lower levels of testosterone compared with age matched non-diabetics or with patients with type one diabetes mellitus (T1DM).[4,5] It has been noted that reduced testosterone (TST) was also related to obesity and metabolic syndrome in males.[6,7] Obesity reduces testosterone level possibly through increased adipose tissue production of estradiol. Estradiol acts centrally to inhibit the secretion of GnRH and LH leading to a state of hypogonadotropic hypogonadism.[8,9]Nevertheless, in male patients with T2DM and low testosterone levels, estrogen levels were also reduced which suggest that this mechanism might not apply to hypogonadism in these patients.[10]Another mechanism by which obesity can reduce testosterone level is through the increased production of adipocytokines which may contributes to the reduction of testicular function in obese men through suppression of hypothalamic GnRH secretion.[11] Leptin also bind directly to its receptors on testicular Leydig cells and inhibit testosterone production.[12]Obesity decreases testosterone levels and low testosterone levels promote the development of obesity and increase visceral fat deposition, a bidirectional causative interaction that resulted in a well-documented negative correlation of testosterone with obesity.[13]Reduced testosterone in patients with T2DM might be a consequence of obesity related mechanisms.[14],Other suggested pathological mechanisms include the effect of insulin resistance and hyperinsulinemia on decreasing sex hormone binding globulin (SHBG) hepatic synthesis and on inhibiting the hypothalamic pituitary axis.[15,16] From the above review, both obesity and T2DM are independently associated with reduced serum testosterone. Hence, obesity and T2DM may have an additive effect on reducing testosterone levels. Their combined additive effects in obese T2DM patients place them at higher risk of decreased testosterone and the associated increased morbidity and mortality. Moreover, the nature of their complicated bidirectional causative interaction generates a continuous positive feedback loop. Therefore, it might be justified to screen obese T2DM patients for biochemical hypogonadism regardless of the presence of overt clinical symptoms to consider testosterone replacement therapy which is the aim of this study. In this study we investigated the association of increased BMI and visceral fat with TST in Sudanese patients with T2DM to estimate the combined effect of overweight and obesity on TST. The study also investigated whether reduction in testosterone was related to central inhibition of hypothalamic function or a primary testicular dysfunction by simultaneous assessment of serum LH level.

2. MATERIALS AND METHODS

The study was conducted during the period between Feb to May 2019. Ethical approval was obtained from the Research Ethics Committee of university of Khartoum With the reference number FM/DO/EC and permission was obtained from the Ministry of Health, Khartoum state. Participants were T2DM patients recruited from Jabir Abu Eliz Diabetic Center, Khartoum State. Inclusion criteria wereT2DM male patients, age 40 to 70 years old (common age of T2DM), duration of T2DM more than 2 years, and signed written informed consent to participate. Male patients on insulin; receiving hormonal replacement therapy, opioids or glucocorticoid and known to have liver disease, prostate cancer or endocrinological abnormality were excluded. Simple random sampling was used in sampling method. All patients signed an informed written consent form. Patients were recruited into four groups based on their BMI: lean (BMI= 18-24.9kg/m^2); overweigh (BMI= 25-29.9kg/m^2), obese (BMI 30–34.9kg/m^2) and morbid obesity (BMI ≥ 35Kg/m^2). After obtaining personal and clinical history, the patient's height and weight were measured and BMI was calculated (BMI= Body weight in Kilograms/Body height in $Meters^2$). Waist circumference (WC) and blood pressure were also recorded. Early morning fasting blood samples were collected from patients and TST and LH were measured by Fluorometric Enzyme Immunoassay (FEIA) using Tosoh AIA system analyzer and AIA–Pack for competitive enzyme immunoassay.[17,18] HbA1c estimations were obtained from patients' records. Low TST was defined as TST < 9nmol/L and the normal range for LH was 1.7-11.2 mIU/ml. The cut off point for normal hormonal levels was based on the kit manufacturer instructions.

3. STATISTICAL ANALYSIS

Statistical analysis was performed by Statistical Package for Social Studies (SPSS v.21). Means were compared using independent sample T test. Increased prevalence of low TST associated with increased BMI was evaluated using Chi square test or Fisher Exact test when appropriate. Correlations of numerical variables were compared using Pearson's correlation coefficient. $P < 0.05$ was considered as statistically significant.

4. RESULTS

4.1 BMI and waist circumference

The study included a total of 152 T2DM male patients: 48 lean, 57 overweight, 37 obese and 11 morbidly obese patients. The patients' age ranged between 40 to 68 (Why you select this age group? it is the commonest age of type2 diabetes mellitus) years with a mean (SD) of 53.8± 6.97 years. Their disease duration ranged between 2 to 40 years with mean (SD) of 9.96±7.03. The four study groups did not differ regarding age nor disease duration (table1).

Table 1: BMI and waist circumference of the study population

	BMI Groups	Number	Minimum	Maximum	Mean	SD	SE
Age	All groups	152	40	68	53.78	6.97	0.57
	Lean	47	40	68	53.8	7.4	1.08
	Overweight	57	40	65	53.7	7.4	0.98
	Obese	37	40	62	53.95	6.44	1.06
	Morbidly obese	11	45	60	53.36	5.10	1.54
BMI * (P=0.000)	All groups	152	18.40	41	27.46	4.81	0.39
	Lean	47	18.40	24.90	22.39	1.90	0.28
	Overweight	57	25.00	29.70	26.89	1.33	0.18
	Obese	37	30.00	34.7	31.75	1.53	0.25
	Morbidly obese	11	35.2	41	37.87	1.83	0.55
Waist circumference * (P= 0.000)	All groups	152	76	139	102.16	13.14	1.07
	Lean	47	76	136	92.43	10.62	1.55
	Overweight	57	83	122	100.91	7.68	1.017
	Obese	37	86	131	109.22	10.12	1.66
	Morbidly obese	11	103	139	126.55	9.84	2.97
DM Duration in years	All groups	152	2	40	9.96	7.03	0.57
	Lean	47	2	30	11.02	7.11	1.04
	Overweight	57	2	40	9.25	7.14	0.95
	Obese	37	2	24	9.91	6.69	1.1
	Morbidly obese	11	2	26	11.00	7.51	2.26
HbA1C	All groups	94	2.1	22.6	9.13	3.38	0.35
	Lean	35	4.6	15.0	9.37	2.82	0.48
	Overweight	33	2.1	22.6	8.26	3.61	0.63
	Obese	19	6.0	22.5	10.34	3.99	0.92
	Morbidly obese	7	6.5	12.9	8.83	2.37	0.89

Significantly difference between groups (ANOVA), SD = standard deviation, SE= standard Error of means

4.2 Testosterone level

Mean TST (Mean ± SD) was 15.6±6 nmol/L in the lean group, 14±6.5nmol/L in the overweight group, 12.2±3.63nmol/L in the obese group and 10.85±3.72nmol/l in the morbidly obese group (Table 2,). Mean TST was significantly lower in the obese (P= 0.003) and in the morbidly obese (P=0.015) groups compared to the lean group (Fig. 1).

Table2: Testosterone in study population

	BMI Groups	Number	Minimum	Maximum	Mean	SD	SE
Testosterone (nmol/L) *(P=0.014)	All groups	152	4.1	35.0	13.84	5.75	0.47
	Lean	47	5.6	25.8	15.61	6.00	0.88
	Overweight	57	4.1	35.0	14.02	6.52	0.86
	Obese	37	5.3	20.8	12.2	3.63	0.59
	Morbidly obese	11	5.3	16.3	10.86	3.72	1.12

Significantly difference between groups (ANOVA)SD = standard deviation, SE= standard Error of means

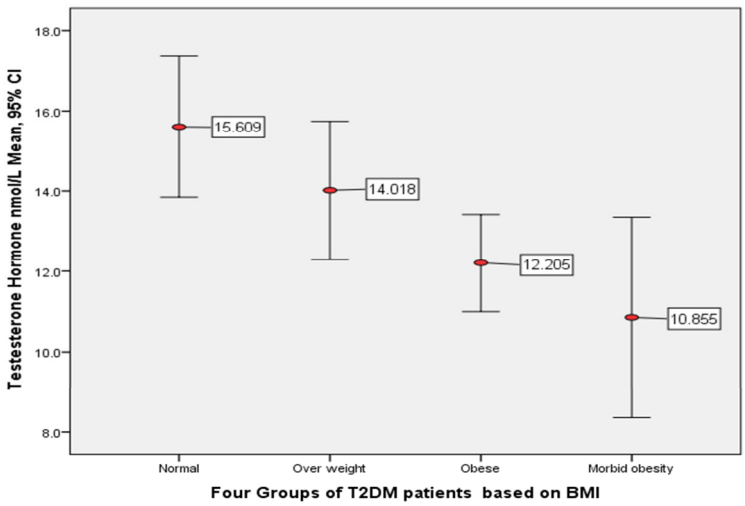

Fig 1: Mean (95% CI) of total serum testosterone level in the four BMI groups.

Overall, 30 patients (19.7%) had low TST. Patients with low TST represented 14.9% (7/47) of lean, 21.1% (12/57) of over-weight, 21.6% (8/37) of obese, and 27.3% (3/11) in morbidly obese patients (P=0.74) (Table 3).

Table 3: The prevalence of low total serum testosterone (TST) in the four BMI study groups

			Testosterone level		
			Low (< 9)	Normal	Total
The four BMI Groups	Lean	Count	7	40	47
		% within lean	14.9%	85.1%	100.0%
	Overweight	Count	12	45	57
		% within overweight	21.1%	78.9%	100.0%
	Obese	Count	8	29	37
		% within obese	21.6%	78.4%	100.0%
	Morbidly obese	Count	3	8	11
		% within morbidly obese	27.3%	72.7%	100.0%
Total		Count	30	122	152
		% within patients with T2DM	19.7%	80.3%	100.0%

P value 0.744, Chi-Square test . Correlation analysis showed a highly significant, negative correlation of testosterone with BMI (r= -0.282; P<0.001) and with WC (r= -0.212; P= 0.009). However, TST did not correlate with HbA1c, serum LH, age, or the duration of diabetes.

1.1 LH level

LH was measured in 103 out of the 152 patients included in the study. The mean ± SD serum LH was 4.2±3.95 mIU/ml. Mean LH level was slightly less in patients with low TST (n=20) compared to patients with normal testosterone level (n=83) (3.8 ± 3.6 mIU/ml and 4.3 ± 4.0 mIU/ml respectively, p value 0.6). In total, 2.9% of T2DM patients (3/103) had elevated LH level, 2 of whom had normal TST. Only one patient with low TST (1/20) had an increased LH level (Table 3). 95% of patients with low TST (19/20) were found to have inappropriate normal LH. Thirty percent (6/19) of those were lean, 30% (6/19) were overweight and 35% (7/19) were obese or morbidly obese. There was no significant association between LH level with BMI or WC.

Table 4: The distribution of low, normal, or high LH levels among T2DM patients with low or normal total serum testosterone levels.

Testosterone level		LH level		
		Low	Normal	High
Low level	Percent within patient with low TST	0.0%	95.0%	5.0%
Normal level	Percent within patients with normal TST	1.2%	96.4%	2.4%

P= 0.548, Fisher's Exact test

5. DISCUSSION

We detected a significantly decreased mean TST levels in obese and morbidly obese patients with T2DM compared to lean T2DM patients and a significant negative correlation of TST with BMI and WC. The prevalence of reduced testosterone level and the association between BMI and low serum testosterone in patients with T2DM was investigated by many research groups and in different ethnicities with controversial outcomes. The sources of most variation between these studies were the characteristics of the study population; variations in the definition of reduced serum testosterone (cutoff point for normal level); and the methodology used in the measurement of the hormones. In our study we detected reduced TST levels (TST< 9nmol/L) in 19.7% (30/152) of T2DM male patients which is comparable to the findings reported by Kapoor et al (2007). Kapoor et al (2007) (study was a cross‐sectional study that included 355 T2DM patients from the UK. They reported that 20% (71/355) of T2DM patients had low TST (<8 nmol/L) and 16% (58/355) had reduced bioavailable testosterone (<2.5nmol/L). Kapoor. al, also reported that symptoms of hypogonadism were found in 17% of T2DM with low TST (overt hypogonadism).[19] A higher prevalence of low testosterone and hypogonadism was reported by a cross sectional study that included 900 T2DM patients from India. They reported that 26.6% (237/900) of T2DM patients had reduced TST of whom as much as 78.5% (186/237) had symptoms of hypogonadism.[22]Both studies used the same cutoff for testosterone and assessed symptoms of hypogonadism using Androgen Deficiency in Aging Male questionnaire (ADAM), therefore variations between these studies may be attributed to ethnic variations. Mirzaei et. al (2012), conducted a study in Iran that included 265 T2DM. [21] The major difference between Mirzaei et al. (2012), and our study was the study population. Mirzaei et al. (2012), included only T2DM patients with positive symptoms of hypogonadism. Interestingly, they reported that only 7.4% of men with T2DM and symptoms of androgen deficiency had low TST (TST ≤8nmol/L).[21]This reflects that symptoms of hypogonadism in T2DM patients are not specific for testosterone deficiency. Mirzaei et. al (2012), also reported that 61.6% of the symptomatic diabetic patients had low calculated bioavailable testosterone (≤2.5 nmol/l), reflecting a stronger relation of symptomatic hypogonadism and androgen deficiency.[21]There is some dissociation between symptoms of hypogonadism and testosterone level in T2DM patients. A considerable proportion of patients symptomatic for hypogonadism have normal testosterone levels and a considerable proportion of patients with reduced serum testosterone are non-symptomatic.[19,21]One explanation is that hypogonadism symptoms, such as erectile dysfunction,

might be a direct vascular or neurological complication of diabetes mellitus. It is very important to emphasize on the fact that testosterone, being an anabolic hormone, has functions related to wellbeing other than its role in reproduction. Therefore, we suggest that direct assessment for TST and bioavailable testosterone is required to determine if a T2DM patient is deficient in testosterone whether they were symptomatic for hypogonadism or not. Screening for testosterone deficiency becomes more urgent in the coexistence of T2DM and obesity. Our study reported a statistically significant correlation of TST level with BMI (r =-0.282; P<0.001) and with WC (r=-0.212; p value 0.009), but no correlation with age, duration of diabetes, and HbA1c. Our results are consistent with the findings of Kapoor et al (2007), who reported that TST significantly and negatively correlated with both BMI (r=-0.247; P=<0.001) and WC (r = - 0.275; P<0.001).[19] The weak correlation (r <0.3) indicates that obesity is not the only cause for reduced testosterone in patients with T2DM a hypothesis which is further supported by the prevalence of low TST in non-obese T2DM patients (14.9% of lean T2DM patients in our study). It is worth noting that the negative correlation of serum testosterone with BMI was also reported in T1DM patients.[22]It has been noted that hypogonadism in T2DM male patients is mostly secondary (hypogonadotropic hypogonadism).[23]In our study, 95% (19/20) of patients with low TST had an inappropriately normal LH and only 5% (1/20) had primary hypogonadism in which there was low testosterone and high LH. Our results are comparable to Alhayek et al (2013), who reported that 83.1% (330/397) of T2DM patients with reduced testosterone level had normal LH and 16.9% had primary hypogonadism.[24] Normal LH despite low serum testosterone in T2DM patients supports the theory that central depression might be a dominant mechanism of reduced testosterone in T2DM. One of the mechanisms responsible for reduced GnRH is hypothalamic insulin resistance. A theory supported by the stimulating effect of insulin on GnRH secretion and by the increased prevalence of hypothalamic hypogonadism in obese subjects in T2DM patients and in patients with metabolic syndrome, but not in T1DM.[25,26] In our study, the inappropriately low/normal LH despite reduced TST was not related to obesity. LH levels did correlate with neither WC nor BMI and 30% of patients with low TSH and normal LH were actually lean. This finding might suggest that the state of secondary hypogonadotropic hypogonadism in T2DM patients is not related to the amount of fat tissue mass. Nevertheless, direct measurements of cytokines, especially TNF-α and IL-6 together with Leptin would provide stronger evidence of the pathogenic mechanism.

6. CONCLUSION

This work showed a significant decrease in mean TST level in the obese and morbidly obese T2DM patients compared to the lean group. We also detected a trend of increasing prevalence of low TST levels along increasing BMI groups but the difference between groups did not reach statistical significance. Our study supported the significant correlation of TST with BMI and WC and that the majority of T2DM patients with low TST have secondary hypogonadotropic hypogonadism.

6.1 Limitations

The study did not include the measurement of bioavailable testosterone or SHBG due to unavailability of the required techniques.

6.2 Recommendations

Based on our finding we encourage that obese and morbidly obese T2DM patients should have their testosterone level measured whether they were symptomatic to hypogonadism or not. This might require studies that evaluate the cost effectiveness of this approach. We recommend for future studies to include measurements of bio-available testosterone, sex hormone binding globulin, estrogen, C reactive protein and adipocytokines based on availability, so as to provide a more detailed view into the pathogenesis of low TST level in T2DM patients in different societies.

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8. AUTHORS CONTRIBUTION STATEMENT

Dr FE Mohamad and Dr.Shaza Elawad conceptualized and gathered the data with regard to this work. Dr. Nisreen Daffa Alla and Dr Rehab Badi analyzed these data and necessary inputs were given towards the designing of the manuscript. All authors discussed the methodology and results and contributed to the final manuscript.

9. CONFLICT OF INTEREST

Conflict of interest declared none.

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