ORIGINAL ARTICLE

Hypogonadism and Subnormal Total Testosterone Levels in Men with Type 2 Diabetes Mellitus

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ABSTRACT

Objective: To determine the frequency of testosterone deficiency syndrome (TDS) in men with type 2 (DM).
Study Design: A cross-sectional study.
Place and Duration of Study: The Gbagada General Hospital, Gbagada Lagos, Nigeria, from December 2009 to May 2010.
Methodology: A total of 203 men with type 2 DM aged 30-86 years were evaluated for TDS by a combination of positive ADAM (androgen deficiency in the ageing male) scores and subnormal total testosterone levels. Mild testosterone deficiency referred to total testosterone (TT) levels of 8-12 nmol/L with symptoms of hypogonadism and severe testosterone deficiency referred to TT levels < 8 nmol/L with or without hypogonadal symptoms.
Results: Mild and severe TDS were present in 18.3% and 17% respectively of the study subjects. Commonly occurring clinical parameters of the TDS were erectile dysfunction and loss of libido which were documented in 63% and 60% respectively in the study subjects. The majority of clinical features of the TDS were comparable in men with and without the TDS.
Conclusion: About a third of men with type 2 DM had the TDS. The majority of the symptoms of hypogonadism are largely non-specific and their occurrence is comparable in men with and without low testosterone levels; thus, underscoring the need to have testosterone levels determined in men presenting with such symptoms.

Key words: *Hypogonadism. Type 2 diabetes mellitus. Total testosterone levels. Prevalence.*

INTRODUCTION

Diabetes mellitus (DM) is one of the most prevalent non-communicable diseases in Nigeria with a reported prevalence rate of 2.2%.[1] It is also one of the commonest reasons for medical admissions and deaths in Nigerian hospitals.[2,3] Reports abound in literature on the relationship between plasma testosterone and type 2 DM. Testosterone levels are not only lower in men with type 2 DM, but also that the risk of developing type 2 DM is increased in men with low testosterone levels.[4-5] Testosterone deficiency syndrome (TDS) or symptomatic hypogonadism is an entity characterized by clinical symptoms and biochemical parameters of testosterone deficiency.[6] The prevalence rate of symptomatic hypogonadism in men with type 2 DM is high and documented rates range from 20-64% with higher prevalence rates reported in the elderly.[7] Some of the clinical features of the TDS include diminished sexual function, changes in mood, decreased intellectual activity, fatigue, sleep disturbance, increased abdominal fat, decreased body hair and bone mineral density. The commonly documented feature of the TDS in men with DM is erectile dysfunction (ED); it is reported to be three times higher in men with DM than in those without DM.[8] In a report from United Kingdom (UK),[9] 20% and 31% of men with type 2 DM had total testosterone below 8 nmol/L and 12 nmol/L respectively. In an Asian report,[10] the prevalence of hypogonadism in men with type 2 DM aged between 28 and 80 years was reported to be 43%. In the same report, the prevalence

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of hypogonadism was noted to have increased from 63% among participants aged 30 through 39 years to 89% in participants aged 80 years and above.[10]

TDS is largely understudied in sub-Saharan Africa. It is imperative to note that the most widely accepted parameters to establish the presence of hypogonadism are the measurements of total testosterone and free testosterone calculated from measured total testosterone and SHBG or measured by a reliable free testosterone dialysis method. However, in a resource-poor endocrine practice, the facilities for measuring SHBG and free testosterone dialysis are unavailable.[11]

The aim of this study was the determination of the pattern and the frequency of occurrence of hypogonadal symptoms and sub-optimal testosterone levels in a clinic population of men with type 2 DM.

METHODOLOGY

This was a descriptive study involving 203 men with type 2 DM aged 30-86 years receiving care at a DM Clinic in Lagos, Nigeria. Ethical consent was obtained from the Hospital authorities and the study subjects gave informed written consent. This work was carried out from December 2009 to May 2010 in accordance with the ethical standards as stated by the Helsinki Declaration of 1983.

Exclusion criteria were prior / present treatment for hypogonadism with testosterone replacement or anti-androgens, documented history of prostate or testicular cancer, history of inflammatory diseases or acute infections and illnesses warranting hospitalization.

Demographic data, data pertaining to DM and hypertension, smoking and alcohol ingestion were documented. The ADAM questionnaire was used for obtaining information pertaining to features of hypogonadism.[12] Other findings documented from clinical examination included body mass index (BMI) and waist circumference measurements. The waist circumference measurement was determined by applying a measuring tape to the midpoint between the inferior margin of the last rib and the crest of the ilium.

Biochemical data were obtained for blood glucose and total testosterone (TT) determinations. Venous blood samples were collected in a fasting state before 10 a.m. in the morning for the analysis of the aforestated biochemical parameters. Blood glucose analysis was done using the glucose oxidase method. The intra and inter-assay coefficient of variation for glucose were 3.45% and 1.33%. respectively. TT estimation was carried out by an enzyme immunoassay technique which is a one-step technique that utilized equal molecular antigen-antibody on microplate wells. Samples of blood were centrifuged and supernants stored at 20°C to ensure pre-analytical uniformity of assay. All assays were done in duplications. The absorbance values of each calibrator controls and test samples duplicate were calculated and concentration of calibrations plotted against their respective absorbance and the values of samples concentrations read off the graph.

The mean detectable concentration (analytical sensitivity) was 0.2 nmol/l; assay dynamic range 0-40 nmol/l; inter-assay precision CV 4.95%; intra assay precision was 6.8%.

Testosterone deficiency syndrome or symptomatic hypogonadism defined a combination of clinical symptoms and biochemical evidence of testosterone deficiency. Mild TDS referred to TT of 8-12 nmol/L with symptoms of hypogonadism or levels of < 8 nmol/L with or without symptoms of hypogonadism.[11] The clinical symptoms of hypogonadism were said to be present if there was a positive answer to question 1, or 7 or more than 3 other questions.[12] Obesity referred to a BMI of ≥ 30 kg/m^2.

Statistical analysis was carried out on SPSS 17. Continuous variables were expressed as means and standard deviation (SD). Testosterone levels were expressed as quartiles. The baseline differences between men with mild, severe and normal testosterone levels were determined with analysis of variance (ANOVA) and chi-square. Clinical and biochemical parameters were compared between men with and without ED using the Mann-Whitney U test. P-values of < 0.05 were considered statistically significant.

RESULTS

The mean age of the study subjects was 61.4 years and the majority of them were on oral hypoglycaemic agents. These results are shown in Table I.

Smoking and alcohol consumption were documented in 51 (25%) and 78 (38%) of the study subjects respectively. History of hypertension was recorded in 97 (47%).

The mean (SD) testosterone level was 17 ± 9.2 nmol/L and the range was 0.2-37.5 nmol/L. The quartiles of testosterone levels showed the values of testosterone at 25, 50 and 75 percentiles are 10.6 nmol/L, 15.7 nmol/L and 22.6 nmol/L respectively. The distribution of various cadre of testosterone levels showed that 36% of the study subjects had symptomatic hypogonadism of which 17.7% and 18.3% had severe and mild testosterone deficiency respectively. All the subjects with subnormal testosterone levels had diagnostic clinical parameters of hypogonadism. The commonly documented features of hypogonadism included erectile dysfunction and reduced libido. Reduced bodily hair and increased sweating were documented in 11 (5%) and 23 (11%) respectively of the study subjects. The proportion of subjects with reduced bodily hair was significantly higher in those with testosterone deficiency compared with those of normal testosterone levels {9 (12.3%) vs. 2 (1.5%), p=0.0001}. Increased sweating was noted more, in subjects with testosterone deficiency compared with men without hypogonadism and this difference was statistically significant {13 (18%) vs. 10 (8%), p=0.02}. A comparison of the frequency of occurrence of the TDS parameters using the ADAM questionnaire in the

Table I: Baseline characteristics of the study subjects.

Parameters	Value	Range
Age (years)	61.4 ± 11.2	30-85
BMI (kg/m²)	26.1 ± 5.7	15.3-42.9
Duration of DM (years)	7.2 ± 6.9	0.1-30
WC (cm)	91.4 ± 12.2	66-132
Marital status		
Married	177 (95.7%)	
Divorced	2 (1.1%)	
Widowed	4 (3.2%)	
Glucose lowering medications (n)		
Oral hypoglycemics (OHA)	166 (82%)	
Combination of insulin and OHA	22 (11%)	
Insulin	15 (7%)	

Table II: Comparison of the clinical features of TDS in subjects with normal and subnormal testosterone levels.

TDS parameter	All subjects 203 (%)	TT deficiency 73 (%)	Normal TT 130 (%)	p-value
Reduced libido	122 (60%)	60 (82%)	62 (48%)	< 0.001
Lack of energy	79 (39%)	36 (49%)	43 (33%)	0.02
Decreased stamina	75 (37%)	32 (44%)	43 (33%)	0.1
Loss of height	14 (7%)	7 (10%)	7 (5.4%)	0.2
Decreased "enjoyment of life"	21 (10%)	10 (14%)	11 (8.5%)	0.2
Feeling sad and grumpy	19 (9%)	10 (14%)	8 (6%)	0.07
Weak erection	128 (63%)	49 (67%)	79 (61%)	0.3
Reduced exercise	88 (43%)	35 (48%)	53 (41%)	0.3
Falling asleep after dinner	59 (29%)	25 (34%)	34 (26%)	0.223
Reduced work performance	30 (15%)	15 (21%)	15 (12%)	0.08

Table III: Comparison of some clinical and biochemical profile of subjects with and without symptomatic hypogonadism.

Variables	Normal status (130)	Mild hypogo-nadism (38)	Severe hypo-gonadism (35)	p-value
Age (years)	61 (10.7)	64.6 (12)	60 (10.7)	0.140
BMI (kg/m²)	26.1 (5)	26 (5.8)	27.6 (7.4)	0.347
WC (cm)	91.2 (11.8)	91.7 (11.2)	91.8 (14.9)	0.954
Testosterone (nmol/L)	22.1 (7.3)	10.6 (1)	5.1 (2)	< 0.001

Table IV: Association of low testosterone levels with some clinical parameters.

Clinical parameters	TT > 12 nmol/L	TT 8-12 nmol/L	TT < 8 nmol/L	p-value
Hypertension	59 (45%)	22 (60%)	13 (36%)	0.194
Obesity	22 (17%)	7 (19%)	13 (36%)	0.030
Central obesity	20 (15.4%)	7 (19%)	12 (33%)	0.041
Smoking history	24 (19%)	13 (35%)	14 (40%)	0.01
Alcohol history	41 (31.5%)	18 (49%)	19 (53%)	0.02
TT > 12 nmol/L (130)	TT 8-12 nmol/L (38)	TT < 8 nmol/L (35)		

subjects with normal testosterone and reduced testosterone levels are shown 1 in Table II.

The highest frequency of occurrence of severe and mild testosterone levels were noted in the eight and sixth decades respectively. The stratification of the prevalence of hypogonadism by age decades is shown in Figure 1.

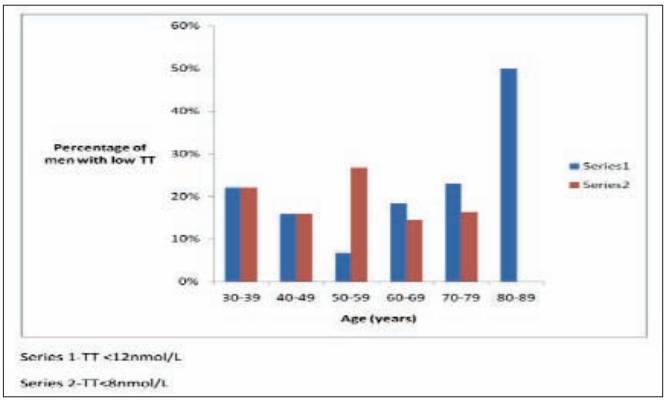

Figure 1: The frequency of occurrence of hypogonadism by age decades.

Using the one way ANOVA to compare continuous data amongst the three cadre of testosterone levels, there were no detected differences for the testosterone levels. These results are shown in Table III.

Fasting plasma and 2 hours postprandial glucose levels were checked for normality using the Kolmogorov-Smirnov test and a p-value of < 0.0001 was obtained. The Mann-Whiney U test was then used to compare the medians of both parameters and the results showed that both level were significant p=0.86 for FPG and p=0.94 for 2HPP both different in hypogonadal and non-hypogonadal men.

However, a comparison of the presence of obesity, central obesity, hypertension significant smoking and alcohol histories by proportions showed some significant associations. These results are shown in Table IV.

Thirty Nine (30%) of the subjects with ED had subnormal testosterone levels and 25 (20%) of the subjects with ED had discussed this problem with their health care givers. Twelve (9%) subjects with ED admitted this to be a source of problems between them and their spouses/partners. Twelve (9%) subjects with ED had used medications for their sexual dysfunction and 5 (4%) had used phosphodiesterase 5 inhibitors. Seven (5.5%) resorted to use of herbal therapies provided by friends/neighbours.

TT levels were significantly lower in men with ED compared with men without ED (37 vs. 138.5, p=0.0001). All other studied clinical and biochemical parameters (age, BMI, WC, duration of DM, FBS, 2HPP) were comparable in both groups.

DISCUSSION

Male hypogonadism has been noted to occur frequently in type 2 DM 12-13. This report demonstrated that a third of Nigerian men with type 2 DM had TDS. The frequency of occurrence of the TDS in this report is comparable to that from a UK study[9] but lower than the prevalence rates documented in an Asian report.[11]

The symptoms of TDS are often non-specific. Save for a reduction in libido and reduction in strength, the presence of other TDS symptoms assessed by the ADAM questionnaire was comparable in the subjects with normal and subnormal testosterone levels. Therefore, we cannot conclude that the ADAM questionnaire is completely valid for the assessment of the clinical symptoms of hypogonadism in Nigerian men with type 2 DM. As reported elsewhere,[14] ED was a common complaint in the study subjects and with reduced libido, were the prevalent clinical features of the TDS. Reported prevalence rates of ED in DM range from to 30-90%.[15,16] Some features of the TDS not included in the ADAMS questionnaire, but which were found to be of significance in this report was reduction in bodily hair, the decreased need to shave and increased sweating. The proportion of subjects with histories of

reduced need to shave and increased sweating was significantly higher in those with subnormal testosterone levels when compared with those with normal testosterone levels. In the Nigerian context, there might be a need to incorporate these TDS defining parameters in studies addressing male hypogonadism.

The findings support the role of testosterone in the maintenance of male sexual functioning. There was a significant difference in testosterone levels between subjects with ED and those without ED and in a third of the subjects with ED, testosterone deficiency was a potential contributory factor. Bodie *et al.* found that 18% of men with ED had subnormal testosterone levels.[17] Studies have shown that circulating androgens are not only important mediators of the erectile process, regulating arterial flow and vasodilation, but also stimulate the central mechanism of sexual activity.[6,18]

The median testosterone level in this report was 15.7 nmol/L and the prevalence rates of mild and severe TDS was18.3% and 17.7% respectively. Kapoor *et al*. reported the prevalence rates of mild and severe TDS to be 17% and 25 % respectively when total testosterone was estimated.[9] It is pertinent to note that sex hormone binding globulin (SHBG) which accounts for 60-80% of testosterone binding rises with age and may serve as a confounding factor when total testosterone is used solely in the evaluation of testosterone levels. Low levels of SHBG on the other hand may occur in the presence of insulin resistance; thus, resulting in low total testosterone levels. 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. However in the above study, the prevalence rates of mild and severe TDS using bioavailable testosterone assessments were found to be comparable to those obtained using total testosterone levels.[9]

Although the increase in the frequency of occurrence of the TDS from age 60 through 69 to 80 years and above, there was no significant difference in the mean age of the subjects with normal, mild and severe TDS. Significant associations were found between obesity, smoking and alcohol histories and subnormal testosterone levels. Kapoor *et al*. had reported significant associations of low testosterone levels with not only obesity, but also with visceral adiposity.[9]

Testosterone replacement not surprisingly has been shown to decrease visceral fat mass, increase lean body mass as well as improve insulin sensitivity which is negatively affected in the presence of visceral adiposity.

Hypertension, a frequently occurring co-morbidity in Nigerians with DM[3] was noted in 47% of the study subjects. We could not assess the influence of hypertension on testosterone levels but we report comparable mean levels of testosterone in subjects with and those without hypertension. The presence of ED was also comparable in subjects with and without hypertension. Kapoor *et al*.[9] also reported a lack of significant association between hypertension and testosterone levels. Although we have not showed a clear relationship between the presence of hypertension and male sexual dysfunction, one may safely infer that the presence of hypertension is unlikely to have a bearing or strong influence on sexual functioning in men with DM if at all. Conversely, a study in men with DM found no effect of testosterone replacement of blood pressure readings.[19]

Sexual dysfunction is not an often discussed problem in our practice. From the present results it is observed that only a fifth of people with ED discussed this problem with their doctor. There results also show gross under treatment of this disorder which is noted to cause friction between partners in 9% of people who have the problem.

In this report, even though we did not have a control group of non-diabetic men, it is pertinent to note that the TDS have been documented more frequently in men with DM than in non-diabetic men.[20] In the Rancho Bernardo study which involved 985 men aged 40-79 years (an age group comparable with study subjects). 110 men with Diabetes had lower total testosterone levels and lower SHBG levels than did the non-diabetic men, even after adjustment for BMI and age.[20] In the same report, 21% of diabetic men compared with 13% of non-diabetic men had suboptimal testosterone levels.[20]

Limitations of this study need to be mentioned. The sample size was relatively small; largely due to technical and financial constraints. Testosterone was not measured by mass spectrometer technology because this technique is not available in Nigeria. Measuring bioavailable testosterone would have been ideal, but this is not available in this practice hence, the report was limited to the determination of total testosterone levels.

CONCLUSION

The prominent features of the testosterone deficiency syndrome in Nigerian men with type 2 DM are loss of libido and erectile dysfunction. This study has demonstrated the importance of assessing testosterone levels in men with clinical features of hypogonadism because of the non-specificity of these clinical parameters.

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