WEST AFRICAN JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Relationship between Serum Testosterone Levels and Features of the Metabolic Syndrome Defining Criteria in Patients with Type 2 Diabetes Mellitus

Relation entre taux de testostérone sérique et des caractéristiques du syndrome métabolique Définition des critères chez les patients avec diabète de Type 2

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ABSTRACT

BACKGROUND: **There are increasing reports on the association between the testosterone deficiency syndrome (TDS) and increased risk of development of the metabolic syndrome – a well recognized cardiovascular risk factor in men with diabetes mellitus.**

OBJECTIVE: **To determine the relationship between serum testosterone levels and components of the metabolic syndrome in Type 2 diabetes mellitus in Nigerian men.**

METHODS: **A total of 203 men with type 2 DM aged 30–86 years were evaluated for the testosterone deficiency syndrome (TDS). The diagnosis of the TDS or hypogonadism was made using a combination of clinical features of hypogonadism and subnormal levels of total testosterone. The presence of the metabolic syndrome was sought for in those with and without the TDS. The metabolic syndrome was diagnosed using the new criteria by the International Diabetes Federation and related bodies.**

RESULTS: **The overall prevalence rates of the TDS and the metabolic syndrome in the study subjects were 36% and 44% respectively. The proportion of the subjects with the Metabolic Syndrome (METS) was comparable in subjects with and without the TDS. (47% vs 43%, p = 0.6). Using the Mann Whitney U test, the mean rank of the testosterone level in the subjects with the METS was lower than that of those without the METS but this difference was not statistically significant (67.2 vs 66, p = 0.9).**

CONCLUSION: **The frequency of occurrence of the metabolic syndrome in men with type 2DM is comparable in those with hypogonadism and those without hypogonadism. There is no correlation between serum testosterone levels and the metabolic syndrome defining parameters. WAJM 2011; 30(4): 277–281.**

Keywords: **Hypogonadism, testosterone deficiency syndrome, metabolic syndrome, type 2 diabetes mellitus.**

RÉSUMÉ

CONTEXTE: Il ya des rapports plus en plus sur l'association entre le syndrome de déficience en testostérone et le risque accru de développement du syndrome métabolique - un facteur de risque bien reconnu cardiovasculaires chez les hommes atteints de diabète sucré.

OBJECTIF: Déterminer la relation entre les taux sériques de testostérone et les composants du syndrome métabolique chez un diabète de type 2 chez les hommes nigérians.

Méthodes: Un total de 203 hommes diabétiques de type 2 âgés de 30 à 86 ans ont été évalués pour le syndrome de déficience en testostérone (TDS). Le diagnostic de la TDS ou hypogonadisme a été faite en utilisant une combinaison de caractéristiques cliniques de l'hypogonadisme et les niveaux sous la normale de la testostérone totale. La présence du syndrome métabolique a été recherché dans ceux avec et sans le TDS. Le syndrome métabolique a été diagnostiqué en utilisant les nouveaux critères de la Fédération Internationale du Diabète et des organismes connexes.

RÉSULTATS: Le taux de prévalence globale de la TDS et le syndrome métabolique chez les sujets de l'étude étaient de 36% et 44% respectivement. La proportion des sujets ayant un syndrome métabolique (MET) a été comparable chez les sujets avec et sans la TDS. (47% vs 43%, p = 0,6). Utiliser le test U de Mann-Whitney, le rang moyen du niveau de testostérone chez les sujets avec les Mets a été inférieur à celui de ceux qui n'ont pas du METS, mais cette différence n'était pas statistiquement significative (67,2 vs 66, p = 0,9).

CONCLUSION: La fréquence de survenue du syndrome métabolique chez les hommes avec 2DM type est comparable à ceux atteints d'hypogonadisme et ceux sans hypogonadisme. Il n'ya pas de corrélation entre les taux sériques de testostérone et le syndrome métabolique définir les paramètres. **WAJM 2011; 30 (4): 277–281.**

Mots-clés: hypogonadisme, syndrome de déficience en testostérone, le syndrome métabolique, diabète de Type 2.

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Abbreviations: BMI, Body mass index; **FBS,** Fasting Blood Sugar; **HDLC,** High density lipoprotein cholesterol; **LDLC,** Low density lipoprotein cholesterol; **TC,** Total cholesterol; **TG,** Triglyceride; **WC,** Waist circumference; **METS,** Metabolic Syndrome; **TDS,** Testosterone deficiency syndrome

INTRODUCTION

The disease burden of DM in developing countries is unacceptably high[1] with cardiovascular morbidity being a prominent feature. The metabolic syndrome (METS) which is a notable cardiovascular (CV) risk factor has been noted to occur in a large majority of patients with type 2 DM or impaired glucose tolerance.[2] In men, testosterone deficiency may contribute to the development of the metabolic syndrome[3] thus placing such men at greater CV risk than those without it. The reported prevalence rates of hypogonadism in men with DM range from 20–64% with higher prevalence rates documented in the elderly.[4] The METS is characterised by a clustering of clinical and biochemical parameters such as central obesity, insulin resistance, atherogenic dyslipidemia, and hypertension. It occurs in 59% to 61% of people with DM.[5–7]

Recent reports suggests an evolving role of testosterone deficiency in the occur-rence of the METS and cardiovascular disease.[8] Lower total testosterone levels and sex hormone binding globulin levels predict a higher incidence of the METS in men. Suggested possible underlying pathophysiological basis for this scenario in men with Type 2 DM include insulin resistance, visceral obesity and adipocytokines which are produced by adipocytes and contribute to reduced insulin sensitivity.[8] Low levels of testos-terone have been found to be associated with visceral obesity and pro-inflammatory profile in men with DM[9] and this further lends credence to the possible relationship of testosterone deficiency to increased cardiovascular risk.

Although different cross-sectional and longitudinal studies have documented a strong association between hypogonadism and diabetes mellitus as well as with metabolic syndrome, only limited data have reported an improvement of insulin resistance by treating hypogonadal diabetic subjects with testosterone.[10–12] Accordingly, current guidelines do not recommend widespread testosterone replacement therapy in subjects with METS or diabetes mellitus.[13]

Although DM-related cardiovascular disease is a significant cause of morbidity and morbidity in Nigerians , the potential relationship between hypogonadism and the metabolic syndrome in Nigerian men with DM is yet to be described.

The aim of this study was therefore to determine relationship between serum testosterone levels and features of the metabolic syndrome in Type 2DM. We also sought to compare the presence of the METS in hypogonadal and non hypogonadal men.

SUBJECTS, MATERIALS, AND METHODS

This was a descriptive study involving 203 men with type 2 diabetes mellitus aged 30–86 years receiving care at the DM clinic of the General hospital, Gbagada, an urban hospital in Lagos state in South Western region of Nigeria. Nigeria. Subjects who met the inclusion criteria and gave their consent were recruited. The inclusion criterion was a diagnosis of type 2 diabetes mellitus in men who gave voluntary informed consent. Exclusion criteria were as follows: Prior or Present treatment for hypogonadism with testosterone replacement, with anti androgens, documented history of prostate or testicular cancer, history of inflammatory diseases or acute infection and illness warranting hospitalisation.

Ethical approval was obtained from the hospital authorities and the study subjects gave informed written consent. This work was carried out in from December 2009 to May 2010 and it was in accordance with the ethical standards as stated by the Helsinki Declaration of 1983.

The clinical parameters that were obtained via interviewer administered questionnaires included history of DM, hypertension, smoking and alcohol ingestion. Anthropometric mearsurements and biochemical tests were carried out on the study subjects.

Hypogonadism was diagnosed using low serum testosterone levels together with one or more clinical symptoms or signs. These symptoms included reduced libido, erectile dysfunction (ED), diminished penile sensation, difficulty attaining orgasm, as well as reduced ejaculate with orgasm. Other symptoms included reduced energy, depression, increased irritability, difficulty concentrating and hot flushes.[14]

Body mass index was obtained from the measurements of the weight (Kg) and height (m), using the formula: Kg /m^{-2}.[15] The waist circumference (WC) was measured at a point midway between the iliac crest and the lowest rib.[15]

Biochemical Assessment: The laboratory parameters that were assessed included total testosterone (TT), total cholesterol (TC), high density lipoprotein (HDL-C), low density lipoprotein (LDL-C), triglycerides (TG)) and blood glucose. Venous blood samples were collected in a fasting state in the morning between 8am –10 am for analysis of the aforestated biochemical parameters. After centrifugation plasma samples were analysed within 48 hours. Total cholesterol assay was done using the modified Liebermann-Burchard's method,[16] LDL-C was calculated using the Friedwalds's formula[17] and TG levels were obtained using enzymatic colorimetric methods.[18]

Total testosterone estimation was carried out by an enzyme immunoassay technique.[19] All assays were done in duplicates and absorbance values were measured on an automated ELISA microwell reader at 450nm. The minimum detectable concentration (analytical sensitivity) was 0.2nmol/l; assay dynamic range 0–40 nmol/l; inter-assay precision CV 4.95%; intra-assay precision was 6.8%. Blood glucose analysis was done using the glucose oxidase method.[15] The intra and inter-assay coefficient of variation for glucose were 3.45% and the inter-assay CVs was 1.33% respectively.

Operational Definitions

Metabolic Syndrome: This was taken as the presence of three or more of any of the following: waist circumference (WC) greater than 102 cm; serum triglycerides (TG) $\geq$150 mg/dL (1.69 mmol/L); high-density lipoprotein cholesterol (HDL-C) level $\leq$ 40 mg/dL (1.04 mmol/L) and blood pressure of at least 130/85 mm Hg.[20]

Testosterone deficiency syndrome or symptomatic hypogonadism refers to a combination of clinical symptoms and

biochemical evidence of testosterone deficiency. Testosterone deficiency included total testosterone (TT) level below 8 nmol/L or a total testosterone level > 8 and < 12 nmol/L. Mild TDS refers to TT of 8–12 nmol/L with symptoms of hypogonadism or levels of <8nmol/L with or without symptoms of hypogonadism.[13]

Statistical Analysis

Test statistics used included Student's t-test for continous variables, chi square to test for association between categorical variables and correlation coefficient to test for the association of testosterone and some biochemical parameters. The statistical package used was SPSS version 17. P values of <0.05 were considered statistically significant.

RESULTS

Summary of the Clinical Parameters of the Study Subjects.

The mean (range) of age of the study subjects was 61.4(30–85) years. The large majority, 177(95.7%), of the study subjects were married, Of whom 166(82%) of the patients were on oral hypoglycaemic agents, 22 (11%) were on insulin and oral agents combination, while 15(7%) were on sole insulin therapy. The mean duration of DM was 7.2 years with a range of 0.1–30 years.

Hypertension was a co- morbidity noted in 97 (47%) of the subjects. Past histories of cerebrovascular accident and heart failure were documented in 13 (7%) and 6 (3%) of the study subjects respectively.

Prevalence of the Testosterone Deficiency Syndrome and the Metabolic Syndromes

The overall prevalence of the TDS was 36%. The mean age (range) of the subjects with TDS was 62 (32–85) years. The mean (SD) of the testosterone levels in subjects with TDS was 7.9(3.2) nmol/L The median testosterone levels in this group of people was 8nmol/L. A comparison of some of the clinical and biochemical features of subjects with and without hypogonadism showed that except for LDLC, all compared parameters were comparable in both groups of the study subjects (Table 1).

The METS was present in 90 of the study subjects thus giving an overall prevalence of 44.3%. The prevalence of the METS in the men with subnormal testosterone levels was higher than that of those with normal testosterone levels but this difference was not statistically significant. (47% vs 43%, p=0.6). Mean testosterone levels were lower in the subjects with METS than in the subjects without the METS but this difference was not statistically significant (17.6nmol/L vs 16.3nmol/L, p=0.3).

Using Pearson's correlation coefficient analysis, there were no significant associations between testosterone and the studied biochemical and clinical parameters as displayed in Table 2.

Table 1: Clinical and Biochemical Variables in Type 2 Diabetes Subjects with and without Hypogonadism

Variable	Mean (SD)		p
	Subjects with Hypogonadism	Subjects without Hypogonadism	
Age(years)	61.7(12.2)	61.2(10.4)	0.7
TC (mg/dl)	179.7(48.1)	170.5(37.2)	0.1
LDLC (mg/dl)	134.4(80.4)	115.5(39.4)	0.02
HDLC (mg/dl)	39.9(13.5)	38.2(12.6)	0.9
TG (mg/dl)	100.5(46.9)	97.8(48.8)	0.6
FBS (mg/dl)	139(72.2)	144.1(81.1)	0.4
2HPP (mg/dl)	191.7(84.2)	194.7(78.0)	0.8
WC (cm)	91.8(13.1)	91.2 (11.7)	0.7

FBS, *Fasting Blood Sugar;* ***HDLC,*** *High density lipoprotein cholesterol;* ***LDLC,*** *Low density lipoprotein cholesterol;* ***TC,*** *Total cholesterol;* ***TG,*** *Triglyceride;* ***WC,*** *Waist circumference;*

Of the components of METS, reduced HDLC was the prevalent defining criteria documented in subjects with normal and subnormal testosterone levels. The distribution of the components of the METS was comparable in subjects with and without hypogonadism (Table 3).

The distribution of hypogonadal men with METS by age is shown in Figure 1. Hypogonadal men with the METS were significantly older than those without the METS (66.1 vs 58 years, p 0.007).

Cardiovascular Events and Risk Factors

A total of 18 (9%) and 9 (4.5%) subjects had past histories of cerebrovascular (CVA) disease and heart failure respectively. The proportion of subjects with hypogonadism who had CVA was statistically significantly higher than those without hypogonadism (11% vs 5%, p=0.04). Mean testosterone levels were lower in men with significant smoking (13nmol/l vs 18.3nmol/l, p=0.0001) and alcohol histories not defined (8.4 9.9nmol/l, p=0.001)) compared to men without such histories.

DISCUSSION

This report has shown that the prevalence rate of the metabolic syndrome in diabetic men with the testosterone deficiency syndrome is comparable to that in non hypogonadal men with type 2 DM . The prevalence rate of the testosterone deficiency syndrome in this report was 38%; this is lower than that reported by Dhindsa *et al*[21] but comparable to the findings of Kapoor *et al.*[22] There was no distinction made between primary and secondary hypogonadism in this report and it is not known if this would have affected the outcome on findings related to the metabolic syndrome. The combination of testosterone deficiency and associated clinical features often go unrecognized in endocrine clinics of developing economies like Nigeria. Hypogonadism although often unrecognised, but unfortunately commonly occurring, has been suggested to be a possible aetiological factor in the development of the metabolic syndrome in men.[23–25] Unlike other reports, we have documented

Table 2: Pearson's Correlation Coefficients between Testosterone vs Clinical and Biochemical Variables

Variable	Correlation coefficient (r)	p
LDLC vs T	–0.12	0.2
TG vs T	0.8	0.4
HDLC vs T	–0.2	0.8
TC vs T	–0.1	0.4
DM Duration vs T	–0.01	0.8
BMI vs T	0.09	0.5
WC vs T	–0.07	0.5
Age vs T	–0.09	0.8

BMI, *Body mass index;* ***DM,*** *Diabetes Mellitus;* ***HDLC,*** *High density lipoprotein cholesterol;* ***LDLC,*** *Low density lipoprotein cholesterol;* ***T,*** *testosterone;* ***TC,*** *Total cholesterol;* ***TG,*** *Triglyceride;* ***WC,*** *Waist circumference;*

Table 3: Frequency of METS defining Characteristics in Subjects

Variable	Number (%)		
	Subjects with TDS	Subjects without TDS	p
Hypertension	35(48)	59(45)	0.7
Elevated TG	9(12)	15(11)	0.9
Reduced HDLC	43(59)	78(60)	0.8
Elevated WC	18(25)	19(15)	0.07

HDLC, *High density lipoprotein cholesterol;* ***TG,*** *Triglyceride;* ***WC,*** *Waist circumference;*

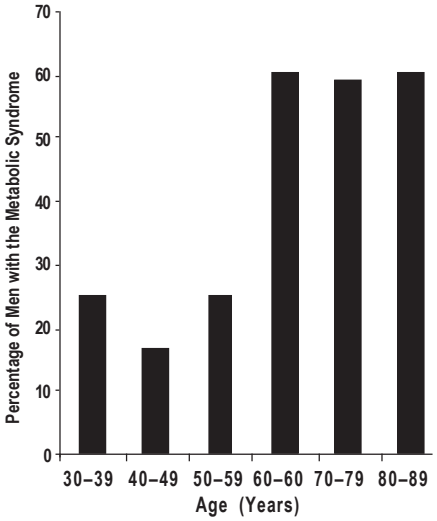

Fig.: Relationship between Age and Occurrence of Metabolic Syndrome in Hypogonadal Diabetic Men

comparable prevalence rates of the METS in subjects with and those without the TDS.

In their study of 800 men who were being evaluated for sexual dysfunction, Corona *et al* [26] noted the presence of the METS in 29.4% of the study population. The presence of type 2DM in our study subjects may be contributory to our documented overall prevalence rate of METS which was 44%.

Unlike findings by Kapoor *et al,*[22] we found no significant association between testosterone and anthropometric indices. The body composition of African men which has been understudied may be appreciably different from that of men from other regions of the world and thus the available normative cutoffs may not be applicable to Africans. These observations may be some of the contributory factors for the high frequency of occurrence of the METS in Africans. In the United States of America, the prevalence rate of the METS in African-Americans is high.[27] Documented prevalence rates of the METS in Nigerians with type 2 DM range from to 59%–86%.[5,28] The prevalence of the METS in the hypogonadal subjects was found to increase with increasing age. The prevalence of the METS in the TDS subjects increased from 25% in hypogonadal men aged 50 through 59 years to 60% in those over 80 years of age. This observation had been noted by in a report on the assessment of the prevalence and gender distribution of the METS in people with type 2 DM.[28] It is pertinent to note that although the mean age of the study subjects with the METS was comparable to those without the METS, in hypogonadal men. However, those who had the METS were significantly older than those without the METS.

Evaluation of the clustering of the components of the METS showed that the commonly occurring parameters of the METS, which were essentially reduced HDL-C and hypertension were also noted to follow the same pattern in non hypogonadal men. Elevated low density lipoprotein cholesterol, a notable cardio-vascular risk factor was found in this report to be significantly higher in hypogonadal men than in men without hypogonadism. Although the focus of this report is on the METS in hypogonadism, it is pertinent to note that risk factors for cardiovascular events (significant smoking and alcohol histories) were documented more in hypogonadal subjects than non hypogonadal subjects. There are differing reports on the impact of smoking on testosterone levels. Whilst some studies report a decline in testosterone[29] levels with smoking, some have noted comparable androgen levels in smokers and non smokers[30] and yet some others have documented higher testosterone levels in smokers compared to non smokers.[31] Our findings of lower testosterone levels in cigarette smokers compared to non smokers are comparable to that of a previous Nigerian report.[32]

Antihypertensive agents which could cause erectile dysfunction such as alpha methyl dopa, beta blockers and diuretics were not sought out for in those who were hypertensive and it is doubtful if these drugs actually reduce the levels of testosterone which is the key defining feature of hypogonadism.

Limitations

Free testosterone and sex hormone binding globulin analyses which are preferable to total testosterone could not be done. The chronic complications of DM and long term glucose control were not evaluated for. Follicle stimulating and luteinizing hormonal levels were not determined so we were not able to classify the type of hypogonadism, whether primary or secondary.

Acknowledgement

I wish to acknowledge Dr W. Ajala who helped with the laboratory work.

Conclusion

The prevalence of the metabolic syndrome in hypogonadal men with type 2DM is comparable to that of non hypogonadal men with type 2 DM. There is no correlation between serum testosterone levels and the metabolic syndrome defining parameters.

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