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Full Length Research paper

Serum testosterone and lipids in relation to sexual dysfunction in males with metabolic syndrome and type 2 diabetes mellitus

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Low serum testosterone is associated with insulin resistance, metabolic syndrome (case 1), type 2 diabetes mellitus (case 2), and cardiovascular disease. This study aims at identifying possible alterations in circulating testosterone and their relationship with plasma lipids in case1 and case2. Ninety-two male subjects were recruited in this prospective, cross-sectional study from two major hospitals in Ibadan and environs, Nigeria. Demographic, sexual and anthropometric characteristics were obtained from questionnaires by use of standard methods. Blood samples (10 ml) were obtained for determination of glucose, total cholesterol, triglycerides and high density lipoprotein by enzymatic methods while low density lipoprotein was calculated. Testosterone was analysed by Enzyme Immunoassay (Fortress Diagnostics, UK.). SPSS software version 16.0 was used for statistical analysis to find associations and relationships. Significantly lower concentrations of testosterone and high density lipoprotein, but higher concentrations of glucose in case 1 and 2 groups were observed compared with controls ($p<0.05$). Testosterone correlated positively with libido and nocturnal/early morning erection but inversely with erectile dysfunction only in case 2 ($p<0.05$). Deficient glucose uptake by the pituitary and the gonads and low circulating high density lipoprotein, consequence of insulin resistance could lead to hypogonadism. Dietary modulation and exercise may therefore be beneficial.

Key words: Type 2 diabetes mellitus, metabolic syndrome, testosterone, dyslipidaemia.

INTRODUCTION

Diabetes mellitus (DM) is one of the most prevalent problems in the elderly (Luchsinger et al., 2001*)* with metabolic syndrome (MS) as a major risk factor (Ashraf-Sohail et al., 2006). It is characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both (Mayfield, 1998; WHO, 1999). It represents one of the greatest threats to global health (Agbaje et al., 2007), with a prevalence rate of 2.7% of DM among Nigerians (Akinkugbe, 1997), over 90% of which is type2 diabetes mellitus (DM2) (Alberti et al., 1990). Metabolic syndrome increases the risk of developing cardiovascular diseases and DM 2 (Ford et al., 2002; Wild et al., 2004). It is a cluster of abnormalities including central (abdominal) obesity, high blood pressure, high triglycerides, low high density lipoprotein-cholesterol (HDL-C) and insulin resistance (IDF, 2005). However, abdominal obesity and insulin resistance appear to be the dominant risk factors for MS (Stumvoll et al., 2000; NCEP/ATP111, 2001). Free fatty acids that are released from visceral fat drain into the portal circulation and go directly to the liver (Kershaw and Flier, 2004; Gastaldelli et al., 2007). The increased flux of free fatty acids from visceral fat through the liver can promote

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gluconeogenesis and hepatic insulin resistance and lead to an accelerated synthesis of very-low density lipoprotein and increased triglyceride levels (Stolar, 2007; Gastaldelli et al., 2007). The triglycerides are diverted from adipose tissue and stored in non-adipose cells and tissues, such as hepatocytes and skeletal muscle (Garg, 2006; Laclaustra et al., 2007; Qatanani and Lazar, 2007). The accumulation of fat in non-adipose cells and tissues contributes further to insulin resistance in these areas, probably by interfering either directly or indirectly, with insulin signaling pathways (Dandona et al., 2005).

One of the complications of DM is the disturbance of sexual and reproductive functions (David and Hunter, 2004; Bhasin et al., 2006). Low circulating testosterone concentration is frequently found in men with MS and DM2 (Dhindsa et al., 2004; Lee et al., 2005; Mulligan et al., 2006; Arver, 2008; Jones, 2008). There is increasing recognition that this hypotestosteronaemia is associated with important cardiovascular risk factors such as visceral obesity, insulin resistance and dyslipidemia (Shores et al., 2006). Whitsel et al. (2001) reported that testosterone reduced total cholesterol and LDL-C while Roger et al. (2007) reported a positive association between HDL-C and testosterone in men with DM2. Well controlled diabetes mellitus had been associated with a normal physiological endocrine testicular function, as shown by plasma androgen levels within physiological range (Handelsman et al., 1995). However, it is not fully clear whether or not this testosterone deficiency is a risk factor for, or a consequence of MS and subsequently DM2 (Bhasin et al., 2006).

The mechanisms by which MS induces hypogonadism are increasingly being elucidated. Firstly, it is postulated that as a key factor in MS, abdominal obesity is associated with low testosterone level and low level of testosterone in turn is a risk factor for development of the MS, thus producing a vicious circle. The male hypogonadal state plays a central role in the development of MS in younger as well as elderly males while reduced risk of developing MS is associated with increased testosterone levels (Muller et al., 2005; Kapoor et al., 2007).

Secondly, insulin has been shown to play a central role in the function of the pituitary and gonads (Adashi et al., 1981; Goodner and Freinkel, 1961; Garris et al., 1984; Kirchick et al., 1979; Bestetti et al., 1985; Seethalakshmi et al., 1987). It enhances luteinizing hormone releasing hormone (LHRH)-induced gonadotrophin secretion *in vitro* (Adashi et al., 1981). A reduced glucose utilization by the anterior pituitary cells, and a decreased response of follicle stimulating hormone (FSH) and luteinising hormone (LH) to gonadotrophin releasing hormone (GnRH) administration has been shown in insulin-deficient rats (Goodner and Freinkel, 1961; Garris et al., 1984; Kirchick et al., 1979; Bestetti et al., 1985; Seethalakshmi et al., 1987).

In Nigeria, studies on sexual and reproductive functions in males with MS and DM2 are sparse. This study therefore aims at determining testosterone and lipid levels in subjects with MS and DM2 which may assist in prevention and management of their sexual and reproductive dysfunctions.

MATERIALS AND METHODS

Study design and duration

The study was a prospective cross-sectional survey conducted over a period of 6 months.

Subjects

A total of 92 male subjects were recruited for this study after informed consent. These were age matched-35 male patients with DM2, 24 men with MS and 33 apparently healthy men. Those on antihypertensive drugs, lipid lowering drugs, hormonal medications, cardiovascular diseases like stroke and subjects who did not give consent were exempted.

Type 2 diabetes mellitus

These were subjects recruited by consultant physicians from the General Out Patient (GOP) Clinic and Medical Out Patient (MOP) Clinic of Adeoyo State Hospital, Ibadan and from Medical Out-Patient (MOP) Clinic of the University College Hospital (UCH), Ibadan.

Metabolic syndrome

These were subjects recruited using International Diabetic Federation (IDF) criteria (abdominal obesity: waist circumference >94 cm and at least two of the following: Hypertriglyceridemia(plasma triglycerides > 150 mg/dl), low HDL-C (plasma HDL-C < 40 mg/dl), high blood pressure (blood pressure >130/85 mmHg) and high fasting glucose (plasma glucose > 100 mg/dl).

Controls

These were apparently healthy eugonadal (testosterone level >300 ng/dl), parous, non-diabetic male subjects without MS using the IDF criteria selected from staff of UCH, University of Ibadan and its environs. Fasting blood glucose was determined.to exclude type 2 diabetes mellitus

DEMOGRAPHIC, ANTHROPOMETRIC AND CLINICAL INDICES

Demographic indices: Age, parity, duration of diabetes and family history of DM2 were obtained through questionnaires administered to subjects.

Sexual characteristics: Libido, erectile dysfunction (ED) and nocturnal/early morning erection were obtained through questionnaires administered to subjects.

Anthropometric indices measured were weight, height, body mass index, waist and hip circumference and waist/hip ratio while the clinical index measured was blood pressure.

Weight

This was taken with a bathroom weighing scale placed on a flat surface. The subjects while wearing light clothing and without any shoes on were made to stand on the scale with the indicator at zero. The reading was recorded to the nearest 0.5 kg.

Height

This was measured against a flat, vertical surface with the subjects standing bare footed in an upright position without any head gear on, without raising the heels from the ground and the feet kept together. Measurements were taken with a sliding headpiece brought to the vertex of the subjects' heads and the reading at this level taken to the nearest 0.1 m.

Body mass index (BMI)

This was calculated from the body weight and height of the subjects using the formula stated below:

$BMI = Weight / Height^2 (kg/m^2)$

Waist and hip circumference

Waist circumference (in centimeters) was measured using a measuring tape placed at the umbilical level while the hip circumference (in centimeters) was measured at the widest circumference of the hip over light clothing, using a non-stretchable measuring tape, without any pressure on the body surface. Both Indices and were recorded to the nearest 0.1 cm.

Waist hip ratio (WHR)

This was calculated from the ratio of the waist circumference to hip circumference.

WHR = [Waist circumference / Hip circumference] (cm)

Blood pressure

This was measured with the use of mercury sphygmomanometer when the subjects have rested for ten minutes and in a sitting position.

Sample collection

10 ml of venous blood were collected aseptically by venepuncture from each subject while fasting. 4 ml of blood were dispensed into potassium ethylene diaminetetraacetic acid (K_3EDTA) bottle for lipid profile, 2 ml were dispensed into fluoride oxalate bottle for plasma glucose estimation while the remaining 4 ml were dispensed into plain bottle containers for determination of testosterone. The blood samples in the plain bottles were allowed to clot and retract. All samples were centrifuged at 500 g for five minutes after which serum and plasma were extracted and stored in small aliquots at -20°C until analysis was done.

Biochemical Investigations

Biochemical indices estimated were plasma glucose, total cholesterol, triglyceride, high density lipoprotein and testosterone while low density lipoprotein cholesterol was calculated.

Glucose

Fasting plasma glucose was determined by glucose oxidase, an enzymatic method, as described by Barham and Trinder, 1972 (Randox Diagnostic-Crumlin, United kingdom).

Trigyceride

Plasma triglyceride determination was estimated by the enzymatic method as described by Cole et al. (1997) (Randox Diagnostic-Crumlin, United Kingdom).

Total cholesterol

Plasma cholesterol determination was done using the enzymatic method as described by Trinder (1969) (Randox Diagnostics (Crumlin, United Kingdom).

HDL-C

Plasma HDL-C determination was carried out using the enzymatic method as described by Frieldwald et al. (1972) (Randox Diagnostics (Crumlin, United Kingdom).

LDL-C

LDL-C was calculated using Friedwald's formula. No chylomicron was present in the sample and the triglyceride concentration did not exceed 400 mg/dl. LDL- cholesterol was calculated as follows:

$$\text{LDL-cholesterol (mg/dl)} = \text{Total cholesterol} - \frac{\text{Triglyceride}}{5} - \text{HDL-cholesterol}$$

Testosterone

Testosterone was estimated by enzyme immunoassay (Fortress Diagnostics, Antrim BT41 1QS, UK).

Statistical analysis

Statistical package for social sciences (SPSS) software version 16.0 computer software was used for analysis of data. Analysis of variances and PostHoc Test were used for comparison of variables. Pearson's correlation coefficient was used to find relationships between quantitative variables. Spearman's correlation coefficient was employed to explore relationships between non qualitative variables. p-value less than 0.05 ($p<0.05$) was considered significant.

RESULTS

At the conclusion of this study, a total of 92 subjects were recruited: 35 of them with DM2, 24 of them with MS while 33 without DM or MS served as controls.

Table 1. Comparison of anthropometric and clinical Indices in male with type 2 diabetes mellitus, metabolic syndrome and controls using ANOVA.

Index	Control (n=33)	Metabolic syndrome (n=24)	Diabetes mellitus (n=35)	F- value	p- value
Age	56.39±1.452	54.38±1.198	56.14±2.011	0.366	0.695
Parity	3.55±0.372	3.83±0.541	5.60±0.540	5.594	0.005*
Height (m)	1.700±0.012	1.700±0.016	1.698±0.012	0.004	0.996
Weight(kg)	65.606±1.903	96.583±2.786	69.457±2.117	50.212	0.000*
BMI (kg/m^2)	22.540±0.497	33.390±0.782	24.088±0.681	70.937	0.000*
Waist circumference (cm)	80.121±1.323	111.625±2.804	87.629±1.724	66.403	0.000
Hip circumference (cm)	92.273±1.139	112.458±2.353	93.286±1.322	47.039	0.000*
WHR	0.866±0.007	0.992±0.012	0.937±0.009	44.262	*0.000
Systolic blood pressure (mmHg)	117.273±1.174	134.583±2.083	121.429±2.279	19.419	0.000*
Diastolic blood pressure (mmHg)	76.667±0.965	87.500±1.535	79.429±1.724	13.001	*0.000*

Values are mean ± SE; *= significant; n= number of subjects; F=analysis of variance; p=probability; BMI=Body mass index; WHR= waist hip ratio; BP=Blood pressure; S.E=Standard error.

Demographic, anthropometric and clinical characteristics

Table 1 compares the mean ±S.E of age, parity, height, weight, BMI, waist circumference, hip circumference, WHR, systolic blood pressure and diastolic blood pressure of males with MS, DM2 and controls.

In individuals with DM2, 7 (20%) had MS while 9 (38%) of men with MS had impaired glucose tolerance. 18 (75%) of individuals with MS and 3 (9%) of diabetic men were obesed. 6 (17%) subjects with DM2, 2 (8%) with MS and 3 (9%) controls had family history of DM2. Duration of DM2 in DM2 patients ranged from 1 to 48 months with mean±S.E. of 10.34±2.07 months. Comparison of demographic, anthropometric and clinical characteristics showed significant differences ($p<0.006$) in mean ± S.E of parity, weight, waist circumference, hip circumference, BMI, WHR, systolic blood pressure and diastolic blood pressure in males with MS, DM2 and controls while no significant differences were observed in age and height ($p>0.05$) (Table 1). All indices except age, height and parity were significantly higher ($p<0.05$) in males with MS compared with controls. Significantly higher differences ($p<0.05$) were observed in weight, waist circumference, hip circumference, BMI, WHR, systolic blood pressure and diastolic blood pressure while significantly lower differences ($p<0.05$) were observed in parity in males with MS compared with men with DM2. Only parity, waist circumference and waist hip ratio were significantly higher ($p<0.05$) in males with DM2 compared with controls (Table 2).

Table 3 shows correlation of demographic, anthropometric and clinical indices in males with MS, DM2 and controls. In men with MS, height significantly correlated negatively with waist hip ratio ($p<0.05$). In men with DM2, age significantly correlated positively with waist hip ratio but inversely with hip circumference. Height and age showed no significant correlation with hip circumference and waist circumference in diabetic ($p>0.05$). Age correlated significantly and inversely with height and weight while height correlated significantly and positively with waist circumference only in controls ($p<0.05$).

Sexual characteristics

In individuals with MS, 7 (29%) had diminished libido, 8 (33%) had erectile dysfunction and 5 (20%) did not experience nocturnal/ early morning erection while in individuals with DM2, 17 (49%) had diminished libido, 19 (54%) had erectile dysfunction and 20 (57%) did not experience nocturnal/ early morning erection.

Biochemical Indices

Table 4 compares the mean levels of testosterone, triglyceride, total cholesterol, high density lipoprotein, low density lipoprotein and glucose in individuals with MS, DM2 and controls.

5 (20%) of individuals with MS and 4 (12%) of diabetic men had high triglyceride levels. 58% of men with MS and 63% of diabetic men had low HDL-C. 38% of men with MS had low testosterone while in individuals with DM, 46% had low testosterone.

Comparison among individuals with MS, DM2 and controls, showed significant differences in testosterone, triglyceride, HDL-C and glucose ($p<0.05$).

Men with MS and DM2 had significantly lower levels of HDL-C and testosterone but significantly higher glucose levels when compared with controls ($p<0.05$). Triglyceride was significantly higher in men with MS ($p<0.05$) but not in men with DM2 when compared with controls. Only glucose concentration was significantly higher in men with

Table 2. Comparison of anthropometric and clinical indices in males with metabolic syndrome, type 2 diabetes mellitus, and controls using Post-Hoc.

Index	Groups	Mean difference	P-value
Parity	MS vs control	0.288	0.693
	DM vs control	2.055	0.002*
	MS vs DM		
Weight (kg)	MS vs control	30.977	0.000*
	DM vs control	3.851	0.200
	MS vs DM	27.126	0.000*
BMI (kg/m^2)	MS vs control	10.850	0.000*
	DM vs control	1.548	0.079
	MS vs DM	9.302	0.000*
Waist circumference (cm)	MS vs control	31.504	0.000*
	DM vs control	7.507	0.004*
	MS vs DM	23.996	0.000*
Hip circumference (cm)	MS vs control	20.186	0.000*
	DM vs control	1.013	0.627
	MS vs DM	19.173	0.000*
WHR	MS vs control	0.126	0.000*
	DM vs control	0.070	0.000*
	MS vs DM	0.055	0.000*
Systolic blood pressure (mmHg)	MS vs control	17.311	0.000*
	DM vs control	4.156	0.110
	MS vs DM	13.155	0.000*
Diastolic blood pressure (mmHg)	MS vs control	10.833	0.000*
	DM vs control	2.762	0.163
	MS vs DM	8.071	0.000*

MS = Metabolic syndrome; DM = Type 2 Diabetes mellitus; p = probability; *= significant.

DM2 compared with men with MS ($p<0.05$) (Table 5).

Table 6 shows correlations of biochemical indices (except testosterone) in men with MS, DM2 and controls. In men with DM2, triglyceride correlated positively and significantly with total cholesterol but inversely with HDL-C while in men with MS, triglyceride positively and significantly correlated with glucose ($p<0.05$). Total cholesterol and LDL-C correlated positively and significantly in men with MS, DM2 and controls ($p<0.05$). Correlations of all other indices were not significant in all groups ($p>0.05$).

Relationships of demographic, anthropometric, clinical and biochemical indices

Table 7 shows correlations of demographic, anthropometric, clinical and biochemical indices in men with MS, DM2 and controls. HDL-C correlated significantly and inversely with weight, BMI and waist circumference in men with DM2 only but significantly and positively with systolic and diastolic blood pressure in men with MS ($p<0.05$).

Relationship of testosterone with demographic, anthropometric, clinical and biochemical indices

Table 8 shows correlation of testosterone with demographic, anthropometric, clinical and biochemical indices in male individuals with MS, DM2 and controls. HDL-C showed significant and inverse correlation with testosterone in male individuals with MS and DM2 but not in controls ($p<0.05$). BMI positively and significantly correlated with testosterone in only individuals with DM2 ($p<0.05$). BMI correlated inversely with testosterone in

Table 3. Correlation of demographic, anthropometric and clinical indices in males with metabolic syndrome, type 2 diabetes mellitus and controls using Pearson's correlation.

Indices	Metabolic syndrome (n =24; r, p-value)	Diabetes mellitus (n = 35; r, p-value)	Control (n = 33; r, p-value)
Age vs height	0.072, 0.738	-0.122, 0.485	-0.474, 0.005*
Age vs weight	0.320, 0.127	-0.272, 0.113	-0.462, 0.007*
Age vs waist circumference	0.497, 0.014*	-0.099, 0.571	-0.377, 0.031*
Age vs hip circumference	0.427, 0.037	-0.341, 0.045*	-0.308, 0.081
Age vs waist hip ratio	0.303, 0.150	0.367, 0.030*	-0.300, 0.090
Height vs weight	0.576, 0.003*	0.346, 0.042*	0.731, 0.000*
Height vs waist circumference	0.171, 0.424	0.046, 0.795	0.555, 0.001*
Height vs hip circumference	0.438, 0.032*	0.200, 0.250	0.632, 0.000*
Height vs waist hip ratio	-0.433, 0,034*	-0.157, 0.366	0.168, 0.351
Weight vs BMI	0.737, 0.000*	0.883, 0.000*	0.856, 0.000*
Weight vs waist circumference	0.657, 0.000*	0.863, 0.000*	0.829, 0.000*
Weight vs hip circumference	0.730, 0.000*	0.905, 0.000*	0.800, 0.000*
Weight vs waist hip ratio	0.107, 0.620	0.426, 0.011*	0.474, 0.005*
BMI vs waist circumference	0.644, 0.001*	0.900, 0.000*	0.771, 0.000*
BMI vs hip circumference	0.513, 0.010*	0.866, 0.000*	0.692, 0.000*
BMI vs waist hip ratio	0.480, 0.018*	0.534, 0.001*	0.521, 0.002*
Waist circumference vs hip circumference	0.888, 0.000*	0.892, 0.000*	0.892, 0.000*
Waist circumference vs waist hip ratio	0.522, 0.009*	0.673, 0.000*	0.674, 0.000*
Systolic B.P vs diastolic B.P	0.708, 0.000*	0.765, 0.000*	0.543, 0.001*

* = significant; p = Probability; BMI = Body mass index; B.P = Blood pressure; r = Pearson's correlation coefficient; n = Number of subjects.

Table 4. Comparison of mean plasma levels of biochemical indices in male with type 2 diabetes mellitus, metabolic syndrome and controls using ANOVA.

Index	Control (n = 33)	Metabolic syndrome (n = 24)	Diabetes mellitus (n = 35)	F-value	p-value
Triglyceride (mg/dl)	63.88±5.09	94.84±14.82	71.11±7.55	3.127	0.049*
Total cholesterol (mg/dl)	170.39±6.53	177.29±11.24	161.20±8.84	0.845	0.433
LDL-C (mg/dl)	111.05±6.92	120.17±11.60	113.92±8.67	0.236	0.790
HDL-C (mg/dl)	46.55±2.34	38.15±2.94	33.06±3.18	7.633	0.001*
Glucose (mg/dl)	81.57±1.48	116.54±5.73	156.46±14.18	16.514	0.000*
Testosterone (ng/ml)	5.11±0.35	3.32±0.29	3.52±0.22	13.872	0.000*

Values are mean ± SE; * = Significant; n = Number of subjects; F = Analysis of variance; p = Probability; S.E = Standard error; LDL-C = Low density lipoprotein cholesterol; HDL-C = High density lipoprotein cholesterol.

males with MS and controls although it was not significant (p>0.05).

Relationship of testosterone with sexual characteristics

Table 9 shows correlation of testosterone with libido, erectile dysfunction and nocturnal/early morning erection in male individuals with MS, DM2 and controls.

Testosterone showed significant and positive correlation with libido and nocturnal/early morning erection but inverse correlation with erectile dysfunction in individuals with DM2 (p<0.05).

DISCUSSION

Sexual health may be a window into men's health and

Table 5. Comparison of mean plasma levels of biochemical indices in male with metabolic syndrome, type 2 diabetes mellitus and controls using Post-Hoc test.

Index	Groups	Mean difference	p-value
Triglyceride	MS vs control	32.283	0.016*
	DM vs control	8.546	0.474
	MS vs DM	23.737	0.071
High- density lipoprotein	MS vs control	-9.740	0.024*
	DM vs control	-14.831	0.000*
	MS vs DM	5.090	0.228
Glucose	MS vs control	35.330	0.017*
	DM vs control	75.245	0.000*
	MS vs DM	-39.916	0.006*
Testosterone	MS vs control	-1.961	0.000*
	DM vs control	-1.765	0.000*
	MS vs DM	-0.196	0.648

MS = Metabolic syndrome; DM = Type 2 diabetes mellitus; p = Probability; * = Significant.

Table 6. Correlation of biochemical indices in men with metabolic syndrome, type 2 diabetes mellitus and controls using Pearson's correlation.

Indices	Metabolic syndrome (n = 24; r, p-value)	Diabetes mellitus (n = 35; r, p-value)	Controls (n = 33; r, p-value)
Triglyceride vs T.C	-0.146, 0.496	0.362, 0.033*	-0.062, 0.732
Triglyceride vs HDL-C	-0.189, 0. 376	-0.358, 0.035*	-0.087, 0.628
Triglyceride vs glucose	0.751, 0.000*	0.185, 0.287	0.081, 0.652
T.C vs LDL-C	0.946,0.000*	0.942, 0.000*	0.944,0.000*

*= P < 0.05 is significant; p = Probability; BMI = Body mass index; B.P. = Blood pressure; r = Pearson's correlation coefficient; n = Number of subjects.

Table 7. Correlation between demographic, anthropometric and biochemical indices in men with metabolic syndrome, type 2 diabetes mellitus and controls using Pearson's correlation.

Indices	Metabolic syndrome (n = 24; r, p-value)	Diabetes mellitus (n = 35; r, p-value)	Controls (n=33; r, p-value)
Weight vs HDL	0.202, 0.343	-0.335, 0.049*	0.258,0,156
BMI vs HDL	0.225, 0.290	-0.388,0.021*	0.205, 0.252
Waist circumference vs HDL-C	-0.065, 0.763	-0.342, 0.044*	0,141,0.434
Systolic blood pressure vs HDL-C	0.582, 0.003*	0.120,0.492	0.144,0.422
Diastolic blood pressure vs HDL-C	0.702, 0.000*	0.084,0.633	0.053,0.769

* = P<0.05 is significant; p = Probability; BMI = Body mass index; MB. P. = Blood Pressure; r = Pearson's correlation coefficient; HDL-C = High density lipoprotein-Cholesterol; n = Number of subjects.

Table 8. Correlation of testosterone with anthropometric, clinical indices and biochemical indices in male with metabolic syndrome, type 2 diabetes mellitus and controls.

Indices	Testosterone		
	Metabolic syndrome (n = 24; r, p-value)	Diabetes mellitus (n = 35; r, p-value)	Control (n = 33; r, p-value)
Age	-0.063, 0.771	-0.017, 0.923	0.322,0.059
Parity	0.205,0.336	-0.091, 0.602	0.010, 0.957
Duration of diabetes	-	0.101, 0.563	-
Body Mass Index	-0.190,0.374	0.361, 0.033*	-0.128,0.478
Waist circumference	-0.130 ,0.545	0.204, 0.240	-0.046,0.799
Hip circumference	-0.127,0.554	0.223,0.197	-0.125,0.487
Waist hip ratio	-0.085,0.692	0.074,0.673	0.133,0.460
Systolic B.P	-0.270,0.201	-0.129,0.461,	0.142,0.429
Diastolic B.P	-0.355,0.089	0.060,0.733	-0.003,0.988
HDL-C	-0.415, 0.044*	-0.414,0.014*	-0.111,0.539
Triglyceride	0.174,0.415	0.103,0.556	0.038,0.832
LDL-C	0.219,0.304	-0.034,0.846	0.209,0.244
Total cholesterol	0.164,0.445	-0.164,0.345	0.194,0.280
Glucose	0.069,0.747	-0.172,0.324	-0.111,0.538

* = P<0.05 is significant; p = Probability; BMI = Body mass index; B.P. = Blood Pressure; r = Pearson's correlation coefficient LDL-C = Low density lipoprotein; HDL-C = High density lipoprotein cholesterol; n = Number of subjects.

Table 9. Correlation of testosterone with sexual characteristics in metabolic syndrome, type 2 diabetes mellitus and controls (using Spearman's correlation).

Indices	Testosterone		
	Metabolic syndrome n = 24 (r, p-value)	Diabetes mellitus (n = 35; r, p-value)	Control (n = 33; (r, p-value)
Libido	0.265, 0.210	0.640, 0.000*	0.160, 0.373
Erectile dysfunction	-0.032, 0.882	-0.336, 0.049*	-0.315, 0.074
Nocturnal/ early morning erection	0.342, 0.102	0.453, 0.006*	0.093, 0.605

* = P<0.05 is significant; r = Pearson correlation; p = Probability; n = number of subjects.

testosterone plays a critical role in male reproductive and metabolic functioning as well as improve life quality. Low testosterone is associated with a variety of comorbidities, including insulin resistance, DM2, obesity, MS, and cardiovascular disease (Rice et al., 2008).

Sexual and reproductive dysfunctions are important complications in men with MS and DM2 and may contribute to depressed mood, low libido, ED and fatigue (David and Hunter, 2004; Dhindsa et al., 2004). In this study, testosterone was significantly lower in men with MS and DM2 compared with controls (p = 0.000). 38% of men with MS had low testosterone while in individuals with DM2, 46% had low testosterone (testosterone < 300 ng/dl). Several studies have found frequently low testosterone levels in men with MS and DM2 (Bhasin et al., 2006; Muller et al., 2005; Jones, 2008).

Androgen deficient men have decreased overall sexual activity (Carani et al., 1997). In this study, high percentage of men (20 to 33% with MS and 49 to 55% with DM2) had deficient sexual characteristics-diminished libido, ED and nocturnal/ early morning erection. Testosterone showed significant and positive correlation with libido and nocturnal/early morning erection but inverse correlation with ED in individuals with DM2 (p<0.05). This finding is consistent with other studies (Kapoor et al., 2007; Rice et al., 2008).

The prevalence of hypogonadism increases with age, and most men diagnosed with DM2 are older than 40 years. However, it remains unclear whether decreased testosterone levels are related to aging or to diabetes and its complications (Ding et al., 2006; Corona et al., 2006; Selvin et al., 2007). In this study, mean age of men with MS was 55 years while that of men with DM2 was 56 years. The observed low testosterone level in this present

study may therefore be attributed to the underlying pathology of the diseases as all three groups tested had similar age ($p>0.05$). Moreover, men with MS and DM2 had significantly lower levels of HDL-C and testosterone but higher glucose levels when compared with controls ($p<0.05$). 18 (75%) of individuals with MS and 3 (9%) of diabetic men were obese. Testosterone has been found consistently low by several studies (Betancourt-Albrecht and Cunningham, 2001; Muller et al., 2005; Kapoor et al., 2006) and vary inversely with waist circumference and BMI in men with MS. Contrarily, in this present study, a direct and significant relationship was observed between BMI and testosterone ($p<0.05$)) in men with DM. The finding in our study could be attributed to the normal mean values of BMI in DM2 patients.

MS increases the risk of developing cardiovascular diseases and DM2 (Ford et al., 2002; Wild et al., 2004). Our study similarly showed significant increases ($p<0.05$) in cardiovascular risk factors such as BMI, waist circumference, hip circumference, WHR, blood pressure, triglyceride, glucose and decreased HDL-C in individuals with MS when compared with apparently healthy controls. These observations give credence to evidence that MS is a probable pre-diabetic prediabetic state and could progress to overt diabetes mellitus. Abdominal obesity is known to predispose individuals to insulin resistance (NCEP, 2002) which may further increase the risk of developing DM2 (Hutley et al., 2005). Ashraf- Sohail et al. (2006) reported high prevalence (46%) of MS in individuals with DM2.

Abdominal obesity and insulin resistance appear to be the dominant underlying risk factors for MS (Stumvoll et al., 2000; NCEP/ATP III, 2001). Abdominal fat is especially active hormonally, secreting a group of hormones called adipokines that possibly impair glucose tolerance (Gabriely et al., 2002; Duman et al., 2003). Increased adiposity raises serum resistin levels (Degawa-Yamauchi et al., 2003; Asensio et al., 2004; Vendrell et al., 2004), which in turn directly correlates with insulin resistance (Hirosumi et al., 2002; Silha et al., 2003; Rajala et al., 2004).

Dyslipidemia characterizes individuals with MS and DM2 (Grundy, 1999; Ashraf –Sohail et al., 2006). Specific indices of dyslipidemia are elevated levels of plasma triglyceride (>150 mg/dl), low levels of HDL-C (<40 mg/dl in men and <50 mg/dl in women) and normal LDL-C levels but smaller and denser particles which increase their atherogenic potential (Grundy, 1999; ADA, 2003; Vinik, 2005). In our study, 58% of men with MS and 63% of diabetic men had low HDL-C and significantly lower levels of HDL-C were found in men with MS and DM2 compared with controls ($p<0.05$). Correlation of HDL cholesterol with cardiovascular risk factors such as weight, BMI and waist circumference showed significant and inverse relationship in men with DM2 only ($p<0.05$). The significant decrease in HDL-C in men with DM2 indicates an increased risk of cardiovascular disease, the leading cause of death in patients with DM2. This is in support of study done in Ibadan, Nigeria by Akanji and Agbedana (1995), which showed an inverse correlation between plasma HDL-C concentrations and atherogenic vascular morbidity risk. They observed that of all the lipoproteins, low HDL-C concentrations exert the greatest influence on cardiovascular morbidity risk.

In our study, triglyceride correlated positively and significantly with total cholesterol but inversely with HDL-C in men with DM2 ($p<0.05$). Waist circumference and waist hip ratio were significantly higher ($p<0.05$) in males with DM2 compared with controls. These findings suggest that individuals with DM2 are prone to cardiovascular risk.

Akanji et al. (1992) also in Nigeria, reported that individuals with DM2 had reduced postprandial triglyceride clearance rates and this was probably responsible for the reduced HDL-C levels in their patients. In our study, HDL-C was the only lipid related with testosterone. HDL-C showed inverse correlations with testosterone which were significant in male individuals with MS and DM2 but not in controls ($p<0.05$). The reason for this is not clear. However, reports of Malkin et al. (2004) in hypogonadal men with diabetes mellitus showed that testosterone correlated negatively with total cholesterol, but had no effect on other components of the lipid profile while others (Van Pottelbergh et al., 2003; Stanworth et al., 2007; Roger et al.,;2007) in their work found a positive association between HDL-C and testosterone. It is possible that reduced pituitary and gonadal function could reduce gonadotrophins and ACTH which ultimately results in reduced clearance and accumulation of HDL-C with low testosterone synthesis. Insulin enhances LH Releasing Hormone induced gonadotrophin secretion *in vitro* (Adashi et al., 1981). Data from animal studies also show that hyperglycemia alters leydig cell function directly by reducing both leydig cell number and consequently, testosterone secretion (Jackson and Hutson*.,* 1984). In humans, there is evidence that persons with DM manifest high prevalence of low testosterone and inappropriately low LH and FSH concentrations, a syndrome called hypogonadotrophic hypogonadism (HH) (Dandona et al., 2008). It is not fully clear whether or not this testosterone deficiency is a risk factor for, or a consequence of MS and subsequently DM2 (Bhasin et al., 2006). However, observations in our study suggests that the observed low testosterone in both MS and diabetic group could be a consequence of insulin resistance present in both groups which leads to reduced glucose utilization by the anterior pituitary cell with resultant HH. This requires further studies.

Early diagnosis, treatment and prevention of MS and DM2 are important in the face of an epidemic of over-weight and sedentary life-style in Nigerians. This may lead to improved performance and better management of sexual and reproductive dysfunction caused by MS and DM2.

Conclusions

Testosterone plays a critical role in male reproductive and metabolic functions and low testosterone has been demonstrated in this study in both MS and DM2. This is attributed to deficient glucose uptake by the pituitary and the gonads leading to hypogonadism. Deficient glucose uptake could be a consequence of insulin resistance as shown by hyperglycemia observed in both MS and type 2 diabetes groups.

Observed low testosterone did not relate to age but could be attributed to abdominal obesity and insulin resistance- the underlying pathology of MS and DM2.

MS which increases the risk of developing cardiovascular diseases and DM2 is probably a prediabetic state which could in future progress to overt diabetes. Dyslipidemia which characterizes individuals with MS can be attributed mainly to HDL-C thereby increasing atherogenic risk in both MS and DM2.

Androgen deficient men have decreased overall sexual activity. There is the need to screen for low testosterone, provide relevant information to patients, and increase clinician awareness of the need to address men's sexual health and implement appropriate strategies.

Our study suggests that in individuals with MS and DM2, deficient glucose uptake by the pituitary and the gonads, a consequence of insulin resistance could lead to hypogonadism. Low concentration of circulating HDL in addition to deficient uptake of cholesterol by the adrenals resulting from insulin resistance may exaggerate the low concentration of circulating testosterone. Factors that can improve HDL and decrease insulin resistance such as diet and exercise may be beneficial.

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