Original Article

Male Sexual Dysfunction, Leptin, Pituitary and Gonadal Hormones in Nigerian Males with Metabolic Syndrome and Type 2 Diabetes Mellitus

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Abstract

Background: Pituitary and gonadal dysfunctions resulting from increased adiposity leading to disturbances of sexual and reproductive functions have been reported in males with metabolic syndrome (MS) and type 2 diabetes mellitus (DM2). The aim of this study was to evaluate sexual dysfunction, leptin, and reproductive hormones in Nigerian males with MS and DM2.

Methods: Participants were 104 men (34 males with DM2, 17 men with MS and 53 men with normal body mass index (18.5-24.9 Kg/m^2) without MS (controls)). The International Diabetes Federation (2005) criteria were used for MS diagnosis. Reproductive history, anthropometry, blood pressure (BP) and 10 *ml* fasting blood samples were obtained by standard methods. Fasting plasma glucose, total cholesterol, triglycerides and high density lipoprotein cholesterol were determined by enzymatic methods while low density lipoprotein cholesterol was calculated. Leptin, follicle stimulating hormone (FSH), luteinising hormone (LH), prolactin, testosterone and oestrogen were determined by enzyme immunoassay (leptin by Diagnostic Automation, Inc.; others by Immunometrics (UK) Ltd.) while oestrogen-testosterone ratio was calculated. Data analyzed using ANOVA, Chi square and multiple regression were statistically significant at $p<0.05$.

Results: Testosterone was significantly lower in MS than controls while oestradiol and ETR were significantly higher in MS compared with controls and DM2 group ($p<0.05$). ETR significantly predicted testosterone in all groups ($p<0.05$). Significantly lower libido was observed in men in MS than controls and DM2 groups ($p<0.05$).

Conclusion: Sexual and reproductive dysfunction may be related to increased conversion of testosterone to oestrogen in increased adipose mass in men with metabolic syndrome and type 2 diabetes mellitus.

Keywords: Cardiovascular disease, Leptin, Lipids, Metabolic syndrome, Pituitary hormones, Sex hormone, Sexual dysfunction, Type 2 diabetes mellitus.
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Introduction

The metabolic syndrome (MS), one of the major public health challenges worldwide is well established in Nigeria (1). Described as a complex entity of metabolic disorders-the concurrence of disturbed glucose and insulin metabolism, overweight and abdominal fat distribution,

mild dyslipidaemia, and hypertension- the MS is thought to be a pre-diabetic state and parallels rising rates of obesity worldwide (2, 3). Measures of adiposity- body mass index (BMI), waist circumference (WC), percentage body fat (PBF), waist to hip ratio (WHR), waist to height ratio (WHT), hip circumference (HC)- are important risk factors for metabolic diseases (4, 5).

Increasing incidence of the MS all over the world accompanies adoption of modern Western lifestyle. The main negative features of this lifestyle include positive energy balance (excessive energy intake and low physical activity) and low-quality food (high fat, energy dense and poor in micronutrients) (6, 7). The MS is known to increase the risk for cardiovascular diseases (CVD) and DM2 in both sexes (8). The prevalence of type 2 diabetes mellitus (DM2) is very high worldwide and has risen to 20.5% in Nigeria (9, 10). It is characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both (11).

Sexual and reproductive dysfunctions are important complications in MS and DM2 and may contribute to metabolic dysfunction resulting in decreased quality of life-depressed mood, low libido, erectile dysfunction and fatigue in both men and women (12-14). CVD and testosterone deficiency are both associated with visceral fat accumulation, MS, type 2 diabetes, increased inflammatory cytokines, hyperlipidaemia, and abnormalities of coagulation (15).

Men with MS and DM2 have low total and free testosterone and low sex hormone–binding globulin (SHBG). Conversely, the presence of low testosterone and/or SHBG predicts the development of MS and DM2. It is thought that visceral obesity, present in men with low testosterone, the MS, and/or type 2 DM acts through proinflammatory factors, which contribute to vascular endothelial dysfunction with adverse sequelae such as increased CVD risk and erectile dysfunction (16).

Obesity suppresses SHBG and as a result total testosterone concentrations and alterations in SHBG confound the relationship between testosterone and obesity (17). However, low total and free testosterone and SHBG levels are associated with an increased risk of developing the MS, independent of age and obesity (18, 19). Aromatase, the enzyme that converts testosterone to oestradiol, is mainly located in adipose tissue. Obesity is associated with elevated oestrogen in men, activating hypothalamic-oestrogen receptors, and triggering inhibition of the hypothalamic-pituitary-gonadal axis. Treatment with aromatase inhibitors reverses the hypogonadotropic hypogonadism associated with obesity (20).

It is hypothesized that continued positive energy balance in MS results in the accumulation of adipose mass with increased aromatase activity. Testosterone is, therefore, metabolized to oestradiol leading to a hypogonadal state. The resultant low testosterone concentration increases lipoprotein lipase enzyme activity and triglyceride uptake, leading to increased obesity (greater fat deposition) with further androgen deficiency and visceral fat deposition. Progressive increase in insulin resistance culminates in various features of the metabolic syndrome (the hypogonadal- obesity cycle) (21, 22).

Our previous study showed significant hypogonadism and sexual dysfunction characterized by low testosterone, diminished libido, erectile dysfunction and poor nocturnal/early morning erection in 20-38% and 46-55% of men with MS and DM2, respectively. It was proposed that deficient glucose uptake by the pituitary and the gonads, a consequence of insulin resistance could lead to hypogonadism. Low concentration of circulating high density lipoprotein cholesterol (HDLC) in addition to deficient uptake of cholesterol by the adrenals resulting from insulin resistance might exaggerate the low concentration of circulating testosterone (2).

Serum leptin correlates with BMI (22-24). Also, increased serum leptin levels observed in participants with MS in our study were attributed to high levels of adiposity measures present in them (25). Increased levels of leptin associated with MS may decrease testosterone levels, likely through a functional leptin receptor isoform on leydig cells. Thus, therapeutic testosterone replacement or supplementation may decrease leptin levels and therefore obesity (13, 26, 27). Since MS predisposes individuals to DM2, hormonal milieu and sexual function may have similar pathophysiology. This study was, therefore, designed to evaluate sexual dysfunction, leptin, pituitary and gonadal hormones in Nigerian men with MS and DM2.

Methods

Study Design: This study was a cohort study conducted over a period of 6 months in the Department of Chemical Pathology, College of Medicine, UI. Ethical approval was obtained from the

Joint Ethical Committee of University of Ibadan/ University College Hospital, Ibadan, Nigeria (UI/ UCH).

Participants: A total of 104 men aged 21-90 years were purposely selected for this study. 34 had DM2, 17 had MS while 53 were apparently healthy (controls). These were part of 730 consenting healthy participants (men and women) who were not aware of their metabolic status and 99 consenting participants (men and women) with DM2, recruited by the study physicians into the cohort study on Risk Assessment of DM2 in Individuals with MS in Ibadan, Nigeria. The men fulfilled the criteria for their respective groups. These participants were not on lipid lowering and hormonal medications and they did not have any known cardiovascular diseases.

Individuals with Type 2 Diabetes Mellitus: These were participants diagnosed with type 2 diabetes mellitus by consultant physicians who had no renal diseases. They were recruited while attending the diabetic clinic at the Medical Out-Patient department of the UCH, Ibadan. Their mean (s.e) microalbuminuria to creatinine ratio on spot urine of 2.98 *mg/g* (1.71) was within normal reference range (28).

Individuals with Metabolic Syndrome: These participants were recruited using International Diabetic Federation (IDF) criteria (abdominal obesity: WC>94 *cm* and at least two of the following: hypertriglyceridemia (plasma triglycerides> 150 *mg/dl*), low HDLC (plasma HDLC<40 *mg/dl*), high blood pressure (BP) (BP>130/85 *mmHg*) and high fasting glucose (plasma glucose>100 *mg/dl*) (29).

Controls: These were apparently healthy, non-diabetic participants with normal body mass index (BMI) of >18.5-24.9 kg/m^2 without MS using the IDF criteria. Fasting plasma glucose was determined to exclude DM2.

Sample Collection: 10 *ml* of venous blood sample was asceptically obtained by venipuncture from the participants after an overnight fast (10-14 *hr*). Next, 4 *ml* was dispensed into potassium ethylene diamine tetra acid (K_3EDTA) tube for the determination of lipid profile (total cholesterol (TC), triglyceride and HDLC) and 2 *ml* was dispensed into fluoride oxalate tube for plasma glucose estimation while 4 *ml* was dispensed into plain serum tubes and kept for 1-2 *hr* to clot to obtain serum for the estimation of hormones. All samples were centrifuged at 500 *g* for 5 *min* after which plasma and serum were aspirated in small aliquots into clean vials and stored at -20 ℃ until analysis was done. Urine was obtained from each subject for the determination of creatinine and microalbumin.

Age, Reproductive History, Anthropometry and Blood Pressure Measurements: Age, reproductive history (parity, libido, sustained penile erection during sex, nocturnal/early morning erection), anthropometry (body weight (BW), height, BMI, WC, HC, WHR, WHT, PBF and BP (systolic and diastolic)) were obtained using methods described elsewhere (2, 25).

Biochemical Indices in Blood: FPG and lipids- triglyceride, TC, HDLC- were estimated by enzymatic methods using commercial kits (Dialab Produktion, Austria) while low density lipoprotein cholesterol (LDLC) was calculated using Friedwald's formula as described elsewhere (25). Serum hormones were estimated by enzyme immunoassay using commercially available kits. Leptin was estimated by kits obtained from Diagnostic Automation, Inc., CA while anterior pituitary hormones (follicle stimulating hormone (FSH), luteinizing hormone (LH) and prolactin) and sex hormones (testosterone and oestradiol) were estimated using kits obtained from Immunometrics UK Ltd. Testicular endocrine milieu was determined by calculating oestrogen-testosterone (ETR).

Statistical Analysis: Data were analyzed using the Statistical Package for Social Sciences (SPSS) software 15.0 version. Analysis of variance (ANOVA) and Duncan Post Hoc tests for multiple comparisons were used for comparison of variables. Chi square test was used to find associations while stepwise multiple regression model was used to predict dependent variables. Data analyzed were significant at $p<0.05$.

Results

Table 1 shows comparison of mean plasma/serum levels of biochemical parameters in participants with MS, DM2 and controls using ANOVA. Significant differences were observed in FPG, HDLC, LDLC, testosterone, oestradiol and ETR ($p<0.05$). Post hoc tests showed significantly higher levels of FPG in DM2 compared with MS and controls ($p<0.05$). HDLC was significantly higher in controls compared with MS and DM2 ($p<0.05$). LDLC was significantly higher in DM2 than controls ($p<0.05$). Testosterone was significantly lower in MS than controls while oestradiol

Table 1. Comparison of mean plasma levels of biochemical indices in male participants with metabolic syndrome, type 2 diabetes mellitus and controls

Index	MS (n=17)	Control (n=53)	DM2 (n=34)	P-value *
Fasting plasma glucose (*mmol/l*)	5.1 (0.3)	4.3 (0.1)	7.1 (0.5)	0<0.001
Triglyceride (*mmol/l*)	0.8 (0.1)	0.7 (0.0)	0.8 (0.1)	0.38
Total cholesterol (*mmol/l*)	3.4 (0.2)	3.7 (0.1)	3.9 (0.1)	0.208
HDLC (*mmol/l*)	0.8 (0.1)	1.3 (0.0)	0.9 (0.1)	0<0.001
LDLC (*mmol/l*)	2.2 (0.2)	2.1 (0.1)	2.6 (0.2)	0.036
Leptin (*µg/l*)	7.8 (1.3)	5.4 (0.6)	7.7 (1.2)	0.124
Testosterone (*nmol/l*)	18.0 (3.2)	32.6 (2.5)	27.0 (3.0)	0.01
Oestradiol (*pmol/l*)	373.3 (54.2)	156.6 (18.6)	175.9 (24.1)	0<0.001
ETR	0.02 (0.02)	0.005 (0.007)	0.007 (0.008)	0<0.001
FSH (*IU/l*)	8.5 (1.8)	12.0 (1.3)	16.5 (2.5)	0.055
LH (*IU/l*)	9.4 (2.0)	13.2 (1.0)	12.2 (2.1)	0.356
Prolactin (*mIU/l*)	341.9 (120.2)	444.1 (103.7)	273.2 (52.7)	0.427

Values are in mean (s.e), MS=Metabolic Syndrome Group, DM=Diabetic Group, HDLC=High Density Lipoprotein Cholesterol, LDLC=Low Density Lipoprotein Cholesterol, LH=Luteinizing Hormone, FSH=Follicle Stimulating Hormone, ETR=Oestradiol Testosterone Ratio, *One Way ANOVA and Duncan Test; n for leptin=control=30, MS=16, DM=21

Table 2. Sexual characteristics of male participants with metabolic syndrome, type 2 diabetes mellitus and controls

Sexual characteristics	MS	DM2	Control	P-value *
Libido	12 (70.6%) n=17	26 (96.3%) n=27	50 (96.2%) n=52	0.002
Sustained penile erection during sex	9 (69.2%) n=13	19 (79.2%) n=24	40 (85.1%) n=47	0.420
Nocturnal/Early morning erection	13 (76.5%) n= 17	25 (80.6%) n=31	46 (90.2%) n=51	0.288

MS=Metabolic Syndrome Group, DM2=Type 2 Diabetes Mellitus Group, *Chi square test

and ETR were significantly higher in MS compared with controls and DM2 ($p<0.05$).

Table 2 shows sexual characteristics of men participants with MS, DM2 and controls using Chi square test. 26 (96.3%) men in the DM2 group and 50 (96.2%) in the control group had significantly higher libido compared with 12 (70.6%) men in the MS group. The association of the men libido in MS, DM2 and controls was significantly different ($p<0.01$).

Table 3 shows comparison of age, parity, anthropometry and BP in men participants with MS, DM2 and controls using ANOVA. Significant differences were observed amongst MS, DM2 and control groups in age, weight, BMI, WC, HC, WHR, WHT, PBF, SBP and DBP. Post hoc tests showed that men in MS and DM2 had higher age, weight, BMI, WC, HC, WHR, WHT, SBP and PBF than controls ($p<0.05$). Similarly, these parameters (except age and WHR) were higher in men with MS than DM2. Age was higher in DM2 group than MS group while DBP was higher in MS than controls and DM2 groups ($p<0.05$).

Table 4 showed multiple regression analyses of testosterone, oestradiol and oestradiol testosterone ratio in controls, MS and DM2. In controls, testosterone and oestradiol positively and significantly predicted each other. Testosterone negatively predicted ETR and vice versa while oestradiol positively predicted ETR and vice versa ($p<0.001$). The overall relationships were significant ($R^2=0.626$, $F=41.888$, $p<0.001$). In MS, ETR, triglyceride and HC had significant overall relationship with testosterone ($R2=0.515$, $F=4.602$, $p=0.021$); ETR, triglycerides, WHR, and DBP had significant overall relationship with oestradiol ($R^2=0.625$, $F=4.995$, $p=0.013$) while oestradiol, age, FBG, TG, LDLC, WHR and testosterone had significant overall relationship with ETR ($R^2=0.769$, $F=4.271$, $p=0.024$). However, only ETR significantly and negatively predicted testosterone and vice versa ($p<0.05$). In DM2, ETR and prolactin had significant overall relation with testosterone, ETR with oestradiol; and oestradiol, WHT, WC and WHR with ETR ($R^2=0.235$, $F=4.749$, $p<0.05$). However, only the negative prediction of testos-

Table 3. Comparison of age, parity, anthropometric and clinical parameters in male participants with metabolic syndrome, type 2 diabetes mellitus and controls

Index	MS (n=17)	Controls (n=53)	DM2 (n=34)	P-value *
Age (years)	56.3 (3.5)	37.9 (1.7)	63.6 (2.0)	0<0.001
Parity	6.8 (0.8)	4.0 (0.6)	5.3 (0.7)	0<0.07
Height (*m*)	1.7 (0.0)	1.7 (0.0)	1.7 (0.0)	0.815
Body weight (*kg*)	86.7 (4.1)	63.6 (1.0)	74.1 (2.6)	0<0.001
BMI (kg/m^2)	30.1 (1.3)	21.9 (0.3)	25.5 (0.8)	0<0.001
Waist circumference (*cm*)	108.0 (2.9)	81.2 (0.8)	96.9 (2.1)	0<0.001
Hip circumference (*cm*)	105.7 (2.2)	91.4 (0.7)	97.2 (1.6)	0<0.001
WHR	1.0 (0.0)	0.9 (0.0)	1.0 (0.0)	0<0.001
WHT	0.63 (0.0)	0.48 (0.0)	0.57 (0.0)	0<0.001
Systolic BP (*mmHg*)	153.2 (7.1)	114.3 (0.8)	128.2 (3.5)	0<0.001
Diastolic BP (*mmHg*)	95.9 (3.3)	73.0 (0.7)	76.6 (1.8)	0<0.001
Percentage of body fat	27.6 (0.7)	17.0 (0.6)	24.8 (0.9)	0<0.001

Values are mean (s.e), BMI=Body Mass Index, WHR=Waist Hip Ratio, WHT=Waist Height Ratio, BP=Blood Pressure, MS=Participants with metabolic Syndrome, DM2=Participants with type 2 diabetes Mellitus, n for parity in control, MS and DM2=29,6, and 7, respectively; n for height, waist circumference, hip circumference, WHR in DM2=33 while that of WHtR=32, *One Way ANOVA and Duncan test

terone by ETR and positive prediction of oestradiol and vice versa were significant ($p<0.05$).

Discussion

The finding of similar levels of LH and prolactin in MS, DM2 and controls is contrary to reports of pituitary hypofunction, supported by low testosterone and inappropriately low luteinizing hormone (LH) and follicle stimulating hormone (FSH) concentrations in diabetics (30). Levels of FSH in MS and DM2 were similar to controls in the present study. Our findings contrast with data from animal studies, which showed that hyperglycemia altered leydig cell function directly by reducing both leydig cell number and consequently, testosterone secretion (31). FPG levels were significantly higher in DM2 compared with control and MS groups ($p<0.01$) in this present study. Hypertriglyceridemia and hyperglycemia were the least prevalent components of MS in the Nigerian population contrary to findings in other populations implicating genetic differences (1).

In this present study, there was significant reduction in testosterone levels in MS group only compared with controls ($p<0.02$). Additionally, oestradiol levels and ETR were significantly higher in MS compared with DM2 and controls ($p< 0.001$). It was observed that oestradiol, testosterone and ETR predicted each other in controls. The relationship of oestradiol with testosterone and ETR was lost in MS while the prediction of ETR by testosterone was lost in DM2 ($p<0.04$). The hypogonadal state plays a central role in the development of metabolic syndrome in younger as well as elderly men (21). Our findings support the hypothesis that continued positive energy balance results in the accumulation of adipose mass which metabolizes testosterone to oestradiol probably through increased aromatase activity (21, 22).

Sexual function is a complex, multicomponent biologic process that comprises central mechanism for regulation of libido and arousability as well as local mechanisms for the generation of penile tumescence, rigidity, orgasm, and ejaculation with overall sexual satisfaction. Testosterone may affect the ability to achieve erections by helping to stimulate the expression of nitric oxide synthase and thereby increase the availability of nitric oxide in cavernosal tissue (32). Androgen-deficient men have decreased overall sexual activity (33).

An association between MS and erectile dysfunction has been reported in several studies (2, 34-36). Chughtai et al. (36) reported that in males with MS, 96.5% had erectile dysfunction, 39.6% had hypoactive sexual desire, 22.7% had premature ejaculation, and 4.8% had delayed ejaculation. The MS may lead to erectile dysfunction through multiple mechanisms. It is postulated that hypogonadism, which may be caused by the MS, can lead to secondary erectile dysfunction through altered testosterone: estrogen levels (37). In our present study, 96.3% and and 96.2% of men in the

Table 4. Multiple regression analyses of testosterone, oestradiol and oestradiol testosterone ratio in control, metabolic syndrome and type 2 diabetes mellitus groups

Groups		Dependent parameter	Predictors	Regression coefficient	P-value
Control	R^2=0.626, F=41.888, p=0<0.001	Testosterone			
			Oestradiol	0.780	0<0.001
			ETR	-0.832	0<0.001
	R^2=0.666, F=49.949, p=0<0.001	Oestradiol			
			Testosterone	0.696	0<0.001
			ETR	0.816	0<0.001
	R^2=0.689, F=55.503, p=0<0.001	ETR			
			Testosterone	-0.691	0<0.001
			Oestradiol	0.760	0<0.001
Metabolic syndrome	R^2=0.515, F= 4.602, p=0.021	Testosterone			
			ETR	-0.505	0.043
			Triglyceride	-0.129	0.601
			Hip circumference	-0.243	0.299
	R^2=0.625, F=4.995, p=0.013	Oestradiol			
			ETR	0.300	0.253
			Triglyceride	0.253	0.251
			Waist hip ratio	-0.262	0.242
			Diastolic blood pressure	-0.324	0.111
	R^2=0.769, F=4.271, p=0.024	ETR			
			Oestradiol	0.598	0.083
			Age	-0.158	0.520
			Fasting plasma glucose	-0.129	0.655
			Triglyceride	-0.161	0.560
			LDLC	0.157	0.479
			Waist hip ratio	-0.006	0.786
			Testosterone	-0.576	0.035
Type 2 diabetes mellitus	R^2=0.235, F=4.749, p=0.016	Testosterone			
			ETR	-0.371	0.030
			Prolactin	0.226	0.176
	R^2=0.325, F=15.406, p<0.001	Oestradiol	ETR	0.570	0<0.001
	R^2=0.487, F=6.420, p=0.001	ETR			
			Oestradiol	0.503	0.001
			Waist height ratio	-0.035	0.938
			Waist circumference	0.053	0.902
			Waist hip ratio	0.388	0.02

ETR=Oestradiol Testosterone Ratio, LDLC=Low Density Lipoprotein Cholesterol

DM2 and control groups, respectively had significantly higher libido compared with 70.6% men in the MS group (p<0.003). These observations may be related to reduced testosterone level in MS. Hypogonadism was present more frequently in patients with MS (36).

Atherosclerosis can also lead to structural damage within the penile tissues. The MS can also lead to endothelial dysfunction, which has been implicated in vascular disorders. Endothelial dysfunction, therefore, leads to a decrease in vascular nitric oxide levels, with resulting impaired vasodilation. The increase in free radical concentration also leads to atherosclerotic damage (38-40). Hyperglycemia induces a series of cellular events that increase the production of reactive oxygen species such as superoxide anion that inactivates nitric oxide to form peroxynitrite and increases oxygen-derived free radicals through activation of protein kinase C and other cellular elements thus leading to erectile dysfunction (38, 39). Hyperglycemia can also lead to glycation of penile cavernosal tissue, leading to an impairment of collagen turnover and potentially erectile dysfunction (41). Contrarily, all groups (including DM2) had similar percentage of men with sustained erection during sex as well as nocturnal and early morning erection in this present study.

In spite of the similar levels of total cholesterol observed in this study, LDLC levels were significantly higher in DM2 than controls (p<0.01). Additionally, MS and DM2 groups showed signifi-

cantly lower differences in HDLC levels compared with controls ($p<0.04$). These observations suggest that disordered metabolism in MS and particularly in DM2 could contribute to cardiovascular risk. Increased leptin levels in our population have been attributed to an increase in adipose tissue mass observed in MS and DM2 (25). The similar levels of leptin in all groups in this study may reflect the lower adipose mass in men compared to females. Our findings in males do not support the review by Chou et al. (2014) that linked leptin to reproductive dysfunction due to energy imbalance (42).

The number of men with MS in this study was small (17) and non-inclusion of glycated haemoglobin measurement to identify men with DM2 with and without control are the limitations of this study. However, the association of measures of adiposity depicting central or subcutaneous obesity and hypertension as CVD risk factors in Nigerians have already been reported (5, 43). Short term dietary modulation of CVD risk factors, oxidative and inflammatory parameters in individuals with MS proved to be beneficial (44). Akinloye et al. (2014) recommended the inclusion of routine measurement of the testosterone level in the management of patients that present with both diabetes and hypertension. They suggested that these patients could benefit from testosterone replacement therapy (45).

Conclusion

Our findings show normal pituitary function in both groups. However, reduced testosterone was seen in MS compared with controls implicating increased aromatase activity in converting testosterone to oestradiol and not leydig cell dysfunction. It is suggested that measures aimed at reduction of adiposity and hyperglycemia in MS and DM groups may be beneficial in their management. This may improve their sexual function and enhance good quality of life.

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Conflict of Interest

Authors declare no conflict of interest.

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