Official Publication of the Faculty of Basic Medical Sciences University of Ibadan, Nigeria

Arch. Bas. App. Med. 5 (2017) 109 – 118
www.archivesbamui.com

ARCHIVES OF BASIC & APPLIED MEDICINE

Research Article

Reproductive Endocrinopathies in Nigerian Males with Zero and Three or More Metabolic Syndrome Components

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Received: June 2017; Accepted in final form: September, 2017

Abstract
Childlessness has adverse social, psychological and economic impact on affected couples. The contributions of males to infertility account for 40%. Hypogonadism in males has been associated with metabolic syndrome (MS). Although endocrinopathies have been observed in infertile men, similar data in males with MS in the general population is sparse. This study is therefore aimed at evaluating the endocrinopathies in Nigerian males with zero (ZMS) and MS. Sixty-seven male participants aged 18 - 70 years were purposely enrolled for this study. Fifty-two males had ZMS (control) while 15 males had MS. Demography, sexual history, blood pressure, anthropometry were obtained by standard methods. Fasting plasma glucose, triglyceride and high-density lipoprotein cholesterol were determined by enzymatic methods. Sex and pituitary hormones were determined by ELISA. Data analysed were statistically significant at $p < 0.05$. The MS group 8 (53.3%) had significantly more males with hypogonadism than the controls 2 (23.1%) ($p<0.05$). Compensatory hypogonadism and suboptimal hypogonadism are the most common endocrinopathies in controls and MS group. 9 (60%) and 5 (33%) of males in the MS group were overweight and obese respectively while 2 (3.8%) and 6 (11.5%) of controls were underweight and overweight. FSH had a direct relationship with age in eugonadal controls and hypogonadal males with MS while LH had an inverse relationship with age in eugonadal males in the MS group. Endocrinopathies are prevalent in Nigerian men irrespective of their metabolic status or age.

Key Words: Endocrinopathies, Metabolic Syndrome, Obesity, Hypogonadism, Nigeria

INTRODUCTION

Children are the essence of marriage in Africa and childlessness results in adverse social, psychological and economic effects on affected individuals (Nieuwenhuies *et al*., 2009; Oladokun *et al*.,2009; Vander *et al*., 2009). An alarming decline in semen quality over the past 60 years worldwide has been reported (Carsen *et al*., 1992; Feki *et al*., 2009). Such decline was observed in Rwanda, where a male factor infertility of 64% was reported (Dhont *et al*., 2010). In Nigeria, the contribution of males to infertile marriages was assessed to be 16.4% in the past (Ojo *et al*., 1968). However, Ilesanmi *et al*. (1996) estimated from clinical reports that 40-45% of clinical infertility was male factor dependent. Emokpae *et al*. (2007) demonstrated significant endocrinopathies among infertile males in Kano, Northwest Nigeria.

Hypogonadism implies deficiency of reproductive hormones with or without defects in fertility. It is defined in males as a state of reduced testosterone and its sequelae that are identified by below normal testosteron levels. Low testosterone levels can result in defective primary or secondary sexual development among males. In primary hypogonadism, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels are usually elevated and suggest a primary defect with the testes whereas in secondary or central hypogonadism, LH and FSH levels are normal or low, suggesting the problem is in the pituitary gland Kumar *et al*., (2010).

Upsurge of obesity has been declared a worldwide epidemic by the World Health Organization. In Nigeria, the most populous African country, the prevalence of obesity ranged from 8.1%–22.2% (Chukwuonye *et al*., 2013). The increasing trend of obesity in Nigeria has been associated with changes in lifestyle especially among urban dwellers (Monteiro *et al*., 2005). In massively obese men, serum total testosterone level was markedly reduced (Kalyani *et al*., 2007). Decreased total testosterone levels in obese individual did not result in increased gonadotrophin levels. Rather, low or sub-normal levels of luteinizing hormone and follicle stimulating hormone

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were observed, suggesting a hypogonadotropic hypogonadal cycle (Loves *et al*., 2008).

Nguyen *et al*. (2008) reported that approximately 25% of obese individuals had Metabolic Syndrome (MS). Metabolic Syndrome represents a constellation of metabolic abnormalities. It is a multifaceted condition, which leads to significant disturbance of numerous physiological processes. It is described as a concurrence of metabolic, renal and cardiovascular risk factors including central (visceral) obesity, hypertension, insulin resistance, dyslipidemia, microalbuminuria, oxidative stress, increased inflammation and hypercoagulation (Charles-Davies *et al*., 2012). The most prevalent form of MS (visceral obesity) contributes to reduced plasma androgen levels (Pasquali *et al*., 1997; Despre *et al*., 2008). Corona *et al*. (2007) reported a higher prevalence of hypogonadism in men with MS and these men had an increased waist circumference (WC) and hyperglycemia. They therefore suggested that elevated WC and hypogonadism may predict MS. Contrarily, Charles-Davies *et al*. (2014) showed that reduced HDL-C was the most frequent MS component in males in Ibadan. Metabolic syndrome may contribute to hypogonadism, resulting in decreased quality of life, depressed mood, low libido, erectile dysfunction in men (Umoh *et al*., 2010).

Several mechanisms have been reported to explain relationships of hypogonadism, MS and obesity. It is hypothesized that increased positive energy balance in MS/obesity results in continued deposition of visceral fat, increased aromatase activity and higher conversion of testosterone to oestradiol, leading to hypogonadal state, which further leads to the deposition of visceral fat contributing to central obesity thereby ensuring a vicious cycle (Despre *et al*., 2008; Fabian *et al*., 2016). Abdominal (visceral) fat is more likely to cause alterations in hormone levels than fat stored in other parts of the body (Cabler *et al*., 2010). Higher oestrogen levels inhibit intra-testicular steroidogenesis through 17-α-hydroxylase and 17,20 lyase, further decreasing testosterone levels (Rohrmann *et al*., 2011).

Obesity and MS which contribute to hypogonadism are associated with advancing age (Umoh *et al*., 2010; Charles-Davies *et al*., 2012, Charles-Davies *et al*., 2014). However, Fabian *et al*. (2016) showed an association of low testosterone levels with increased risk of developing MS in males independent of age and obesity. Emokpae *et al*. (2007) detected hormonal abnormalities in infertile Nigerian men. Reproductive endocrinopathies in males with metabolic syndrome as well as in the apparently normal males with zero components of MS is unknown. This study is aimed at evaluating the endocrinopathies in Nigerian men

MATERIALS AND METHODS

A total of 67 apparently healthy male participants aged 18 to 70years were purposely enrolled for this study based on their metabolic status. These were part of 730 apparently healthy participants (males and females) who were unaware of their metabolic status, enrolled into a cohort study described elsewhere (Fabian *et al*., 2016). 15 participants had ≥ 3 metabolic syndrome components (MS group) while 52 participants had zero component of metabolic syndrome (control group).

Participants with Metabolic Syndrome: These were participants enrolled into the study using the Joint Interim Statement (JIS) criteria. The criteria include the following risk factors; elevated waist circumference (≥ 94cm), elevated serum triglyceride ≥ 150mg/dL (≥ 1.7mmol/L), reduced serum HDL cholesterol < 40mg/dL (<1.0mmol/L), elevated blood pressure (systolic blood pressure ≥ 130mmHg or diastolic blood pressure ≥ 85mmHg), elevated fasting blood glucose ≥ 100mg/dL (≥ 5.6mmol/L) (Alberti *et al*., 2009).

Gonadal Status: The gonadal status of the MS and the control groups were determined based on the classification by Emokpae *et al*., (2007) and Okoli *et al*., 2015. The patterns were: eugonadism (normal levels of LH, FSH, total testosterone and prolactin), hypergonadotrophic hypogonadism (high levels of LH, FSH, low total testosterone levels and normal prolactin levels), compensated hypogonadism (high levels of LH and FSH, normal total testosterone levels and prolactin levels), suboptimal hypogonadism (normal LH, FSH, prolactin and low total testosterone), sertoli cellular failure (normal levels of LH, total testosterone, prolactin, and high levels of FSH), hyperprolactinemia/pituitary adenoma high prolactin levels, FSH and/or LH levels) and hypogonadotrophic hypogonadism (low levels of LH, FSH and testosterone, high or normal levels of prolactin).

Demography, Social Habit, Diet, Exercise, And Sexual History

Demographic indices, social habits (smoking and alcohol) exercise and dietary history were obtained from each participant using a semi-structured questionnaire.

Sample Collection: 10 mL of venous blood was collected aseptically by venepuncture (using sterile needle and syringe) from each participant. The blood obtained was dispensed into tubes; 4 mL was dispensed into potassium ethylene diaminetetracetic acid (K¬¬3EDTA) tubes for triglycerides and high density lipoprotein cholesterol estimation. 2 mL was dispensed into fluoride oxalate tubes for glucose estimation while the remaining 4 mL was dispensed into plain serum tubes kept for 1-2 hours to clot to obtain serum for the estimation of hormones. Thereafter, all samples were centrifuged at 500g for five minutes, plasma and serum were aspirated in small aliquots into clean vials and stored at -20°C.

Fasting plasma lipids and glucose: Triglyceride, HDLC and FPG were estimated by enzymatic methods (Dialab, Austria) (Charles-Davies *et al*., 2012).

Hormones: Testosterone, oestradiol, LH, FSH, and prolactin were estimated by enzyme immunoassay (Immunometrics UK Limited).

Statistical Analysis

Data obtained were analysed using Fisher's exact test, chi square, Kruskal-Wallis test, Mann-Whitney test) and multiple regression statistical models. Values were expressed in median (interquater range). Data were statistically significant at $p < 0.05$. The statistical package for the social science (SPSS version 22.0) was used for all statistical analysis.

RESULTS

Table 1 shows comparison of demographic characteristics and social habits between the MS group and controls. Participants

in the control group had a significantly higher educational status compared with the MS group (p<0.05).

Table 2 shows comparison of physical exercise and diet between the MS group and controls. No significance differences were observed in physical exercise, vegetable/fruit and red meat intake in the MS group compared with controls (p>0.05). However, significantly higher intake of refined carbohydrate and dairy products were observed in the control compared with the MS group (p<0.05).

Table 1
Demographic Characteristics and Social Habits of Participants in the Control and the Metabolic Syndrome Group

Indices	Control	MS Group	Total	P
	n=52 (77.6%)	n=15 (22.4%)	n=67 (100%)	
DEMOGRAPHY				
Marital Status				
Single	4 (8.0)	0 (0.0)	+65(100)	0.340
Married	46 (92.0)	15 (100.0)		
Educational Status				
NFE	6 (12.5)	6 (40.0)		
PSC	3 (6.3)	2 (13.3)		
JSC	5 (10.4)	1 (6.7)	+63(100)	0.030*
SSC	29 (60.4)	4 (26.7)		
Graduate	5 (10.4)	1 (6.7)		
Post Graduate	0 (0.0)	1 (6.7)		
SOCIAL HABIT				
Smoking(Cigarette)				
Yes	1 (2.0)	0 (0.0)	+64(100)	0.766
No	48 (98.0)	15 (100)		
Alcohol intake				
Yes	12 (24.5)	4 (26.7)	+64(100)	0.555
No	37 (75.5)	11 (73.3)		

*values are in numbers of participants with percentage in parenthesis, n = number of participants in each group, (%) = percentage, p= value for fisher Exact test, *= significance, p<0.05 is considered significance, control = group with zero component of metabolic syndrome, MS group= group with three or more components of metabolic syndrome, NFE= No formal education, PSC= Primary school certificate, JSC= junior secondary certificate, SSC=senior secondary certificate., + = number of participants that responded to the question in the questionnaire.*

Table 3 shows comparison of gonadal status, endocrinopathies and sexual history between the MS group and controls (p<0.05). Significantly higher proportion of males in the MS group {8 (53.3%)} were hypogonadic compared with the control group{12 (23.1%)} (p<0.05). However, {47 (90.4%) and 13 (86.7} of males in the control and the MS group respectively had various endocrinopathies. Most of the males in the control group (50%) had compensatory hypogonadism while most of the males in the MS group (26%) had suboptimal hypogonadism.

Table 4 shows comparison of age, BMI, MS components and reproductive hormones between the MS group and controls. Age and BMI were significantly higher in the MS group compared with controls (p = 0.001). Only 1 (6.7%) of the MS group compared with 44 (84.6%) of the controls, had normal weight. 9 (60%) and 5 (33.3%) of the MS group were overweight and obese while 2 (3.8%) and 6 (11.5%) of the controls were underweight and overweight respectively.

Table 2
Physical Exercise and Diet of Participants in the Control and the Metabolic Syndrome Group

Indices	Control	MS Group	Total	p
	n=52 (77.6%)	n=15 (22.4%)	n=67 (100%)	
PHYSICAL EXERCISE				
Yes	37 (75.5)	11 (73.3)	+64 (100)	0.555
No	12 (24.5)	4 (26.7)		
DIET				
Vegetable/Fruit intake				
Often	32 (76.6)	14 (93.4)	+63 (100)	0.059
Occasionally	16 (33.3)	1 (6.7)		
Never	0 (0.0)	0 (0.0)		
Refined CHO/Sugar Intake				
Often	22 (45.9)	6 (40.0)		
Occasionally	26 (54.2)	6 (40.0)	+63 (100)	0.031*
Never	0 (0.0)	3 (20)		
Dairy Product Intake				
Often	26 (54.2)	7 (46.6)		0.047*
Occasionally	22 (45.8)	7 (46.7)	+63 (100)	
Never	0 (0.0)	1 (6.7)		
Red Meat Intake				
Often	33 (76.7)	8 (51.6)	+56 (100)	0.575
Occasionally	8 (18.6)	4 (30.8)		
Never	2 (4.7)	1 (7.7)		

*values are in numbers of participants with percentage in parenthesis, n = number of participants in each group, (%) = percentage, p= value for fisher Exact test, *= significance, p<0.05 is considered significance, control = group with zero component of metabolic syndrome, MS group= group with three or more components of metabolic syndrome, CHO= carbohydrate, = number of participants that responded to the question in the questionnaire.*

None of the males in the MS group was underweight while none in the controls was obese. Comparison of the BMI classes between the MS group and the control was significant (p=0.001). MS components were significantly higher in the MS group compared with the controls (p= 0.001) except TG and FPG which showed no significant difference between the groups (p>0.05). LH, FSH and testosterone were significantly higher in the controls compared with the MS group (p<0.001) while oestradiol and ETR were significantly higher in the MS group compared with the control group (p<0.001).

Table 3
Gonadal Status, Endocrinopathies and Sexual History of Participants in the Control and the Metabolic Syndrome Group

Indices	Control	MS Group	Total	X^2	p
	n=52 (77.6%)	n=15 (22.4%)	n=67 (100%)		
GONADAL STATUS					
Eugonadal	40 (76.9)	7 (46.7)	+67 (100)	5.09	0.024*
Hypogonadal	12 (23.1)	8 (53.3)			
ENDOCRINOPATHIES					
EUG	5 (9.6)	2 (13.3)	7 (10.4)		0.649
HHG	9(17.3)	2(13.3)	11(16.4)		
CHG	26 (50.0)	2 (13.3)	26 (41.7)		
SOH	1 (1.9)	4 (26.6)	5 (7.4)		
SCF	3 (5.7)	3 (20.0)	6 (8.9)		
HP/PA	8 (15.3)	2 (13.3)	10 (14.9)		
SEXUAL HISTORY					
Nocturnal/Early Morning Erection					
Yes	44 (89.8)	11 (73.3)	+64 (100)		0.121
No	5 (10.2)	4 (26.7)			
Libido					
Yes	42 (91.3)	9 (64.3)	+60 (100)		0.025*
No	4 (8.7)	5 (35.7)			
Penile Erection Maintained during Sex					
Yes	39 (86.7)	9 (69.2)	+58 (100)		0.147
No	6 (13.3)	4 (30.8)			

*values are in numbers of participants with percentage in parenthsis, n = number of participants in each group, (%) = percentage p= value for fisher Exact test, *= significance, p<0.05 is considered significance, X2= chi-square, control = group with zero component of metabolic syndrome, MS group= group with three or more components of metabolic syndrome, + = number of participants that responded to the question in the questionnaire. chi-square test was used for gonadal status and fisher's test for endocrinopathies and sexual history*

Table 5 shows comparison of age, BMI, MS components, reproductive hormones and sexual history between hypogonadic and eugonadic controls. Eugonadic controls showed significantly higher levels of total testosterone and oestradiol, and lower ETR when compared with the hypogonadic controls (p<0.001), while no significant differences were observed in other hormones (LH, FSH and prolactin) between the groups (p>0.05).

Table 6 shows comparison of age, BMI, MS components, reproductive hormones and sexual history among the different endocrinopathies of the controls. No Significant differences were observed in age, BMI, WC, HDL-C, FPG, BP, TG, sexual history, FSH, oestradiol and ETR across the groups (p>0.05). However, luteinizing hormone, total testosterone and prolactin showed significant differences among the various endocrinopathies (p<0.001). Comparisons between groups of endocrinopathy (using Mann-Whitney U test) showed significantly higher levels of LH in participants with compensated hypogonadism and hypergonadotrophic hypogonadism compared with the participants with eugonadism and sertoli cellular failure (p<0.001).

Table.4
Age, Body Mass Index, Metabolic Syndrome Components and Reproductive Hormones of Participants in the Control and the Metabolic Syndrome Group

Indices	Control Group	MS Group	Z	p
	n=52	n=15		
Age (years)	33.5 (30-42)	55.0 (45-70)	4.338	<0.001*
BMI	21.7 (20.5-23.3)	28.4 (25.5-31.2)	5.491	<0.001*
BMI Class				
Underweight	2 (3.8)	0 (0.0)		0.001*
Normal weight	44 (84.6)	1 (6.7)		
Overweight	6 (11.5)	9 (60.0)		
Obese	0 (0.0)	5 (33.3)		
MS COMPONENTS				
HDL-C (mg/dL)	47.5 (43.0-58.5)	30.0 (26.0-37.0)	5.871	<0.001*
TG (mg/dL)	57.0 (44.2-77.5)	66.0 (55.0-84.0)	1.264	0.206
WC (cm)	80.0 (76.0-85.0)	104.0 (98.0-110)	5,844	<0.001*
SBP (mmHg)	115.0 (110-120)	150.0 (130-160)	5.417	<0.001*
DBP (mmHg)	70.0 (70.0-80.0)	90.0 (90-100)	5.599	<0.001*
FPG (mg/dL)	76.0 (72.0-86.0)	79.0 (76.0-114.0)	2.153	0.31
REPRODUCTIVE HORMONES				
LH (IU/L)	11.0 (8.2-16.6)	6.5 (4.1-8.8)	3.084	0.002*
FSH (IU/L)	8.3 (6.5-15.3)	4.6 (3.0-10.6)	2.437	0.015*
TT (nmol/L)	29.0 (15.6-50.2)	14.2 (7.8-31.5)	2.409	0.016*
E_2 (nmol/L)	0.09 (0.06-0.2)	0.3 (0.2-0.5)	3.913	<0.001*
ETR	0.004 (0.002-0.008)	0.02 (0.007-0.04)	4.332	<0.001*
Prolac (mu/L)	189.8 (20.0-574.6)	169.8 (22.3-439.6)	0.287	0.774

*values in median (interquarter range), Z= Mann-Whitney U test, p= p value, p<0.05 is considered significance, * = significance, Control = group with zero component of metabolic syndrome, MS group = group with ≥3 components of metabolic syndrome, *= significance, p<0.05, n= number of participants, SBP= systolic blood pressure, DBP= diastolic blood pressure. FPG= fasting plasma glucose, TG= triglyceride, HDL-C= high density lipoprotein cholesterol, WC= waist circumference, LH= luteinizing hormone, FSH= follicle stimulating hormone, TT = total testosterone, E2= oestradiol, ETR= oestradiol testosterone ratio, Prolac = prolactin. reference range: reference range: TT(15-40nmol/L), LH(<8.0IU/L), FSH(<8.0 IU/L), E2 (0.05-0.16), prolactin(110-510IU/L.stastistical test used (Mann-Whitney U test).*

Participants with eugonadism, compensated hypogonadism, sertoli cellular failure and hyperprolactinemia/pituitary adenoma had significantly higher testosterone levels than those with hypergonadotrophic hypogonadism (p<0.001).

Table 5
Age, Body Mass Index, Metabolic Syndrome Components, Reproductive Hormones and Sexual History of Hypogonadic and Eugonadic Controls

Indices	Hypogonadal	Eugonadal	Total	Z	P
	TT(<15nmol/L) n=12 (23.1%)	**TT(≥15nmol/L) n=40 (76.9%)**	**n=52 (100%)**		
Age (years)	34.0 (28.0-48.0)	33.5 (30.0-41.5)		0.163	0.870
BMI	22.4 (20.5-23.9)	21.5 (20.5-23.1)		0.706	0.480
MS COMPONENTS					
FPG (mg/dL)	73.5 (67.0-82.5)	76.5 (72.0-86.0)		1.033	0.302
TG (mg/dL)	54.5 (48.0-85.7)	59.5 (42.5-77.5)		0.434	0.664
HDL (mg/dL)	50.0 (46.5-60.0)	47.0 (42.2-58.5)		1.164	0.244
WC (cm)	83.0 (77.5-87.7)	80.0 (76.0-83.2)		1.035	0.301
SBP (mmHg)	110.0 (110.0-120.0)	120.0 (110.0-120.0)		0.697	0.486
DBP(mmHg)	70.0 (70.0)	70.0 (70.0-80.0)		1.730	0.084
REPRODUCTIVE HORMONES					
TT (nmol/L)	9.5 (8.1-12.4)	37.9 (24.0-52.2)		5.222	<0.001*
LH (IU/L)	14.3 (9.1-22.8)	10.8 (8.0-15.7)		1.347	0.178
FSH (IU/L)	8.9 (6.4-21.9)	8.0 (6.6-15.3)		0.326	0.745
E_2 (nmol/L)	0.06 (0.06-0.13)	0.124 (0.06-0.251)		2.011	0.044*
ETR	0.007 (0.004-0.021)	0.003 (0.002-0.006)		3.345	0.001*
Prolac (mU/L)	381.6 (163.4-609.7)	120.9 (20.0-508.0)		1.737	0.082
SEXUAL HISTORY					
Nocturnal/Early Morning Erection					
Yes	11 (91.7)	33 (89.2)	49 (100)		0.644
No	1 (8.3)	4 (10.0)			
Desire for Sex					
Yes	10 (90.9)	32 (91.4)	46 (100)		0.679
No	1 (9.1)	3 (8.6)			
Penile Erection maintained during sex					
Yes	10 (100)	29 (82.9)	45 (100)		0.199
No	0 (0.0)	6 (17.1)			

*+ =values in median (interquarter range), p<0.05 is considered statistically significant, *= significant, X2 = chi-square, Z= Mann-Whitney U test, p= p value, FPG= fasting plasma glucose, TG= triglyceride, HDL-C= high density lipoprotein cholesterol, WC= waist circumference, SBP= systolic blood pressure, DBP= diastolic blood pressure, TT= total testosterone, LH=luteinizing hormone, FSH= follicle stimulating hormone, E2= oestradiol, prolac= prolactin, values for age, BMI, MS components and reproductive hormones were reported in median (interquarter range) and statistical test used for analysis(mann whitney U). statistical test for sexual history (fisher's test)*

Significantly higher levels of prolactin were observed in participants with hypergonadotrophic hypogonadism and hyperprolactinemia/pituitary adenoma than those with eugonadism (p=0.003), furthermore, participants with hyperprolactinemia/pituitary adenoma had significantly higher prolactin levels than those with compensated and hypergonadotrophic hypogonadism (p=0.001), while those with sertoli cellular failure had significantly lower prolactin levels than those with compensated hypogonadism and hypergonadotrophic hypogonadism (p=0.020) (Table

Table 8 shows multiple regression of age, MS components, BMI and reproductive hormones of hypogonadic and eugonadic controls. In the hypogonadic men LH showed significant and negative relationship with TG, HDL-C, WC and DBP (p=0.003). Also, FSH showed significant and positive relationship with HDL-C (p=0.001), and negative relationship with WC (p=0.002). ETR showed significant and positive relationship with DBP (p=0.006). Moreover, total testosterone showed significant and positive relationship with FPG (p=0.046), and negative relationship with WC (p=0.005). In the eugonadic men FSH showed significant and positive relationship with age (p=0.047), also, ETR showed significant and positive relationship with HDL-C (p=0.040).

Table 9 shows multiple regression of age, MS components, BMI and reproductive hormones of hypogonadic and eugonadic males in metabolic syndrome group. In the hypogonadic men ETR showed significant and positive relationship with HDL-C (p=0.044), and negative relationship with age (p=0.010), while FSH showed positive and significant relationship with age (p<0.001). In the eugonadic men LH showed significant and negative relationship with age (p=0.010), and positive relationship with FPG (p=0.004), while total testosterone showed significant and negative relationship with BMI (p=0.002), however, FSH showed significant and negative relationship with HDL (p=0.032).

DISCUSSION

There are concerns on the decline in semen quality which may predispose males to infertility (Feki *et al*., 2009). Nutritional factors appear to underlie hypogonadism in males (Umoh *et al*., 2010). This observation is corroborated in this study. Although the proportions of hypogonadism in both groups studied were high, the MS group (53.3%) had significantly more males with hypogonadism than the controls (23.1%). Moreover, 35.7% of the MS group as against 8.7% of the controls had reduced libido. This was attributed to increased conversion of testosterone to oestradiol by aromatase in increased adipose tissue (Fabian *et al*., 2016).

Surprisingly, 90.4% of the controls as against 86.7% of males with MS had various forms of endocrinopathies, though no significant difference was observed between groups Emokpae *et al*. (2007) observed earlier that endocrine abnormalities were common in the infertile men with unknown reasons. Although MS components, HDL-C, WC and blood pressure were significantly altered in MS group compared with the controls no significant differences were observed in all the MS components between hypogonadal and eugonadal in both MS and controls. A previous study showed no relationship between hypogonadism and MS (Wang *et al*., 2011). Olaniyan *et al*. (2016) showed increase in the level of inhibin B, an indicator of spermatogenesis in males with MS than those without MS. These findings suggest that factors other than MS may underlie pituitary and testicular alterations in the general population. The pollution of the environment in several urban cities including Ibadan is well known (Alberti *et al*., 2009; Adekola *et al*., 2016).

Table 6
Age, Body Mass Index, Metabolic Syndrome Components, Reproductive Hormones and Sexual History of the Controls with different Endocrinopathies

Indices	EUG	HHG	CHG	SOH	SCF	HP/PA	p
	n=5	n=9	n=26	n=1	n=3	n=8	
Control							
Age(years)	40.0 (29.5-48.5)	33.0 (28.0-48.5)	33.5 (30.0-40.5)	28.0	30.0	39.0 (32.0-46.7)	0.563
WC(cm)	82.95 (76.9-85.2)	81.0 (74.0-86.0)	80.0 (76.3-85.2)	92.0	80.0	79.0 (74-85.0)	0.707
HDL(mg/dL)	45.0 (41.0-61.0)	51.0 (44.0-59.0)	47.0 (42.7-55.5)	49.0	47.0	49.5 (44-66.5)	0.916
FPG(mg/dL)	72.0 (66.0-86.5)	74.0 (67.0-83.5)	77.0 (74.0-86.0)	72.0	72.0	76.0 (29-96.0)	0.705
SBP(mmHg)	120.0 (110.0-120.0)	110 (110.0-120.0)	110.0 (110.0-120.0)	120.0	110.0	120 (102-120)	0.737
DBP(mmHg)	70.0 (70.0-80.0)	70.0 (70.0-75.0)	70 (70-80)	70.0	70.0	70 (70-80)	0.841
TG(mg/dL)	42.0 (33.0-68.0)	53.0 (48.0 -71.5)	55.0 (41.7-70.7)	145.0	88.0	75 (57-99.7)	0.097
LH(IU/L)	6.6 (5.0-6.6)	14.7 (10.5-24.6)	12.6(9.0-18.0)	6.5	6.2	9.8 (6.6-15.6)	0.001*
FSH(IU/L)	5.8 (4.0-5.8)	9.6 (6.4-18.3)	9.7 (7.0-19.1)	2.4	11.6	7.7 (5.9-12.8)	0.059
TT(nmol/L)	42.8 (27.4-53.1)	9.7 (8.2-13.6)	34.5 (23.6-53.7)	10.0	19.4	45.4 (20.6-53.4)	0.001*
E_2(nmol/L)	0.1 (0.1-0.3)	0.06 (0.06-0.1)	0.08 (0.06-0.2)	0.06	0.06	0.1 (0.08-0.2)	0.747
ETR	0.002 (0.001-0.008)	0.007 (0.004-0.01)	0.003 (0.002-.009)	0.005	0.004	0.004 (0.003-0.006)	0.166
PROLAC(mU/L)	20.0(19.1-87.5)	307.2 (103.8-603.8)	121.4 (20.0-290.4)	342.8	20.0	684.3(599.4-1527.2)	<0.001*
BMI	21.9(20.9-22.5)	21.5(19.9-23.8)	21.7(20.5-23.4)	25.8	22.5	21.1(20.0-23.2)	0.689
SEXUAL HISTORY							
Nocturnal/Early Morning Erection							
Yes	3 (6.8)	8 (18.2)	22 (50.0)	1 (2.3)	3 (6.8)	7 (15.9)	0. 818
No	1 (20.0)	1 (20.0)	3 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Libido							
Yes	4 (9.5)	8 (19.0)	21 (50.0)	1 (2.4)	3 (7.1)	5 (11.9)	0.887
No	0 (0.0)	0 (0.0)	4 (100)	0 (0.0)	0 (0.0)	0 (0.0)	
Penile Erection Maintained during Sex							
Yes	4 (10.3)	7 (17.9)	18 (46.2)	1 (2.6)	3 (7.7)	6 (15.4)	0.467
No	0 (0.0)	0 (0.0)	6 (100)	0 (0.0)	0 (0.0)	0 (0.0)	

*values in median (interquarter range), only median reported when n<3, p= value, p<0.05 is considered significance, *= significance, n= number of participants, Control = group with zero component of metabolic syndrome, SBP= systolic blood pressure, FPG= fasting plasma glucose, TG= triglyceride, HDL-C= high density lipoprotein cholesterol, WC= waist circumference, LH= luteinizing hormone, FSH= follicle stimulating hormone, TT = total testosterone, E2= oestradiol, ETR= oestradiol testosterone ratio, Prolac = prolactin, DBP= diastolic blood pressure, EUG(eugonadic)= normal LH, FSH, TT and prolactin, HHG(hypergonadotrophic hypogonadism)= high LH, FSH, low TT and normal prolactin, CHG(compensated hypogonadism)= high LH, FSH, normal TT and prolactin, SOH (suboptimal hypogonadism)= normal LH, FSH, prolactin and low TT, SCF (sertoli cellular failure)= normal LH, TT, prolactin and high FSH, HP/PA(hyperprolactinemia/pituitary adenoma)= high prolactin. reference range: reference range: TT(15-40nmol/L), LH(<8.0IU/L), FSH(<8.0 IU/L), E2 (0.05-0.16), prolactin(110-510IU/L.statistical test used(Kruskal Wallis*

Table 7
Reproductive Hormones in the Controls with different Endocrinopathies

Indices	Gonadal status	Median (interquarter range)	Gonadal status	Median (interquarter range)	p=value
Reproductive hormone					
LH (IU/L)	EUG	6.6 (5.0-6.6)	CHG	12.6 (9.0-18.0)	<0.001*
	EUG	6.6 (5.0-6.6)	HHG	14.7 (10.5-24.6)	0.003*
	CHG	12.6 (9.0-18.0)	SCF	6.2	0.005*
	HHG	14.7 (10.5-24.6)	SCF	6.2	0.013*
TT	EUG	42.8 (27.4-53.1)	HHG	9.7 (8.2-13.6)	0.003*
	CHG	34.5 (23.6-53.7)	HHG	9.7 (8.2-13.6)	<0.001*
	HHG	9.7 (8.2-13.6)	SCF	19.4	0.012*
	HHG	9.7 (8.2-13.6)	HP/PA	45.4 (20.6-53.4)	0.004*
PROLAC	EUG	20.0 (19.1-87.5)	HHG	307.2 (103.8-603.8)	0.019*
	EUG	20.0 (19.1-87.5)	HP/PA	684.3 (599.4-1527.2)	0.003*
	CHG	121.4 (20.0-290.4)	SCF	20.0	0.029*
	CHG	121.4 (20.0-290.4)	HP/PA	684.3 (599.4-1527.2)	0.001*
	HHG	307.2 (103.8-603.8)	SCF	20.0	0.020*
	HHG	307.2 (103.8-603.8)	HP/PA	684.3 (599.4-1527.2)	0.009*

*values are in median (interquater range), p<0.05 is considered statistically significant, *= significance, p= p value, EUG(eugonadic)= normal LH, FSH, TT and prolactin, HHG(hypergonadotrophic hypogonadism)=high LH, FSH, low TT and normal prolactin, CHG(compensated hypogonadism)= high LH, FSH, normal TT and prolactin, SOH (suboptimal hypogonadism)= normal LH, FSH, prolactin and low TT, SCF (sertoli cellular failure)= normal LH, TT, prolactin and high FSH, HP/PA(hyperprolactinemia/pituitary adenoma= high prolactin, TT= total testosterone, prolac= prolactin, LH=luteinizing hormone stastistical test used (Mann-Whitney U test)*

Some endocrine disruptors accumulate in increased adipose tissue to alter the endocrine milieu of the testes leading to hypogonadism. Chikezie *et al*. (2017) recently reported that occupational exposure to endocrine distrupting heavy metals such as lead and mercury could induce oxidative stress resulting in testicular dysfunction in males with normal adipose tissue.

Low and subnormal levels of LH and FSH suggestive of hypogonadotrophic hypogonadal cycle were observed in massively obese men (Loves *et al*., 2008). In this present study, none of the males in both controls and MS group had hypogonadotrophic hypogonadism. Rather, 50.0% of males in the controls had compensated hypogonadism while 26.6% of the MS group had suboptimal hypogonadism. The observation in this study corroborates the studies of Fabian *et al*. (2016) on the limited contribution of the pituitary hormones to hypogonadism.

Table.8
Multiple Regression of Age, Metabolic Syndrome Components, Body Mass Index and Reproductive Hormones of Hypogonadic and Eugonadic Controls

Groups	Dependent	Predictors	Beta	p
HYPOGONADAL				
R^2 Adj=0.275,F=5.1 P=0.046	FPG	TT	0.584	0.046*
R^2Adj=0.484,F=11.3 P=0.007	TG	LH	-0.729	0.007*
R^2 Adj=.646,F=11.0 p=0.004	HDL-C	FSH LH	0.940 -0.485	0.001* 0.039*
R^2Adj=0.904,F=35.3 P=<0.001	WC	FSH LH TT	-0.504 -0.447 -0.380	0.002* 0.003* 0.005*
R^2Adj=0.58,F=8.75, P=0.008	DBP	LH ETR	-0.705 0.573	0.006* 0.018*
EUGONADAL				
R^2Adj=0.077,F= 4.2, P=0.047	AGE	FSH	0.317	0.047*
R^2Adj=0.082,F= 4.5, P=0.040	HDL-C	ETR	0.326	0.040*

*p<0.05 is considered statistically significant, *= significance, p= p value, Eugonadal= group with total testosterone levels ≥ 15nmol/L, Hypogonadal= group with total testosterone level < 15nmol/L, FPG= fasting plasma glucose, TG= triglyceride, HDL-C= high density lipoprotein cholesterol, WC= waist circumference, SBP= systolic blood pressure, DBP= diastolic blood pressure. Prolac= prolactin, FSH= Follicle stimulating hormone, LH= Luteinizing hormone, TT= total testosterone, ETR= oestradiol-testosterone ratio. Statistical test used (stepwise multiple regression).*

Males in the MS group had significant higher BMI compared with the controls. BMI classes in the controls were different from those in MS group. Sixty and thirty-three percent of males in the MS group were overweight and obese respectively while 3.8% and 11.5% of controls were underweight and overweight. This corroborates studies that showed that BMI and MS measure different regions of fat (Charles-Davis *et al*., 2014).

Males in the MS group had significantly higher age and BMI compared with the controls similar to earlier observations (Charles-Davies *et al*., 2012). However, comparison between hypogonadal and eugonadal males in both controls and MS group showed no significant differences in age and BMI. This may indicate that BMI and MS may be associated with age but not gonadal status. Olaniyan *et al*. (2016) recently showed that Inhibin B had no relationship with BMI and age. However, FSH had a direct relationship with age in eugonadal controls and hypogonadal males with MS while LH had an inverse relationship with age in eugonadal males in the MS group. No parameter tested in this study showed any relationship with age in hypogonadal males in the control group. These observations may implicate age and corroborate the relevance of factors other than MS in the aetiology of hypogonadism in Nigerians.

Table 9
Multiple Regression of Age, Metabolic Syndrome Components, Body Mass Index and Reproductive Hormones of Hypogonadic and Eugonadic Males in Metabolic Syndrome Group

Groups	Dependent	Predictors	Beta	*p*
HYPOGONADAL				
R2 Adj=0.954, F=73.5, P=<0.001	AGE	FSH ETR	0.963 -0.325	<0.001* 0.010*
R2 Adj=0.43,F=6.44, P=0.044	HDL-C	ETR	0.720	0.044*
EUGONADAL				
R2 Adj=0.718,F=16.2 , p=0.010	AGE	LH	0.874	0.010*
R2 Adj=0.838,F=32.0, p=0.002	BMI	TT	-0.930	0.002*
R2 Adj=0.806,F=26.0, P=0.004	FPG	LH	0.916	0.004*
R2 Adj=.564,F=8.70, P=0.032	HDL-C	FSH	-0.798	0.032*

*p<0.05 is considered statistically significant, *= significance, p= p value, Eugonadal= group with total testosterone levels ≥ 15nmol/L, Hypogonadal= group with total testosterone level < 15nmol/L, FPG= fasting plasma glucose, TG= triglyceride, HDL-C= high density lipoprotein cholesterol, WC= waist circumference, SBP= systolic blood pressure, DBP= diastolic blood pressure. Prolac= prolactin, FSH= Follicle stimulating hormone, LH= Luteinizing hormone, TT= total testosterone, ETR= oestradiol-testosterone ratio.*

In conclusion, there is significant hypogonadism in Nigerian males. MS and obesity are prevalent in Nigerian men and are related with age but not hypogonadism. There appears to be mild testicular failure in many Nigerian males probably due to environmental factors. The presence of age-dependent hypogonadism and contribution of individual MS components to specific pituitary and testicular hormone synthesis are indicated but requires further studies.

Acknowledgements
This study was partly funded by the University of Ibadan MacArthur Foundation grant.

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