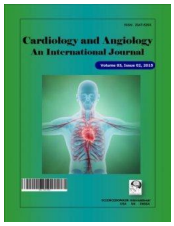

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Sex Hormones and Their Relationship with Leptin and Cardiovascular Risk Factors in Pre and Post-Menopausal Nigerian Women with Metabolic Syndrome

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Authors' contributions

The authors contributed to the intellectual content of this paper and have met the following requirements: a) Significant contributions to the concept and design, data acquisition, analysis and interpretation; b) Drafting and reviewing the article for intellectual content; c) Final approval of the article for publication.

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ABSTRACT

Metabolic Syndrome (MS), which affects 33.1% of Nigerians, predisposing them to cardiovascular disease (CVD) risk, has been associated with the female gender. The cardioprotective effect of oestradiol against CVD is now controversial and was investigated in premenopausal with MS (PRMMS) and postmenopausal women with MS (POMMS).

A total of 191 women (44 PRMMS, 126 POMMS and 21 premenopausal women without MS (PRM) (controls) with mean (s.d) age of 40.0 (6.9), 57.0 (8.8), 29.0 (6.8) years were participants of this study. Demography, blood pressure (BP), anthropometry, hormones, fasting plasma glucose (FPG) and lipids were obtained by standard methods. Data were significant at (P<.05).

Age, parity, all anthropometric measures, FPG, leptin, ET ratio and FSH were significantly higher while HDLC, testosterone and prolactin were significantly lower in PRMMS compared with controls (P<.03). In comparison of POMMS with PRMMS, age, parity, WHR, systolic BP, TG, FSH and LH were significantly higher while body weight, HC, and leptin were lower in POMMS compared with PRMMS (P<.05). DBP positively predicted oestradiol in PRM only (P=.044) while oestradiol positively predicted testosterone in PRMMS only (P<.001). In POMMS only, DBP positively predicted testosterone; testosterone, ET ratio and FSH positively predicted oestradiol while LDLC and oestradiol positively predicted the ET ratio (P<.03).

Metabolic syndrome may predispose both pre and postmenopausal women to the risk cardiovascular disease and type 2 diabetes mellitus. Oestradiol may protect against cardiovascular diseases in women without metabolic syndrome only.

Keywords: Sex hormones; metabolic syndrome; cardiovascular disease; menopause; leptin.

1. INTRODUCTION

Cardiovascular disease (CVD) is a major cause of morbidity and mortality worldwide especially in women and the elderly in Western countries [1,2]. The negative cardiovascular profile observed in MS, which has also been associated with the female gender, may be determined by its main features- abdominal obesity and insulin resistance [3,4]. Contrary to observations in other regions of the world, elevated waist circumference (WC), reduced high density lipoprotein cholesterol (HDLC) and high blood pressure (BP) are prevalent MS components in the Nigerian with gender differences. Elevated WC was more frequent in females while reduced HDLC was more frequent in males [5]. These observations may be important in the management of CVD in the Nigerian, the most populous sub-Sahara African country as hormonal signaling has been implicated in the regulation of cardio-protective mechanisms [1].

Oestrogen is a female sex hormone produced by the ovaries and known to have several cardio-protective mechanisms that change the vascular tone by increasing nitrous oxide production, stabilize the endothelial cells and enhance antioxidant effects. These mechanisms get lost with the onset of menopause [6,7], when the ovaries cease to produce significant amounts of oestrogen. The loss of ovarian follicular activity due to falling follicle stimulating hormone levels explains the decline in oestrogen at menopause [8,9].

Menopause is the permanent cessation of menstruation for a period of one year and marks the transition from reproductive (premenopausal) to non-reproductive (postmenopausal) status, occurring at a mean age of 51 years [7,10]. This transition is associated with increased susceptibility to cardiovascular events possibly due to the protective effect of oestrogen in premenopausal women without MS (PRM) [2,7,11,12]. It is postulated that abdominal tissue redistribution in menopause could be related to a relative deficit in circulating oestrogens [12,13]. It is not clear whether such effects could manifest in women with MS.

Menopause has been reported to have a negative impact on plasma lipoprotein-lipid levels, adverse changes in glucose and insulin metabolism and body fat distribution [7,14]. Though controversial, recent evidence suggests that oestrogen may not be cardio-protective [5]. Studies on cardioprotective effects of sex hormones in PRM women with MS are sparse in our geographical region. Thus, the association of sex hormones with cardiovascular risk factors was investigated in PRM, premenopausal and postmenopausal Nigerian women with MS (PRMMS and POMMS respectively).

2. METHODOLOGY

2.1 Study Design

The study was a cohort study conducted over a period of 6 months. Ethical approval was obtained from the University of Ibadan/University College Hospital (UI/UCH) Joint Ethical Committee.

2.2 Participants

A total of 191 apparently healthy women consisting of 44 PRMMS, 126 POMMS of >1 year duration and 21 PRM women (controls)] with mean (standard deviation) ages of 40.0 (6.9), 57.0 (8.8), 29.0 (6.8) years respectively from Bodija and University College Hospital, Ibadan community, and environs; enrolled in this study at the Department of Chemical Pathology, University of Ibadan, Ibadan, after written informed consent. They were part of the cohort of 784 participants in the study on Risk Assessment of Type 2 Diabetes Mellitus in Individuals with MS, in Ibadan, South West Nigeria. All the participants were non-diabetic (from their pretest questionnaire) and were not aware of their metabolic status. Those on antihypertensive, lipid lowering and hormonal medications or hormonal contraceptives, cardiovascular diseases like stroke and those who did not give consent were excluded from the study. Diagnosis of MS was made using the International Diabetes Federation diagnostic criteria [15]. The criteria include central obesity measured as WC (≥80 cm) and any two of raised triglycerides (TG): ≥150 mg/dL(1.7 mmol/L), reduced HDLC (females: <50 mg/dL, raised BP (≥130/ ≥85 mmHg) or raised fasting plasma glucose (FPG) (≥100 mg/dL).

2.3 Sample Collection

Ten ml of venous blood sample was aseptically obtained by venepuncture from the participants during the follicular phase of their menstrual cycle, after an overnight fast (10-14 h). 4 ml was dispensed into potassium ethylene diamine tetra acetic acid (K_3EDTA) tube for the determination of lipid profile (total cholesterol (TC), triglyceride (TG) and HDLC). Two ml was dispensed into fluoride oxalate tube for FPG estimation while 4 ml was dispensed into plain tubes for the estimation of hormones. All samples were centrifuged at 500 g for 5 min after which plasma/serum were aspirated in small aliquots into clean vials and stored at -20ºC until analyses were done [16].

2.4 Anthropometric and Blood Pressure Measurements

Reproductive history was obtained through semi structured pretest questionnaire administered to participants. Adiposity measures (body weight, height, body mass index (BMI), waist circumference (WC), hip circumference (HC), waist hip ratio (WHR), percentage body fat (PBF)) and blood pressure (BP) (systolic and diastolic) were obtained from the participants by standard methods described elsewhere [3,17].

2.5 Biochemical Estimations

TG, TC, HDLC and FPG were estimated by enzymatic methods while low density lipoprotein cholesterol (LDLC) was calculated using Friedwald's formula as described by Charles-Davies et al. [3]. Leptin was estimated by enzyme-linked immunosorbent assay (Diagnostic Automation, Inc., CA). Oestradiol, testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH) and prolactin were determined by enzyme immunoassay {Immunometrics (UK) Ltd.} while oestradiol-testosterone ratio (ET ratio) was calculated.

2.6 Statistical Analysis

Data obtained were analysed statistically using Student's t-test for comparison of variables. Stepwise Multiple Regression model was used to identify specific determinants of dependent variables. $P < .05$ was considered significant.

3. RESULTS AND DISCUSSION

3.1 Results

Table 1 shows comparisons of mean (s.e) age, parity, blood pressure, anthropometric measures and biochemical parameters among PRMMS, POMMS and PRM. All parameters except, TG, TC, LDLC, LH, oestradiol were significantly different when PRMMS was compared with PRM ($P>.05$). Age, parity, all anthropometric measures, FPG, leptin, ET ratio and FSH were significantly higher while HDLC, testosterone and prolactin were significantly lower in PRMMS compared with controls ($P<.03$). In comparison of POMMS with PRMMS, age, parity, WHR, systolic BP, TG, FSH and LH were significantly

higher while body weight, HC, and leptin were lower in POMMS compared with PRMMS (*P*<.05).

All CVD risk factors, LH, FSH and prolactin with dependent variables- testosterone, oestradiol, and testosterone oestradiol ratio, in a stepwise multiple regression model showed the following relationships: DBP positively predicted oestradiol in PRM only (*P*=.044) while oestradiol positively predicted testosterone in PRMMS only (*P*<.001). In POMMS only, DBP positively predicted testosterone; testosterone, ET ratio and FSH positively predicted oestradiol while LDLC and oestradiol positively predicted the ET ratio (*P*<.03) (Table 2.)

3.2 Discussion

Metabolic syndrome predisposes individuals to the development of CVD. Nigerians with MS have shown higher levels of cardiovascular risk factors than those without MS. Interestingly, MS appears more common in females than males and differences in MS components have been observed between males and females [5].

Protecting the myocardium against the deleterious consequences of myocardial ischaemia may reduce the high mortality of the disease particularly in females. Age, parity, blood pressure and all anthropometric measures were significantly higher in PRMMS compared with controls (*P*<.05) (Table 1). These findings are consistent with our earlier observations in the general population [5,18] and suggest that PRMMS are at high risk of CVD.

Oestrogen is a female hormone and is thought to prevent the development of atherosclerosis [19]. All steroid hormones (including oestradiol) are derived from cholesterol, mainly circulated in blood as low density lipoprotein. Comparisons of TG, TC, LDLC (known atherogenic risk factors), LH and oestradiol were not significantly different between PRMMS and controls (*P*>.05) suggesting that these indices may have limited role in CVD risk in PRMMS. Moreover, DBP positively predicted oestradiol only in PRM only (*P*<.05) (Table 2). Additionally, leptin, ET ratio, FSH and FPG were significantly higher while HDLC and testosterone were significantly lower in PRMMS when compared with controls (Table 1). In our previous study, elevated leptin levels were associated with increased adiposity and might be involved in compensatory mechanisms aimed at maintaining normal blood pressure in individuals with MS [16].

In PRM, oestradiol level is controlled by FSH through negative feedback mechanism. It appears that this control may be reduced or lost in MS implicating oestradiol synthesis in adipose tissue. The increase in ET ratio and reduced testosterone levels in PRMMS compared with controls (*P*<.001) suggests that aromatase enzyme in increased adipose mass (non-gonadal site) in MS increases conversion of testosterone to oestradiol. Oestadiol predicted testosterone positively in PRMMS only (*P*<.001) (Table 2). There may also be the compensatory effect of FSH, which is raised in PRMMS compared with controls to maintain oestradiol levels due to possible loss of feedback mechanism. It is also possible that this process might be due to the older age of the PRMMS compared with PRM as a result of aging follicles. However, the observed reduction of HDLC and elevated FBG levels in PRMMS compared with the PRM group may implicate mechanisms of MS. Reduced HDLC and elevated FBG are components of metabolic syndrome [15]. Reduction in HDLC and testosterone, and increase in FPG levels were observed in males with MS and type 2 diabetes mellitus in an earlier study [17]. Over 80% of Nigerian males and females with type 2 diabetes mellitus had MS [20]. Moreover, age did not predict any of the sex hormones or their ratio in any of the groups in our present study (Table 2).

Hip circumference measures subcutaneous adipose tissue while WHR together with WC and WHT measure abdominal fat. WHR correlates with all metabolic risk factors and its increase may reflect either a relative abundance of abdominal fat (increased WC) or a relative lack of gluteal muscle (decreased HC) [5]. WHR is positively and independently related to the occurrence of arterial HTN [21]. Abdominal tissue redistribution in menopause could be related to a relative deficit in circulating oestrogens [12,13]. Age, parity, WHR and systolic BP were significantly higher while body weight and HC were lower in POMMS compared with PRMMS (*P*<.05) (Table 1).

Menopause is associated with ovarian failure and removal of feedback inhibition as observed by other studies [9,10]. We observed significantly higher levels of TG, LH and FSH lower leptin level in POMMS compared with PRMMS (*P*<.05) (Table 1). In POMMS only, DBP positively predicted testosterone; testosterone, ET ratio and FSH positively predicted oestradiol while LDLC and oestradiol predicted ET ratio (*P*< .05)

(Table 2). These findings may be attributed to menopause since MS is common to both groups. However, the similarity of levels of oestradiol in POMMS and PRMMS, implicate non-gonadal oestrogen synthesis from testosterone particularly from increased adipose tissue mass. Elevated triglyceride level is a component of MS [15]. Our earlier report showed TG as the least component of MS observed the general population [15]. Although, similar level of TG was observed in both PRM and PRMMS, TG was significantly higher in POMMS than PRMMS in this present study (P<.05). Our findings suggest that CVD risk is exaggerated in menopause. Menopause has been epidemiologically linked with increased CVD risk [1]. During the menopausal transition, there is an emergence of the characteristics of the metabolic syndrome which increases cardiovascular risk [11,12].

Menopause has been reported to have a negative impact on plasma lipoprotein-lipid levels, adverse changes in glucose and insulin metabolism and body fat distribution [7,14]. The menopausal transition has been associated with an accelerated increase of total cholesterol and triglyceride concentrations [22]. Systolic and diastolic BP have been shown to correlate inversely with age at menopause and positively to the length of the postmenopausal period. These reports are partially contrary to our observations, which we attribute to MS and not menopause. Although low level of female steroids has been reported as a major factor for blood pressure elevation [23], In this present study, increase in elevation of BP was observed in both pre and postmenopausal women in association with normal oestrogen levels (Table 1). Only one (0.8%) of the 127 postmenopausal

Table 1. Comparison of age, parity, blood pressure, anthropometric measures and biochemical parameters in premenopausal women with metabolic syndrome, postmenopausal women with metabolic syndrome and premenopausal women without metabolic syndrome (controls)

Index	PRMMS n=44	PRM (Control) n =21	POMMS n = 126	P_1	P_2
Age (years)	40.0 (1.0)	29.0 (1.5)	57.0 (0.8)	<.001*	<.001*
Parity	4.3 (0.2)	2.9 (0.6)	6.3 (0.2)	.016*	<.001*
Height (m)	1.60 (0.0)	1.57 (0.0)	1.59 (0.0)	.011*	0.112
Body weight (kg)	77.8 (2.3)	53.2 (1.3)	72.5 (1.2)	<.001*	0.029*
Body mass index (kg/m^2)	29.9 (0.8)	21.5 (0.4)	28.6 (0.4)	<.001*	0.124
Waist circumference (cm)	101.3 (1.6)	75.8 (1.0)	102.5 (1.0)	<.001*	0.545
Hip circumference (cm)	110.8 (1.5)	92.6 (1.2)	104.9 (0.8)	<.001*	0.001*
Waist Hip Ratio	0.9 (0.0)	0.8 (0.0)	1.0 (0.0)	<.001*	<0.001*
Systolic BP (mmHg)	142.7 (3.8)	112.4 (1.5)	154.3 (2.3)	<.001*	0.010*
Diastolic Blood Pressure(mmHg)	89.3 (1.9)	71.9 (0.9)	90.2 (1.3)	<.001*	0.714
Percentage body fat	42.3 (0.9)	28.4 (1.1)	40.9 (0.6)	<.001*	0.218
FPG (mmol/L)	5.7 (0.4)	4.4 (0.1)	5.1 (0.2)	.021*	0.123
Triglyceride (mmol/L)	0.8 (0.1)	0.6 (0.1)	0.9 (0.0)	.170	0.020*
Total Cholesterol (mmol/L)	3.6 (0.2)	3.8 (0.2)	3.9 (0.1)	.546	0.112
HDLC(mmol/L)	0.9 (0.0)	1.5 (0.1)	0.9 (0.0)	<.001*	0.735
LDLC (mmol/L)	2.4 (0.1)	2.0 (0.2)	2.6 (0.1)	.161	0.232
Leptin (µg/L)	33.6 (5.0)	12.6 (2.0)	18.7 (2.2)	.006*	0.003*
Testosterone (nmol/L)	5.9 (1.0)	16.1 (2.0)	8.0 (0.8)	<.001*	0.155
Oestradiol (nmol/L)	2.1 (0.7)	0.3 (0.1)	1.4 (0.3)	.055	0.283
ET ratio	0.29 (0.1)	0.02 (0.1)	0.2 (0.0)	.025*	0.265
LH (IU/L)	19.8 (2.8)	14.0 (1.9)	26.7 (1.3)	.180	0.014*
FSH (IU/L)	25.1 (4.3)	10.4 (2.8)	54.3 (2.5)	.027*	<0.001*
Prolactin (mIU/L)	453.8(58.3)	945.6 (286.1)	328.9(33.8)	.025*	0.063

*values are in mean (s.e), PRM=premenopausal women without metabolic syndrome (controls), PRMMS= premenopausal women with metabolic syndrome, POMMS=postmenopausal women with MS, t=student's t-test, P_1=probability between PRMMS & PRM (controls), *=significant, n=number of participants, P_2=probability between PRMMS & POMMS, FPG=fasting plasma glucose, HDLC=high density lipoprotein cholesterol, LDLC=low density lipoprotein cholesterol, ET ratio=estrogen-testosterone ratio, LH=luteinizing hormone, FSH=follicle stimulating hormone, n=number of participants, n for leptin is PRMMS=23, PRM=14, POMMS=50; n for parity is PRMMS=42, PRM=10; POMMS=111; n for percentage body fat is PRM=20.*

Table 2. Multiple regression analyses in premenopausal women without metabolic syndrome (Controls), premenopausal and postmenopausal women with metabolic syndrome

Groups	Dependent parameter	Predictors	β	T	*P*
PRM					
R^2=.196, F=4.630, *P*=.044	Oestradiol	Diastolic BP	.443	2.152	.044*
PRMMS					
R^2=.567, F=54.998, *P*= <.001	Testosterone	Oestradiol	.753	7.416	<.001*
POMMS					
R^2=.107, F=5.768, *P*=.020	Testosterone	Diastolic BP	.328	2.402	.02*
R^2=.299, F=52.507, *P*=<.001	Oestradiol	Testosterone	.456	6.469	<.001*
R^2=.447, F=49.378, *P*=<.001	Oestradiol	ET ratio	.342	5.242	<.001*
R^2=.503, F=40.751, *P*=<.001	Oestradiol	FSH	.261	3.665	<.001*
R^2=.132, F=18.733, *P*=<.001	ET ratio	Oestradiol	.369	4.490	<.001
R^2=.177, F=13.145, *P*=<.001	ET ratio	LDLC	.212	2.587	.011

*PRM=premenopausal women without metabolic syndrome (controls), PRMMS= premenopausal women with metabolic syndrome, POMMS=postmenopausal women with MS, t=Student's t-test, P=probability, *=significant, β=beta coefficient, F=F statistics, BP=blood pressure, ET ratio=oestradiol-testosterone ratio, FSH=Follicle Stimulating Hormone, LDLC=low density lipoprotein cholesterol*

participants did not have MS and was excluded from the study, which is the limitation in this study. It is possible that mechanisms involving leptin may be involved in maintaining oestrogen levels in MS in both stages in an attempt to normalize blood pressure [16]. Leptin level, though significantly lower in POMMS than PRMMS, was higher in POMMS than PRM (Table 1).

Cardioprotection of oestrogen and the use of hormone replacement therapy (HRT) on postmenopausal women are controversial. It is thought that HRT may actually increase the risk of cardiovascular events. Patients and clinicians are therefore reluctant in continuing the use of HRT regimes [1]. Contrarily, Ciccone et al. [24] showed improvement in CVD risk on oestradiol administration in postmenopausal women. Both general and central obesity were associated with MS in our previous studies [3,5]. This is confirmed by our present findings of significant and negative alterations of these indices in PRMMS compared with PRM, which were aggravated in POMMS. Our observations suggest association of MS with CVD risk in pre and postmenopausal women irrespective of oestradiol levels. The observed elevated FPG and reduction of HDLC and testosterone levels in addition to increase in adipose tissue mass both in PRMMS and POMMS may be important in CVD and type 2 diabetes mellitus risk. Short-term dietary modulation and the use of carotenoids have been shown to improve cardiovascular risk, inflammation and oxidative stress associated with MS [25,26]. We postulate that postmenopausal women without MS may benefit from oestrogen replacement therapy because of expected menopause induced reduction of oestradiol levels. However, testosterone replacement therapy may benefit individuals with MS. DBP predicted testosterone in POMMS only in this present study (Table 2). Functional androgen receptors are present in the heart and testosterone acts directly at the myocardium suggesting that testosterone confers cardio protection by direct action on the myocardium. Moreover, low testosterone in patients with ischemic disease and alleviation of observed symptoms with testosterone treatment have been reported [27]. Further studies possibly in younger MS and non-MS premenopausal women as well as MS and non-MS postmenopausal women may be necessary to elucidate these findings.

4. CONCLUSION

Observations from our present study suggest that oestradiol may protect against cardiovascular risk in premenopausal women without MS only. This protection diminishes as these women develop MS, which worsens as women attain menopause, with redistribution of abdominal tissue. Hormone replacement therapy may take MS status into consideration in the management of postmenopausal women with CVD risk. Dietary modulation and the use of carotenoids may improve cardiovascular risk, inflammation and oxidative stress associated with MS.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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