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EVALUATION OF LIPIDS AND LIPOPROTEIN LEVELS OF PREMENOPAUSAL AND POST MENOPAUSAL WOMEN IN PORT HARCOURT METROPOLIS

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ABSTRACT

Background: Menopause is regarded as one of the risk factors for cardiovascular diseases. **Objective**: This study was designed to estimate the serum levels of total cholesterol, triglycerides, high density lipoprotein cholesterol, low density lipoprotein cholesterol, very low density lipoprotein cholesterol and atherogenic index of plasma and Castelli risk index 1 and 11 and the effect of body mass index (BMI) and blood pressure (BP) in pre-menopausal and post-menopausal women in Port Harcourt metropolis. **Methodology**: The lipoproteins, blood pressures and BMI were determined using standard procedures. **Results**: The mean age of the pre-menopausal women was significantly different ($p<0.05$) from that of the post-menopausal women. Significant increase ($p<0.05$) in means of the lipoproteins between the two groups of women was found in TC, HDL-C and LDL-C. Remarkable increase in the systolic and diastolic blood pressure of the post-menopausal women up to 40% (hypertensive) above the normal range was observed. Higher percentage of the post-menopausal women were over weight and obese. The AIP and CRI (I and II) ratios between the two groups were seen to be higher in the post-menopausal women. **Conclusion**: The present study shows that dyslipidaemia, blood pressure and body mass index are significantly associated with menopausal transition. The lipid profile of the post-menopausal women in this study is very unfriendly. Thus, it is proposed that lipoprotein ratios and triglyceride based index (atherogenic index of plasma; AIP) should be routinely done in post-menopausal women since they can add significant diagnostic value when assessing the cardiovascular risk of menopausal women.

KEYWORDS: Lipoprotein, Pre-menopausal, Post-menopausal, Cardiovascular disease, Atherogenic Index of Plasma, Castelli Risk Index.

INTRODUCTION

Atherosclerotic cardiovascular diseases have been reported to occur more in men than in premenopausal women. However, after menopause, this incidence steeply increases, resulting in no difference between men and women in individuals older than 70. Menopause is therefore regarded as one of the risk factors for cardiovascular diseases.[1,2] The levels of total cholesterol and low density lipoprotein (LDL) cholesterol have been shown to increase after menopause.[3,4] The controversy as to what extent these atherogenic lipids are elevated have been reported. Cross-sectional studies have shown a considerable influence[2-4], whereas most longitudinal follow-up studies reveal only small changes.[5-8] It is not certain whether the transition from pre-menopause to post-menopause in a women leads to a decrease in high-density lipoprotein (HDL) cholesterol.[7-8]

Menopause is defined by cessation of menstruation for a period longer than one year, and begins with changes in ovarian function. Increased levels of cholesterol, triglycerides, LDL, apolipoprotein B and decreased levels of HDL and apolipoprotein A are characteristics of lipid profile in menopause. With increase in LDL concentration, the composition of LDL molecule also changes so that participation of low density lipoprotein is increased by 30-40%.[9] During menopause, concentration of triglycerides also increases, which is related to the increase of the abdominal fat amount and insulin resistance. Menopause causes decrease of HDL concentration and changes in HDL structure as well.[10]

Variations in the distribution of serum lipids and lipoproteins have therefore been implicated in the aetiology of arteriosclerosis and cardiovascular diseases but the extent to which these variations occur in the transition from premenopausal to menopausal in women in Port Harcourt has been poorly .investigated. Thus, this study was designed to estimate the serum levels of total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C), and atherogenic index of plasma and Castelli risk index 1 and 11 and the effect of body

mass index (BMI) and blood pressure (BP) in pre-menopausal and post-menopausal women in Port Harcourt metropolis.

MATERIALS AND METHODS

This research was aimed at establishing differences in lipid status in premenopausal with regular menstruation and menopausal women whose menstruation has sized for over a year. Also, we intended to establish the influence of body mass index and blood pressure on the women recruited into the study. Premenopausal and postmenopausal women living within Port Harcourt and its environs were recruited for the study. The study group consisted of one hundred women (50 premenopausal) of average age range 16-46 years and (50 post-menopausal) women of age range 49-80 years with average menopause length of 1.5 to 30 years. The exclusion criteria used to select the subjects included the following: no hormonal therapy administered, no medications that affect lipid profile administered, no smoking and abstinence from alcohol.

The consent of subjects were obtained via a questionnaire and the purpose and objectives of the study was clearly explained to them. Ethical clearance was granted by the Rivers State Ministry of Health Local Ethics Committee. The ages, health status, drug therapy status, smoking and drinking habits and other personal data were obtained via a comprehensive questionnaire. Fasting venous blood were collected into plain sample containers. The serum was extracted according to the method of Sood[11] and analyzed immediately for lipid profile. The height was measured (in metres) to the nearest 0.1 m with a calibrated meter rule placed horizontally against the wall according to WHO.[12] Weight was measured (in kilograms) with participants wearing light clothing and no shoes, and recorded to the nearest 0.1 kg.[12] The Hana Bathroom Scale (Pese-Personne Br 9011), made in China, weighing balance, was used in measuring the weight of the participants. BMI was taken as the ratio of weight (kg) to the square of the height (m^2).[12] The BMI was classified as follows: ≤ 18.5 kg/m^2, underweight; 18.5 to 24.9 kg/m^2, normal; 25.0 to 29.9 kg/m^2, overweight; 30.0 to 4.9 kg/m^2 class 1 obesity; 35.0 to 39.9 kg/m^2, class 2 obesity≥40.0 kg/m^2 class 3 obesity.[12] Blood pressure was obtained 3 times from each subject during the survey. Each measurement was made using a mercury sphygmomanometer, with the participant seated. The arithmetic mean was then calculated using all available systolic and diastolic readings. In this analysis, individuals with a systolic blood pressure lower than 140 mm Hg and diastolic blood pressure lower than 90 mm Hg who were not receiving antihypertensive treatment were defined as normotensive. Individuals were classified as hypertensive if they had a mean blood pressure of 140 mmHg or higher (systolic) or 90 mmHg or higher (diastolic) or reported current use of medication for hypertension.[13]

Total cholesterol was measured by the method of Trinder.[14] Triglycerides was isolated enzymatically by glycerol-3-phosphate oxidase –phenol + aminophenazone method as described by Schettler and Nussel[15]. The method of Lopes-Virella et al. [16] was used for the measurement of high-density cholesterol in serum. Low density lipoprotein cholesterol was calculated using the Friedewald[17] formula:

LDL-C (mmol/L) = TC – (HDL-C + TG/2.2).

VLDL C was calculated using the formula

VLDL-C (mmol/L) = TG/2.2.[17]

All the analytes were measured using a spectrophotometer at 520 nm wavelength.

The atherogenic ratios were calculated as follows:

Atherogenic Index of Plasma (AIP) = log TG/HDL-C.[18]

Castelli's Risk Index (CRI-I) = TC/HDL-C.[19]

Castelli's Risk Index (CRI-II) = LDLC/HDL-C.[19]

The results obtained were statistically analyzed and compared between different groups of the study. The values of the parameters studied are expressed as mean ± standard deviation. Comparison of mean was done using the student t=test and analysis was performed with the GraphPad Instat Version 3.10, 12 bit for Windows. Statistical significance was considered at $p<0.05$.

RESULTS

The mean age for the pre-menopausal women was 27.86±8.46 years while that for the post-menopausal women was 54.02±8.12 years and the difference in the age was significant ($p<0.05$, $t=15.78$). The mean ±SD of TC, HDL-C, LDL-C, TG and VLDL-C in the pre-menopausal women were 3.22 ±0.77 mmol/L, 1.69±0.74 mmol/L, 2.10 ± 0.64 mmol/L, 1.05 ±0.47 mmol/L and 0.46±0.34 mmol/L respectively. Similarly, the mean ±SD of TC, HDL-C, LDL-C, TG and VLDL-C of the post-menopausal women were 4.58 ±1.01 mmol/L, 1.11±0.24 mm0l/L, 3.00±0.85 mmol/L, 1.12±0.48mmol/L and 0.47±0.23 mmol/L respectively. The TC was increased in the post-menopausal women than in the pre-menopausal women and the difference was significant ($p<0.05$). Also, significant differences ($p<0.05$) in means were observed in the HDL-C and LDL-C between the pre-menopausal and post-menopausal women. No significant difference ($p>0.05$) in means were observed in the means of TG and VLDL-C between the pre-menopausal and post-menopausal women. This is shown in table 1.

The distribution of the blood pressure in the pre-menopausal and post-menopausal women is shown in table 2. Amongst the pre-menopausal women, 6% had systolic blood and diastolic blood pressure measurement above 140 mmHg and 90 mmHg (hypertensive) while 94% had blood pressure within the normal range (normotensive). However, there was remarkable increase in the systolic and diastolic blood pressure of the post-menopausal women up to 40% (hypertensive) above the normal range. The proportion of the post-menopausal

women with normal systolic and diastolic blood pressures was 60%.

The classification of the body mass index in the pre-menopausal and post-menopausal women is shown in table 3. While 46% of the pre-menopausal women were within the WHO recommended BMI for normal, the proportion decreased to 18% in the post-menopausal women. The table further shows that 30% and 24% of the pre-menopausal women were over- weight and obese respectively while remarkably increased proportion of 36% and 46% were over-weight and obese in the post-menopausal women respectively.

Table 4 shows the TC/HDL-C, LDL-C/HDL-C and AIP ratios between the two groups. The ratios were seen to be higher in the post-menopausal when compared to pre-menopausal women.

Table: 1. Comparison of age, serum total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, Triglycerides and very low density lipoprotein cholesterol between the study groups

Parameters	Pre-menopausal women (n=50)	Post-menopausal women (n=50)	t- value	Significance
Age (years)	27.86 ±8.46	54.02±8.12	15.78	p<0.05
TC (mmol/L)	3.22±0.70	4.58±1.01	3.54	p>0.05
HDL-C(mmol/L)	1.69±0.74	1.11±0.24	6.77	p<0.05
LDL-C (mmol/L)	2.10±0.64	3.00±0.85	3.67	p<0.05
TG (mmol/L)	1.05±0.47	1.12±0.48	1.45	p>0.05
VLDL-C (mmol/L)	0.46±0.34	0.47±0.23	1.19	p>0.05

Table: 2. Distribution of systolic and diastolic blood pressure in the premenopausal and post- menopausal women

Blood pressure (mmHg)	Pre-menopausal women	Post-menopausal women
	Percentage (%)	Percentage (%)
Hypertensive	6%	40%
Normotensive	94%	60%
Hypotensive	-	-

Table: 3. Distribution of body mass index in the pre-menopausal and post-menopausal women

BMI Classification	% of the BMI levels in the population (kg/m^2)	
	Pre-menopausal	Post-menopausal
Under weight (< 18.5 kg/m^2)	-	-
Normal weight (18.5-24.8 kg/m^2)	22.2 (46%)	22.9 (18%)
Over weight (25.0-29.9 kg/m^2)	26.8 (30%)	27.2 (36%)
Obese (30.00 and above kg/m^2)	31.0 (24%)	35.2 (46%)

Table 4: Atherogenic Index of plasma, Castelli Risk Index 1 and Castelli Risk Index 11 in pre-menopausal and post-menopausal women

Study subjects	TC (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	TG (mmol/L)	TC/HDL	LDL/HDL/	TG/HDL-C	Log TG/HDL-C
Pre-menopausal women	4.22	1.69	2.10	1.05	2.625	1.312	0.621	-0.206
Post-menopausal women	4.58	1.11	3.00	1.12	4.126	2.703	1.009	0.004

DISCUSSION

In this study, attempts were made to evaluate the serum levels of lipids and lipoprotein levels in pre- and post-menopausal women. Menopause is a natural event in the ageing process and signifies the end of reproductive years with cessation of cyclic ovarian functions as manifested by cyclic menstruation. It is heralded by menopausal transition, a period when the endocrine, biological and clinical features of approaching menopause begins.[20] The hormonal changes associated with menopause e.g. low plasma levels of estrogen and marked increase in gonadotropic hormones such as luteinizing and follicle stimulating hormone levels exerts a significant effect on the metabolism of plasma lipids and lipoproteins.[21] Atherogenic changes in lipid and lipoprotein profiles have been found in menopause

induced by surgery[22, 23] and epidemiological studies comparing premenopausal women with menopausal and postmenopausal women.[24,25] Although atherogenesis is a multifactorial process, abnormalities in lipoprotein metabolism are one of the key factors, representing around 50% of the population-attributable risk of developing cardiovascular disease.[26] Therefore, estimation of cardiovascular risk has become the cornerstone of cardiovascular prevention. In this study, the mean age for the pre-menopausal women was 27.86±8.46 years while that for the post-menopausal women was 54.02±8.12 years implying that the age in the menopausal women is greater than that in the pre-menopausal women and the difference in the age between the two groups has been reported to be responsible for the difficulty encountered in designing studies that can separate the effects of the normal aging process from natural menopause which usually take place between 45 and 50 years.[27]

In our study, significant difference ($p<0.05$) in the level of total cholesterol between the pre-and post-menopausal women was observed when compared with their pre-menopausal counterparts. The LDL-C concentration was also significantly higher ($p<0.05$) in post-menopausal women in this study than in the pre-menopausal women. The lower LDL-C levels (of the premenopausal women in this study could be explained by the increased HDL-C (1.69±0.74 mmol/L) which scavenges cholesterol esters, reducing its availability for LDL-C formation. These findings are compatible with the observations made in other studies by Kalavathi et al[28], Matthews et al.[29], Muzzio et al.[30] and Shenoy and Vernekar.[31]

However, Kuller et al.[32] found n o significant changes in LDL cholesterol concentrations in women passing from premenopausal to postmenopausal. The observed increase in the levels of LDL-C in the post- menopausal women is mainly due to the role of lipoprotein lipase (LPL) in the metabolism of lipids. Lipoprotein lipase (LPL) is regulated by circulating estrogen. LPL catalyses the hydrolysis of VLDL to form intermediate-density lipoprotein and later LDL. Estrogen deficiency after menopause increases the plasma LPL and hepatic TG lipase activity causing plasma LDL to accumulate and also leads to down-regulation of LDL receptors.[30,33]

Mechanisms responsible for increased cholesterol concentrations in the early postmenopausal period are far from being clear. The mean age of the post-menopausal women in this study was 54 years indicating early menopause. However, increase in TC and LDL in post-menopausal women has been reported to be caused by deficiency of estrogen.[29,30] There is also epidemiological evidence that higher than normal cholesterol levels may be associated with abdominal body fat distribution in either obese or non-obese individuals.[34] However, Cho et al.[35] opined that these increases in total cholesterol and LDL cholesterol in post-menopausal women may not be related to changes in body weight or fasting blood sugar, but mainly to changes in female sex hormones. The deterioration of lipid metabolism especially hypercholesterolemia, seems to be closely related to the onset of atherosclerosis, which has been considered to cause cardiovascular disease (CVD) as angina, myocardial infarction, cerebral infarction, etc.[36]

In this study, we observed a significant decrease ($p<0.05$) in HDL-C in the post-menopausal women when compared with the levels in the pre-menopausal women. In two prospective studies women who became post-menopausal showed a slight but significant reduction in high density lipoprotein (HDL-) cholesterol and the HDL-C could remain unaffected or decreased in advanced menopause.[37] In pre-menopausal women, positive correlation between estradiol and HDL and apolipoprotein A affirms mutual performance of HDL, apolipoprotein A and estrogen[38], a relationship that do not exist in post-menopausal. This implies that a combination of factors including estrogen, estradiol and apolipoprotein A affect and regulate HDL concentration in menopause. Menopausal status was unlikely to alter HDL-C level, since no significant inter-group differences were found regarding its levels. Our finding was compatible with findings in certain previous studies [39, 23] and incompatible with findings in others.[40,41]

It was also observed in this study that TG concentration of pre-menopausal women when compared to post-menopausal women was not significantly different ($p>0.05$). This finding is, however, inconsistent with the studies reported by Welty[42], Hallberg and Svanborg[43] and Shenoy and Vernekar[31] Usoro et al.[44] who investigated on the lipid profile of post-menopausal women in Calabar, Nigeria, a community within the same geo-political zone with P ort Harcourt where the present investigation was done, did not also observe significant variation in the TG concentration between the two groups. Although triglyceride levels did not change with menopause, several variables are related to changes in triglyceride levels. Factors related to changes in triglyceride levels are rather different from those related to changes in cholesterol levels. Changes in triglyceride levels are dependent both on body weight and female sex hormones, especially estradiol.[45]

The Hypertension in Seven Latin American Cities: the Cardiovascular Risk Factor Multiple Evaluation in Latin America (CARMELA) study showed that prevalence in hypertension increased with age (>55 years of age) and was higher in women than in men.[46] Prevalence of hypertension in menopausal women was higher has been shown to be higher than in pre-menopausal women. An Italian study (the Study on Hypertension Prevalence in Menopause in the Italian Population [SIMONA])[47] showed a higher prevalence in postmenopausal women (64.1%) as compared with perimenopausal and premenopausal women, with this increase independent of

age and BMI. Prevalence approaches 60% in women older than 65 years, largely because of progressive arterial stiffening and abruptly falling estrogen levels, which in turn activate the renin-angiotensin-aldosterone and sympathetic nervous systems.[48] The unfavourable effects attributable to menopause are due to the more advanced age of menopausal women.[49] In this study, the percentage prevalence of hypertension amongst post-menopausal women was 40%, suggesting an increase in blood pressure in post- menopausal women in this population while 60% of them were normotensive. The mean age of the post-menopausal women in this study is 54 years. The low prevalence rate of hypertension in this study may be due to the mean age of the post-menopausal women and the fact that multiple mechanisms are sometimes involved in the onset of hypertension in menopausal women.[50] However, some authors have also observed that blood pressure is not increased by menopause[51, 52] and that on the contrary, a combination of risk factors can be found in pre-menopausal women who are traditionally considered to be at low cardiovascular risk.[53]

The prevalence of obesity is rising in developed and developing nations and studies have demonstrated a role for weight gain in morbidity and mortality risk.[54, 55] When the BMI of pre-menopausal and post-menopausal women in this study was stratified according to the WHO (12) criteria, it was observed that while 30% of the pre-menopausal women were over-weight (BMI=26.8 kg/m^2), in the post-menopausal population 36% (BMI=27.2 kg/m^2) were over-weight. The percentage of the pre-menopausal women that were obese was 24% (BMI=31.0 kg/m^2) while that for post-menopausal women was 46% (BMI=35.2 kg/m^2). These findings were similar to the observations made in a study of post-menopausal women in Calabar, Nigeria Usoro et al.[44] where a mean BMI of 23.31 and 25.97 kg/m2 for premenopausal and post- menopausal women respectively were determined.[47] Gavaler and Rosenblum[56] reported an increase in BMI with menopause and identified smoking, moderate drinking, fat as percent of total calories, neuro-endocrine factors, and being Black or Asian as significant predictors for increased BMI.

Hypoestrogenism resulting from menopause has been implicated as one of the main cause of obesity, vasomotor, urogenital and psychological symptoms, as well as for poorer sexual performance and the high profile or morbidity and mortality in women after the age of 50, when associated with environmental, psychosocial and cultural factors.[57] Although estrogen level was not measured in this study, as reported earlier, the mean age of the post-menopausal women in this study was 54.02 years which is in agreement with the age within which these events are expected in post-menopausal women. It is thus possible to postulate that the high prevalent rate of obesity observed in the post-menopausal women in this study could be contributed by hypoestrogenism or other multiple factors associated as the main causes of obesity in women, including changes inherent to the aging process itself, as well as changes in lifestyle such as a less active lifestyle and increased consumption of energy dense food.[58]

The total/high-density lipoprotein (HDL) cholesterol ratio, known as the atherogenic or Castelli index and the LDL/HDL cholesterol ratio are two important components and indicators of vascular risk, the predictive value of which is greater than the isolated parameters. The total/HDL cholesterol ratio has high discriminatory power for coronary heart disease, as well as its great predictive capacity.[59] In this study, the TCLHDL ratio for the pre-menopausal women was 2.625 while that for the post-menopausal women was 4.126, a value that is predictive of cardiovascular risk for the post-menopausal women.[60] Again the LDL/HDL ratio was also increased in the post- menopausal group and it has been shown that LDL/HDL ratio is a significant predictor for the development of atherosclerosis both in Caucasians and Nigerians.[61, 62]

Like the total/HDL cholesterol ratio, LDL/HDL cholesterol may have more predictive power if triglyceridaemia is taken into account.[63] The predictive risk for LDL/HDL ratio for women is >3.00.[64] Individuals with a high total/HDL cholesterol or LDL/HDL cholesterol ratio have greater cardiovascular risk owing to the imbalance between the cholesterol carried by atherogenic and protective lipoproteins. This may be due to an increase in the atherogenic component contained in the numerator, a decrease in the anti-atherosclerotic trait of the denominator, or both. [65]

Atherogenic Index of Plasma (AIP) has been shown to be a strong marker of CVD with the potential to predict the risk of atherosclerosis and coronary heart disease.[66-68] The true relationship between protective and atherogenic lipoprotein and its association with the size of pre- and anti- atherogenic lipoprotein particle is usually reflected by the atherogenic index of plasma (AIP).[69] It has been suggested that an AIP value of under 0.11 is associated with low risk of CVD; the values between 0.11 to 0.21 and upper than 0.21 are associated with intermediate and increased risks, respectively[18,69] The AIP obtained for the post-menopausal women though less than 0.11 is still than that of the pre-menopausal women. Increases in the AIP value has been observed and it is possible to estimate that as the age of the post-menopausal women increases, all things being equal greater chances of atherogenicity could be anticipated in this group.

CONCLUSION

The present study shows that dyslipidaemia, blood pressure and body mass index are significantly associated menopausal transition. The lipid profile of the post-menopausal women in this study is very unfriendly. Thus, it is proposed that lipoprotein ratios and triglyceride based index (atherogenic index of plasma;

AIP) should be routinely done in post-menopausal women since they can add significant diagnostic value when assessing the cardiovascular risk of menopausal women.

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