Atherogenic index of plasma as useful predictor of cardiovascular risk among postmenopausal women in Enugu, Nigeria

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Abstract

Background: Menopausal health in our environment has received little attention. As an independent risk factor for dyslipidaemia, the degree and pattern of derangement, though difficult to assess may adversely affect the cardiovascular health of our women.

Objectives: To estimate the serum lipid profile and the atherogenic index of plasma in normal post menopausal women.

Methods: This is a cross sectional study involving 80 apparently healthy women voluntarily recruited from staff of the University of Nigeria and the Teaching Hospital (UNTH) located in Enugu. They include 50 postmenopausal subjects aged between 50 and 70 years and 30 premenopausal controls aged between 25 and 49 years. Total cholesterol (TC), and the various subfractions ;high density lipoprotein cholesterol (HDL-C), very low density lipoprotein cholesterol (VLDL-C), low density lipoprotein cholesterol (LDL-C) and triglycerides (TG) were determined. Atherogenic index of plasma (AIP); log (TG/HDL-C) was calculated.

Results: There were statistically significant increases ($P< 0.0001$) in TC, TG, LDL-C, VLDL-C and AIP but a statistically significant decrease ($P<0.0001$) in HDL-C in postmenopausal women when compared with the premenopausal subjects. Except HDL-C that showed insignificant reduction, there were statistically significant derangement of other lipid subfractions as the duration of menopause increased.

Conclusion: Menopause, no doubt alters lipid profile. A triglyceride based index (AIP) can significantly add value when assessing the risk of developing atherosclerosis in Nigeria.

Key Words: Lipid profile, atherogenic index of plasma (AIP), postmenopausal women, dyslipidaemia, atherosclerosis

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Introduction

Menopause, which is the cessation of monthly menstrual cycles results from the loss of ovarian function and a decrease in oestrogen production. The median age for the final menstrual period is about 51 years, when the ovarian follicular reserve and indeed oestrogen production is significantly reduced[1]. Reports also indicate that while a woman may stop menstruating at this time, endogenous cycling and ovulation may still occur for months or even years[2]. Decreased oestrogen during and after menopause causes structural, physiological and biochemical changes that alter the general health status of the woman. The anti-atherogenic effect of oestrogen and the protection of females against coronary artery disease are well defined during the premenopausal period[3]. Indeed it has been shown that post menopausal women have less cardiovascular friendly lipid profiles than before menopause[4].

Lipid profile consists of a group of biochemical tests often used in predicting, diagnosing and treating lipid-related disorders including atherosclerosis[5]. Generally, the hyperlipidemias are of interest to the physician in the context of risk factors for ischaemic heart disease (IHD) and peripheral vascular disease[6]. The first step in diagnosis of hyper- and hypolipoproteinaemias is to define the lipoprotein pattern by chemical analysis of the plasma lipids and lipoproteins[7]. Abundant evidence has accumulated relating the concentrations of lipids (total cholesterol and triglycerides) and their associated blood transporting lipoproteins (HDL-C, LDL-C, VLDL-C) with the occurrence of atherosclerosis in general and coronary artery disease (CAD) in particular[8]. The strong association between the risk of coronary artery diseases (CAD), high levels of LDL-C and low levels of HDL-C has been well established[9, 10]. However the enormous contributions of triglycerides (TG) to cardiovascular risk have been underestimated especially in our environment[11]. Indeed high levels

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have been associated with an increased incidence of CAD[12] and an increased population of small dense LDL-C particles[13].A lot of work has been done on the relationship between TG and HDL-C, and it has been shown that the ratio of TG to HDL-C was a strong predictor of myocardial infarction[14]. Universally, atherogenic index of plasma (AIP) calculated as log (TG/HDL-C) has been used by some practitioners as a significant predictor of atherosclerosis[15, 16]. Although this index has been used to predict the risk of atherosclerosis in hypertensive postmenopausal women in south East Nigeria[11], there is paucity of literature on its application to normotensive postmenopausal women.

In Nigeria, despite the abundant natural resources, most of our people are laden with poverty, with a lot of communicable diseases ravaging our communities. Maternal mortality is embarrassingly very high and is still rising. Understandably, the main focus has been on how to tackle these problems and this invariably results to neglecting menopausal health.

In this study, we ascertained the clinical utility of adopting this triglyceride based index as an indicator and a significant adjunct for predicting atherosclerosis in normotensive postmenopausal women.

Methods

This is a cross-sectional study involving 80 female subjects recruited from serving and contract staff of the University of Nigeria, Enugu Campus and the University of Nigeria Teaching Hospital, Enugu, Nigeria. They were selected by simple random sampling using a lucky dip of yes or no. They include 50 apparently healthy postmenopausal women (age 50 – 70 years) who are not on any form of medication. Thirty (30) apparently healthy premenopausal women (age 25 – 49 years) served as control subjects. Informed consent was obtained from both groups and ethical clearance was obtained from the relevant authority. Those with history of menstrual disorders were excluded. Other exclusion criteria include obesity, diabetes mellitus, hypertension, hormonal contraception, pregnancy, smoking and heavy exercise. All the women belong to the Ibo tribe of the Nigerian nation and are domiciled in Enugu metropolis, South East Nigeria.

Fasting blood samples (3.0mls) were collected by venopuncture from the antecubital vein, into sterile plain tubes, under aseptic conditions. For the premenopausal women, samples were collected on the last day of the menstrual period in other to exclude pregnancy. The blood samples were allowed to clot and centrifuged at 3000 rpm for 5 minutes. Serum was stored frozen at -20^0 C and the analysis was carried out within one week of sample collection. The serum was used for the analysis of total cholesterol, triglycerides, and HDL-cholesterol levels. Total cholesterol was measured using established enzymatic methods of Allain et al [17] with the Randox cholesterol kit (Randox England).HDL-C was estimated by HDL-C precipitant method[18].Triglyceride was assessed enzymatically[19]. LDL-C was calculated using the Friedewald formula [20]. VLDL-C was calculated based on the formula VLDL-C=TG/2.2[21].

Statistical Analysis

This was done using SPSS for windows version 11. Results were presented as mean ± standard deviation (Mean ± SD).Test for significance was done using Student's T-test and Analysis of variance (ANOVA) where applicable. Multiple comparisons of the mean differences among the variables were done using the Tukeys post-hoc test .P values less than or equal to 0.05 were considered as significant.

Results

The Results are presented in tables 1 to 2. Table 1 shows the mean, standard deviation of total cholesterol and its sub-fractions. There were statistically significant increases (P<0.0001) in TC, TG, LDL-C and VLDL-C in the two groups studied and a statistically significant decrease (P< 0.0001) in HDL-C. The AIP (log TG/HDL-C) was -0.17±0.09 before menopause and significantly increased to 0.15±0.35 during the post menopausal period (p<0.0001).The mean, standard deviation of TC, and its sub-fractions in early (10 years) and late (20 years) postmenopausal women are presented in table 2.

Table 1: Total cholesterol and subfractions (mmol/l)

Variables	Premeno pausal (n= 30)	Postmeno pausal (n= 50)	P value
TC	4.6 ± 0.62	6.43±0.92	P<0.0001
TG	1.02± 0.44	1.68± 0.63	P<0.0001
HDL	1.52± 0.36	1.19± 0.28	P<0.0001
LDL	2.71±1.13	4.46±0.68	P<0.0001
VLDL	0.46± 0.20	0.76±0.20	P<0.0001
AIP	-0.17±0.09	0.15±0.35	P<0.0001

Table 2 showing lipid profile and duration of menopause (mmol/l)

	Premeno pausal (n= 30)	10- years Post meno pausal (n=30)	20- years Post meno pausal (n=20)	P Value
TC	4.6± 0.62	6.05±1.03	6.80±0.81	P<0.0001
TG	1.02± 0.44	1.4± 0.80	1.96± 0.45	P<0.0001
HDL-C	1.52± 0.36	1.20 ±0.27	1.17± 0.28	P=0.117
LDL-C	2.71± 1.13	4.21± 0.81	4.70± 0.55	P<0.0001
VLDL-C	0.46± 0.20	0.63± 0.37	0.89± 0.41	P<0.0001
AIP	-0.17±0.09	0.07±0.47	0.22±0.21	P<0.0001

Apart from a decrease in HDL-C that was insignificant (p=0.117),there were statistically significant increase in other lipid subfractions with the duration of menopause (p<0.0001).Multiple comparisons using the post hoc test did not show any significant changes between 10 and 20 years post menopause for TC (p=0.111) and LDL- C (p=0.064). Other post hoc tests were statistically significant. For TC, premenopause versus 10 and 20 years post menopause (p<0.0001). TG, premenopause versus 10 years postmenopause (p=0.001), 10 years postmenopause versus 20yrs postmenopause (p<0.0001). LDL-C, premenopause versus 10 and 20 years post menopause (p<0.0001). VLDL-C, premenopause versus 10 years post menopause (p=0.026), premenopause versus 20 years post menopause (p<0.0001), 10 years versus 20 years post menopause (p=0.002).The value of AIP significantly increased from -0.17±0.09 before menopause, to 0.07±0.47, 10 years post menopause, and 0.22±0.21 20 years post menopause (p<0.0001).However, multiple comparisons did not show any significant difference between 10 years and 20 years post menopause (p=0.116).

Discussion

In the present investigation, there were statistically significant increases in TC, TG, LDL, VLDL and AIP when post menopausal Ibo women were compared to their premenopausal counterparts. There was also a statistically significant decrease in the HDL of postmenopausal women when compared to the premenopausal counterparts. These findings are similar to reports from Nigeria and other parts of the world[4, 10,11,22,23].

Studies have shown that menopause is associated with low HDL-C levels[24, 25]. There have been suggestions that isolated low HDL-C levels themselves may be major risk factors for coronary heart disease (CHD) in postmenopausal women[26, 27]. Furthermore it has also been estimated that for any 1.0mg/dl (0.026mmol/ml) increase in HDL-C, there is a 3% decrease in risk of coronary artery disease and a 4.7% decrease in the risk of mortality from cardiovascular disease[28].

In our environment, most studies done on lipid profile and menopause have mainly been cross-sectional. Due to logistic and peculiar socioeconomic difficulties, none has been able to follow up the patients with dyslipidaemia in other to ascertain the percentage that will develop atherosclerosis. Until such is done the need to develop other indexes for assessing the risk of atherosclerosis cannot be overemphasized, and these should act to compliment the existing ones. Isolated elevation of cardio unfriendly or reduction in cardio protective lipoproteins may not on its own be enough to assess cardiovascular risk. Ultimately, there may be diversities in absolute values obtained as a result of some inadvertently; un-excluded co-founding variables which will as a matter of fact not affect the ratios. Indeed, HDL-C/LDL-C ratio has been of great value in the assessment of cardiovascular risk, especially when the absolute values of the individual lipoproteins seem normal. Thus, the use of other indexes which has been minimally applied should be encouraged.

Isolated elevation in triglycerides increases CHD risk more in women than men, ,but its effect can be counteracted by the levels of HDL-C[29].The atherogenic index of plasma which is a mathematical relationship between TG and HDL-C has been successfully used as an additional index when assessing cardiovascular (CV) risk factors[15,16].Indeed, it has been suggested that AIP values of -0.3 to 0.1 are associated with low, 0.1 to 0.24 with medium and above 0.24 with high CV risk[30]. Based on our findings, post menopausal women in our environment are thus at a medium risk of developing CAD. Although the differences in AIP did not show statistically significant increase as menopause progressed, the absolute values indicate that the first decade of menopause is associated with low risk while the second decade is associated with medium risk for CAD. Indeed, It has been demonstrated that the development of CAD is a function of the particle size of LDL-C and HDL-C, with the small particle size exhibiting great atherogenic potential[31]. Indeed, cholesterol etherification rate in HDL-C plasma (FER_{HDL}) has a strong relationship between lipoprotein particle sizes and thus can be considered

as a functional risk marker for CAD[15, 32]. More recently, researchers have shown that the log arithmetically transformed ratio TG/HDL-C is the best determinant for FERHDL and thus a better predictor of cardiovascular risk than other previously used lipid parameters[33].Furthermore, in situations where other atherogenic risk parameters appear normal, AIP may be the diagnostic alternative. This scenario was typified in hypertensive menopausal women in Eastern part of Nigeria, where the value of AIP approached high risk levels (0.36), despite the apparent nonsignificant changes in the classical lipid markers[11].

In Nigeria, there is a general tendency that focuses more attention towards premenopausal health to the detriment of health issues in the postmenopausal period. This trend may not be unrelated to the great importance attached to pregnancy and child bearing[34] .The resultant effect is the paucity of literature in events associated with or directly related to menopause. The present study is, therefore, a contribution to the development and standardization of values of lipid profile that will enable the establishment of a working range of values for our peculiar environment.

Dyslipidaemia in our postmenopausal women is indicative of their susceptibility to atherosclerosis and other cardiovascular disorders, however we were unable to follow up these women to determine those that will develop CAD. Thus we advocate more research so as, to provide a reliable working global or regional range of values. Identified postmenopausal women with dyslipidaemia should be followed up for years to detect development of atherosclerosis. This will go a long way in improving the healthcare of postmenopausal women in our region and even globally. For now, follow up in our environment is extremely very difficult due to sociocultural, economic and technical difficulties.

Conclusion

Until this is rectified, AIP which can easily be calculated from standard lipid profile can act as an adjunct that significantly adds predictive value beyond that of the individual lipids, and/or TC/HDL-C, LDL/HDL-C ratios. Dietary interventions and increased physical activity should also be encouraged in postmenopausal women, especially when there are other associated risk factors.

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