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Reduced antioxidant potential (AOP) of LDL with increased waist circumference (WC): Predisposing factors for coronary heart disease in post-menopausal women

[*1] Dr. Nivedita Singh, [2] Dr. Sanjeev Kumar Singh, [3] Dr. Neelima Singh

[1, 2] Associate Professor, Department of Biochemistry, G. R. Medical College, Gwalior, Madhya Pardesh, India
[3] Professor & Head, Department of Biochemistry, G. R. Medical College, Gwalior, Madhya Pardesh, India

Abstract
Objective: Changes in sex hormone during the menopausal transition are thought to have an important impact on weight gain. Visceral adiposity is more common in post-menopausal women, is measured by Waist circumference (WC). Coronary heart disease (CHD) is a major complication in post-menopausal women. The peroxidation of lipoproteins, especially low density lipoproteins (LDL) play a significant role in the pathogenesis and progression of atherosclerosis. This peroxidation reaction is countered by antioxidants present in LDL known as its antioxidant potential (AOP).
Methods and Results this study was carried out in 100 women ranging in age from 20 to 65 yrs. All women were categorized into two groups. 54 of the women were postmenopausal, aged between 40-65 years, while 46 of the women were pre-menopausal (20-35 year). AOP of LDL was measured in isolated LDL by xanthine oxidase system. AOP was significantly decreased ($p < 0.05$) in postmenopausal group compared to premenopausal group. A significant negative correlation ($p < 0.001$) was found between WC and AOP.
Conclusion These results demonstrate that post-menopausal women experience increased cardiac risk that could be due to decreased AOP of LDL highly relating with increased WC. Therefore AOP of LDL can serve as a predictor for future cardiac events in post-menopausal women.

Keywords: alcohol, energy drinks, lipids, atherogenic indices

Introduction

Menopause is one of the critical periods of a women's life during which weight gain and onset or worsening of obesity are favored. In this period the prevalence of obesity is the highest [1, 2]. Body composition changes as women progress through the menopause. These changes include an increase in overall and central adiposity, especially visceral adipose tissue and a decrease in total and central lean tissue mass [3]. In particular, central adiposity in postmenopausal women is measured by the waist circumference (WC), is recognized as an independent risk factor for developing cardiovascular diseases [4]. According to World Health Organization, Asian women with a waist circumference of more than 80 cm & Asian men with a waist circumference of more than 90 cm have increased risk for developing chronic diseases like CHD. The Body Mass Index (BMI) is commonly utilized to represent the degree of body fat; it however does not capture body fat distribution which the waist circumference does. Many studies have indicated that even with a "normal" BMI, those with an elevated waist circumference can have a two fold increase risk of cardiovascular disease (CVD) [5]. There is paucity of data on the role of obesity in cardiovascular mortality and morbidity in postmenopausal women.

CVD, particularly coronary heart disease (CHD), is a major complication in post-menopausal women. Oxidative conversion of low density lipoprotein (LDL) to oxidized LDL which is considered to be a key event in the biological process that initiates and accelerates the development of the early atherosclerotic lesion- fatty streak in progression of CHD [6]. Antioxidant compounds provide resistance to this process and have been suggested to possess lower atherogenicity [7]. LDL contains different lipophilic antioxidants (β-tocopherol, carotenoids, and ubiquinol-10) which increase the LDL resistance against the oxidative modification known as its antioxidant potential (AOP). Although, LDL has its own capacity (potential) to prevent its oxidation but in postmenopausal women due to lack of estrogen the susceptibility of LDL oxidation could be increased.

Therefore in the present study an attempt has been made to assess the WC, the measures of abdominal obesity & AOP of LDL in postmenopausal women and compared them with the premenopausal women served as a control group, and finally investigated the correlation between WC and AOP of LDL in postmenopausal women for showing the effect of visceral obesity on AOP of LDL.

Methods

The present study was carried out in G. R. Medical College, Gwalior, India. Total 100 women ranging in age from 20 to 65 yrs were selected for the study, and categorized into two groups 1. Control group (premenopausal), 2. Subject group (postmenopausal). 54 of the women were postmenopausal aged between 40-65 years, while 46 of the women were premenopausal (20-35 year). Postmenopausal women selected were at least 1 year amenorrhoeic due to a natural cause and were not using any type of hormone replacement. The premenopausal women were regularly menstruating, non-pregnant, and non-lactating with no use of hormonal contraception for at least 1 year. Women who were diabetics,

hypertensive, who smoke cigarette, drink alcohol, amenorrhoeic due to hysterectomy or cessation of periods other than by a natural cause were identified and excluded from the study. The study was undertaken after obtaining consent from the participants and approval from the Ethical Committee of G. R. Medical college of Gwalior.

Waist circumference (in centimeters) was measured at a point midway between the lowest rib and the iliac crest using flexible metric tape, with the subject standing. 5ml of fasting blood samples were taken for the estimation of AOP of LDL. Blood was allowed to clot at room temperature, and serum was obtained immediately by centrifugation at 3500 rpm for 10 min. Serum was aliquoted into plastic tubes and stored at -27°C until assayed. AOP of LDL was determined by xanthine oxidase method in which LDL was precipitated by heparin-citrate method [8]. Briefly 5 ml 0.064M Na citrate buffer, pH 5.04 with 50,000 IU/L heparin was mixed with 0.5 ml of serum, vertexed and centrifuge at 1000g for 10 minute. The supernatant was removed and LDL precipitate was dissolved in 1ml 1% triton X 100. For the measurement of AOP, LDL samples were incubated with xanthine-xanthine oxidase system in the presence of cod liver oil [9]. After 1h incubation, malondialdehyde levels were measured in all samples.

SPSS 18 (SPSS Inc., Chicago, USA) was used for all statistical analyses. Results were presented as Mean ± SD and Significance of values was calculated by independent student "t" test. The Pearson's correlation coefficient test was performed to determine correlation among risk factors. A level of $p < 0.05$ was considered statistically significant.

Results

Waist Circumference (WC) is important parameter for the assessment of abdominal adiposity. Table 1 reveals that waist circumference was higher (* $p < 0.05$) in the subject group (postmenopausal women) than control group (premenopausal women) (93.04 ± 1.60 vs. 78.87 ± 1.30 cm. respectively) (Figure 1). Table 2 shows that AOP of LDL was highly significantly decreased (* $p < 0.05$) in subject group (postmenopausal women) control group (premenopausal women) as compared to control group (premenopausal women) (1.42 ± 0.41 vs. 3.70 ± 0.72 nmol/ ml.h. respectively) (Figure 2). To assess the relative importance of waist circumference with AOP of LDL, their correlation was measured. Table 3 displays the correlation between waist circumference and AOP of LDL. Significant negative correlation ($r = - 0.334$, **$p < 0.001$) was observed.

Table 1: Anthropometric data of pre and postmenopausal women

	Control Group (n = 46)	Subject Group (n = 54)	p* value
Mean age (years)	32.19 ± 9.03	56.15 ± 7.92	> 0.05
WC (cm)	78.87 ± 1.30	93.04 ± 1.60	< 0.05
SBP (mmHg)	115 ± 5.02	125 ± 5.38	< 0.05
DBP(mmHg)	78 ± 4.30	83 ± 4.10	< 0.05

WC: Waist Circumference, SBP: Systolic Blood Pressure, DBP:Diastolic Blood Pressure. Values are expressed as Mean ± SD. * Independent sample t-test was used.

Table 2: Comparison of mean levels of AOP of LDL in pre and post menopausal women

Variable	Control group (n = 46)	Subject group (n = 54)	p* value
AOP of LDL (nmol/ml. h)	3.70 ± 0.72	1.42 ± 0.41*	< 0.05

AOP of LDL: antioxidant potential of low density lipoproteinValues are presented as Mean ± SD, * Independent sample t-test was used.

Table 3: Correlation between AOP of LDL and WC in postmenopausal women (n = 54)

	AOP of LDL	p * Value
WC	- 0.334	< 0.001

WC; Waist Circumference, AOP of LDL: antioxidant potential of owdensity lipoprotein * Pearson's correlation test was used.

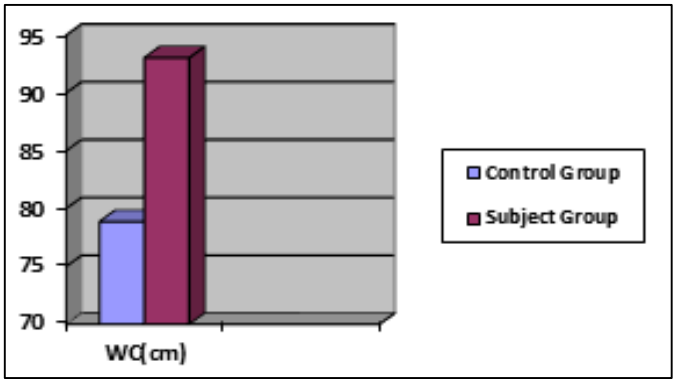

Fig 1: Showing comparison of WC (waist circumference) in pre and post-menopausal women

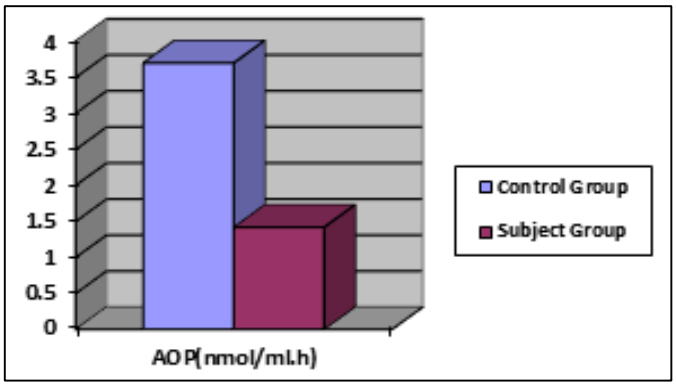

Fig 2: Showing comparison of AOP (antioxidant potential of LDL) in pre and post-menopausal women

Discussion

CVD is the leading cause of morbidity and mortality among postmenopausal women. The escalating rates of CVD observed in older, postmenopausal women may be related to the substantial adverse cardiovascular changes that occur as a woman transitions from pre- to post-menopausal status. In many women, CVD risk factors, including dyslipidemia, hypertension and abdominal adiposity, develop during the menopausal transition [10]. During this period, many women

experience loss of lean mass and gains in weight fat mass and central fat deposition [11, 12]. Measures of central obesity, compared with total body fat, are more consistently related to CHD events [13]. There is general agreement that menopause is associated with increased central adiposity, particularly visceral fat [14] which is measured by the Waist circumference (WC). Another factor implicated in the menopausal weight gain is a decrease in resting energy expenditure with estrogen loss during the menopause. Current evidence suggests that a WC ≥ 90 cm in men and of ≥ 80 cm in women is associated with increased health risk [15, 16].

In present study we also observed that WC was more in post-menopausal women than premenopausal women (table 1). WC is surrogate markers for visceral adiposity, a portion of the abdominal fat depot closely related to dyslipidemia. Dyslipidemia is the alterations in lipid metabolism caused by estrogen deficiency are thought to be a substantial component of CHD development in postmenopausal women [17]. The most common cause of CHD is atherosclerosis (hardening of the arteries), where fatty deposits including cholesterol and other fats, carried in the blood, build up as a plaque on the inside of the artery wall. In the formation of plaque the peroxidation of lipoprotein, especially LDL plays significant role [18]. Oxidative modification of LDL is recognized as one of the major processes involved in the early stage of atherosclerosis. Normally LDL is not oxidized because it is very rich in antioxidants and ability of LDL to protect it from oxidation is known as its AOP. In the subject group (postmenopausal women), AOP of LDL was lower than control group (premenopausal women) (table 2). It means LDLs of post-menopausal women are more susceptible to oxidation. Oxidation of LDL induces LDL-C accumulation [19]. During this metabolism, oxygen radicals may be produced, and under insufficient antioxidant capacity of LDL or low AOP of LDL these radicals may also trigger lipid peroxidation in LDL, increasing susceptibility of LDL to oxidation. Therefore if oxidation of LDL in the sub-endothelium of coronary arteries contributes to foam cell formation, to an unstable atherosclerotic plaque, to plaque rupture and resultant thrombosis [20], intervention modalities to decrease LDL oxidation may offer distinct benefits to individuals at risk for atherosclerosis. This study and some previous studies [21, 22] strongly indicate that antioxidants supplementation decreases susceptibility of LDL to oxidation. Much of the protective effect of antioxidants appears to be related to its transport in LDL and increasing its AOP.

In this study, another important finding was correlation of AOP of LDL with abdominal obesity i.e. WC. We found a negative correlation between AOP of LDL & WC in the postmenopausal women (table 3). The present study indicates that postmenopausal women with higher WC are greater risk of CHD than control group of premenopausal women with lower WC due to low AOP of LDL. It has also been proved that detrimental lifestyle changes, such as an increase in sedentary behaviors that are common as one age have been suggested to play a critical role in CVD development [23, 24]. The lowest risk of CHD was observed in premenopausal women having lower WC and more AOP of LDL. Thus this study firstly, to the best of our knowledge, demonstrated that low level of AOP of LDL can serve as a predictor for future cardiac events in postmenopausal women. Therefore, measurement of AOP of LDL may be helpful for identifying high-risk of CHD. Our study also indicates that WC and AOP of LDL are independently associated with risk of CHD.

In conclusion, Weight gain during postmenopausal stage was associated with a significantly increased risk of CHD due to low AOP of LDL. Participation in regular physical activity and supplementations of antioxidants like α tocopherol, β carotene appear effective to decrease LDL oxidation by improving its AOP, which may give same insight of cardiovascular benefits in post-menopausal women.

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