INFLUENCE OF MENOPAUSE ON SERUM LIPOPROTEIN (A)[LP_{(a)}]
SULTANA N^1, AHMED S^2, PARVIN S^3, MAHAL M^4, CHOWDHURY NS^5

Abstract:
A case control study on seventy women from community was designed and carried out in the Department of Biochemistry, Dhaka Medical College, Dhaka, from July 2005 to June 2006, to study of serum lipoprotein(a) [LP_{(a)}]. LP_{(a)} is a LDL like special type of lipoprotein which is claimed to be an atherogenic lipoprotein by many researches. Among the study subjects, cases were 30 post menopausal women (group A) and controls were 40 women of reproductive age, divided into two groups; group B_{1} (25-35 years) and group B_{2} (36-45 years). Serum LP_{(a)} of all the study subjects was measured. The mean serum LP_{(a)} concentration in group A, B_{1} and B_{2} were 35.77±31.90, 18.40±11.46 and 19.20±14.89 mg/dl, respectively. The results were compared between different groups by unpaired Student’s ‘t’ test. The LP_{(a)} concentration of group A compared to group B_{1} and B_{2} were found to be significantly higher (P<0.05). But the mean serum LP_{(a)} concentration of group B_{1} and B_{2} did not differ significantly.

Key words: Serum lipoprotein (a)[LP_{(a)}], menopause


Introduction:
Menopause is defined as the permanent cessation of menstruation due to loss of ovarian activity. Many physiological changes occur in women after menopause; including hormonal and metabolic changes. Hormonal changes include diminished secretion of estrogen and progesterone, increased pituitary secretion of luteinizing and follicle stimulating hormone^1. It has been observed that serum lipid and lipoproteins are significantly altered as a consequence of hormonal changes^2. Lipoproteins are conjugated proteins consisting of lipids and special protein known as apoprotein. The classical lipoproteins are chylomicron, very low density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL). Besides these classical types, almost all people have a special type of non classical lipoprotein called lipoprotein(a)[LP_{(a)}]. LP_{(a)} concentration in human plasma is significantly correlated with the risk of atherosclerotic heart disease, which was described by Berg in 1963. Regarding plasma lipid modifications after menopause, LDL, triglyceride and LP_{(a)} tend to increase, where as HDL decreases. Altered lipid profile is responsible for atherosclerosis^2. Among the classical serum lipoproteins, LDL, serum total cholesterol and triglycerides are primarily atherogenic, but LP_{(a)} is both atherogenic as well as thrombogenic. Therefore, LP_{(a)} acts as a dual cardiovascular and cerebrovascular pathogen^3. LP_{(a)} is a low density lipoprotein. Triglyceride, cholesterol and phospholipid together constitute its lipid portion, and the protein portions are apoprotein B-100 and apoprotein(a). Apo_{(a)} is a glycoprotein and it is homology to plasminogen, differentiates it from other apolipoprotein^4.

It is hypothesized that elevated LP_{(a)} slows the breakdown of blood clots that trigger heart attacks because it competes with plasminogen for the binding of plasminogen activators. LP_{(a)} and LDL has got the same receptor, but due to low affinity of LP_{(a)} for LDL receptor, it accumulates in vessel walls and directly increase the arterial permeability and traverse the endothelium to the intima. In the intima,
it binds the tissue matrix components facilitating foam cell formation. Lp(a) comes in contact with the endothelial injured sites, gets oxidative modification resulting in uptake by macrophages, leading to accelerated foam cell formation\(^5\). It is the key event for atherosclerosis. Another mechanism for the atherogenic activity of Lp(a) is the promotion of smooth muscle cell proliferation\(^6\).

Both retrospective and prospective population studies have shown a positive association between plasma levels of Lp(a) and risk of CAD and stroke\(^7,8\). After menopause, CAD risk progressively increases due to lack of oestrogen. Because oestrogen can protect females to a large extent from the potentially deleterious effects of high Lp(a) until menopause\(^9\). This mechanism of action of oestrogen has been explained by some researchers. Oestrogen influence the assembly of apo\(_{a}\) to apo\(_B\), which is believed to occur through a disulfide linkage in the hepatocyte. Oestrogen lower Lp(a) through an increased clearance\(^10\). Therefore, oestrogen may protect females in reproductive age, but this advantage is lost after menopause.

In conventional approaches, triglyceride, total cholesterol, LDL-cholesterol and HDL-cholesterol were measured as risk indicator for CAD. But a good number of patients suffering from the major clinical events of atherosclerosis surprisingly present a normal lipid profile or normal lipoprotein level\(^11\). In these classical normolipidaemic patients, Lp(a) has been found to be significantly correlated with increased Lp(a), so increased Lp(a) is a useful marker for CAD severity among postmenopausal women.

Again, Lp(a) is a better marker for CAD risk than LDL because Lp(a) is considered a risk factor at a concentration of 20mg/dl, where as LDL-cholesterol is considered to be a risk factor for atherosclerosis at about 300 to 400mg/dl, which is 15 to 20 times as much as Lp(a)\(^12\). Therefore, the present study was designed to find out the importance of Lp(a) as a risk factor for developing CAD in postmenopausal women and to assess the serum Lp(a) as a laboratory tool for the prevention of CAD. Postmenopausal women having significantly higher level of serum Lp(a) may adopt anti-atherogenic lifestyle and diet. These are regular physical activity, maintenance of normal body weight, consumption of a diet low in saturated fat and high in fruits and vegetables.

**Materials and Methods:**

This case control study was carried out in the Department of Biochemistry, Dhaka Medical College, Dhaka, in collaboration with the Department of Immunology, Bangladesh Institute of Research and Rehabilitation in Diabetics, Endocrine and Metabolic Diseases (BIRDEM), Dhaka, during the period of July 2005 to June 2006. All the subjects were randomly selected from community and grouped as Group A, postmenopausal women as case and Group B, premenopausal women as control. Group A includes 30 women of age range 55-70 years, and Group B includes 40 women of age range 25-45 years. Group B again subdivided into B\(_1\) and B\(_2\). Group B\(_1\) comprises reproductive age of female having ages between 25-35 years and Group B\(_2\) comprises reproductive age of female having age between 36-45 years. By taking history and doing clinical examination and laboratory investigations, diabetes mellitus, hypertension, malignant disease, liver disease, thyroid disease, renal disease, medication of oral contraceptive and obese (BMI >30) were excluded from study subjects. Ethical clearance for the study was taken from the Ethical Review Committee of Dhaka Medical College, Dhaka. Informed written consent was taken from all study subjects. Prior to sample collection, all the subjects were cordially requested to remain on 12-hour fast from 8pm to 8am next morning. At end of 12 hour fasting, 6ml venous blood was collected from all study subjects with full aseptic precaution. One milliliter blood was kept in fluoride containing oxalated test tube and 5ml in plain test tube. Oxalated blood was centrifuged, and the separated plasma used for estimation of plasma glucose immediately to exclude diabetes mellitus. Five milliliters blood in plain test tube was allowed to clot and centrifuge. Separated serum was then collected in Eppendorf and preserved at -35\(^\circ\)C after proper labeling, and late on used for the measurement of lipid
profile and Lp(a) concentration. All data were recorded systematically in a preformed data collection form and were expressed as their mean values ± SD. Mean values of the findings were compared between groups. Unpaired student ‘t’ test were used to see the level of significance. Confidence limit 95% (p < 0.05) was taken as level of significance. All the statistical analyses were performed by using SPSS version 11.0.

Result:
Total 70 women were selected for this study. Selected women were grouped as group A, 30 postmenopausal women and group B, 40 women within reproductive age were selected. Group B again divided into two groups, group B1, 20 women of 25-35 years age range and group B2 another 20 women of 26-45 years age range (Table–I). Serum Lp(a) of all groups was measured. Concentration of serum Lp(a) in different groups was expressed as their mean value in mg/dl. Table- II shows the serum Lp(a) in different study groups, which in group A, group B1 and B2 were 35.77±31.90 mg/dl, 18.40±11.46 mg/dl and 19.20±14.89 mg/dl. Comparison of mean serum Lp(a) concentration between different groups are shown in table–III.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of subjects(n)</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>30</td>
<td>59.67±3.14</td>
</tr>
<tr>
<td>B1</td>
<td>20</td>
<td>31.15±2.89</td>
</tr>
<tr>
<td>B2</td>
<td>20</td>
<td>39.40±2.85</td>
</tr>
</tbody>
</table>

Table – II
Serum lipoprotein(a) levels among study subjects.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of subjects(n)</th>
<th>Serum Lp(a) (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>30</td>
<td>35.77±31.90</td>
</tr>
<tr>
<td>B1</td>
<td>20</td>
<td>18.40±11.46</td>
</tr>
<tr>
<td>B2</td>
<td>20</td>
<td>19.20±14.89</td>
</tr>
</tbody>
</table>

Table – III
Comparison of serum Lp(a), level among different groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean ± SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A vs B1</td>
<td>35.77±31.90 vs 18.40±11.46</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>A vs B2</td>
<td>35.77±31.90 vs 19.20±14.89</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>B1 vs B2</td>
<td>18.40±11.46 vs 19.20±14.89</td>
<td>&gt;0.05NS</td>
</tr>
</tbody>
</table>

P value reached from unpaired t test, *Significant, NSNot significant.

Discussion:
Menopause is one of the stages of life in women. Many physiological and metabolic changes occur in women after menopause, which may increase the risk of coronary artery disease. It has been observed that serum lipids and lipoproteins are significantly altered as a consequence of the hormonal changes. Classical lipoproteins are chylomicrons, VLDL, LDL and HDL. These are well established CAD risk factors. Besides these classical lipoproteins, there is another special type of atherogenic lipoprotein, called lipoprotein(a). A good number of women suffering from major clinical events of atherosclerosis, surprisingly they present a normal lipid profile or normal classical lipoprotein patterns. In these classical normolipidaemic patients Lp(a) has been found to be significantly elevated. So increased Lp(a) may be a useful marker of CAD among postmenopausal women.

In the present case control study, the serum lipoprotein and lipid profile in post menopausal women (group A) and women in reproductive age group (group B1 and B2) have been measured to observe the effect of menopause on plasma level of Lp(a). Present study has revealed the mean Lp(a) concentration, 35±31 mg/dl in group A. In group B1 and B2, it was 18.40±11.46 and 19.20±14.89 mg/dl respectively.

Study has shown mean serum Lp(a) level is significantly higher in postmenopausal women group than in reproductive age group. Same phenomenon observed in other studies. But when it was compared within the two groups of reproductive ages, there was no significant
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difference. The increased level of serum LP_{(a)} is related to the decreased level of estrogen^{16}. In this study, postmenopausal elevation of LP_{(a)} may be due to decreased level of estrogen in menopause.

The Framingham offspring study^{16} showed that LP_{(a)} values was significantly higher in postmenopausal women than in premenopausal. Seven hundred, thirty-six premenopausal women and 647 postmenopausal women were participating in that study. LP_{(a)} is a unique molecule comprising a lipoprotein resembling LDL particle that is covalently bound to apo_{(a)}; a plasma glycoprotein. The individual characteristics of these 2 components are thought to be responsible for the apparent pathogenic role of LP_{(a)}, which has no known physiologic function.

The LDL-cholesterol likely contributes to atherogenesis, whereas apo_{(a)}, similar in structure to plasminogen may promote thrombosis. Thus LP_{(a)} may serve as a link between the pathogenic processes of atherosclerosis and thrombosis^{17}.

The Heart and Estrogen/progestin Replacement Study (HERS) demonstrate that LP_{(a)} is associated with recurrent CHD events in women. This association was independent of other significant predictors. The increased incidence of cardiovascular disease after menopause suggests that estrogen is an important inhibitor of atherosclerotic process in women. The positive effects may partly result from the influence of estrogen on serum lipids^{18}. LP_{(a)} are associated with an increased risk of cardiovascular disease. Hormone replacement therapy causes a diminution in LP_{(a)} concentration in postmenopausal women^{19}. Diet, exercise and some drugs such as niacin may delay the appearance of risk factors for cardiovascular diseases, especially in postmenopausal women^{20}.

Present study shows that LP_{(a)}, which is an atherogenic non-classical lipoprotein is increased in postmenopausal women. Therefore, increased LP_{(a)} has got a positive association with menopause.

**Conclusion:**
As from review of other studies we find that LP_{(a)} is associated with coronary artery disease (CAD), the increased LP_{(a)} level in menopausal women may be a risk factor of CAD. Menopausal women may be screened for serum LP_{(a)} and if it is found to be increased they may be advised to adopt antithrombotic lifestyle and diet.

**References:**


