Lipoprotein(a) as a Marker of Coronary Artery Disease and Its Association with Dietary Fat

Archana Burman*, Kajal Jain*, R Gulati**, V Chopra***, DP Agarwal****, S Vasisht+

Abstract
Objective: The main objectives of the study were to evaluate the effect of dietary fat on plasma lipoprotein(a) [Lp(a)] levels and to study the potential of Lp(a) as a more reliable marker for CAD compared to other lipids and lipoproteins.

Methods: Twenty CAD patients and 20 healthy controls were recruited for the study. Their fasting plasma Lp(a) levels and complete lipid profile were assayed. The fat intake was calculated using 24 hours dietary recall method. The patients and controls were each divided into two subgroups: Group A consuming dietary fat > 30% and Group B consuming dietary fat ≤ 30% of the total kilo-calories/day.

Results: Results indicated that plasma Lp(a), total serum cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and LDL-C/HDL-C ratio of CAD patients were significantly higher than the controls. High fat intake was found to be associated with higher plasma Lp(a) levels (p<0.05) in patients only. No significant correlation was found between Lp(a) levels and other conventional lipoproteins.

Conclusion: The lack of correlation between Lp(a) and other lipoproteins indicates its potential as an independent risk factor for CAD. High fat intake led to higher plasma Lp(a) levels in patients; hence it would be worthwhile to evaluate the effect of quality and quantity of fat intake on plasma Lp(a) levels in a larger sample size.

INTRODUCTION
Cardiovascular diseases (CVD) are the most potent killers particularly so in the advanced countries of the world. People hailing from Indian subcontinent had a higher probability of dying due to coronary artery disease (CAD).1 It is a multifactorial disease. Some of the predisposing factors are - hereditary, hyperlipidemia, obesity, hypertension, environmental factors and lifestyle variables like stress, smoking, alcohol consumption etc.2-4 Diet, especially fat plays an important role in the development of premature CAD. Lipoprotein profile has been investigated extensively in recent years, which is found to be deranged in large proportion of CAD patients. However, a significant proportion of patients have a normal lipoprotein profile.5 There is a need to study such patients in greater detail and identify some other parameters, which may indicate their CAD risk. Lp(a) is emerging as one such important risk parameter. It is proposed to have atherogenic and thrombogenic potentials.

Lp(a) is related to LDL in its structure and probably also in its function. The apoprotein (a), the major apoprotein of Lp(a) is a dimer of apo B-100 found in LDL. Lp(a) also has a higher density range compared to LDL.6 In 1979, Berg et al7 reported an association between Lp(a) and CAD. Atherogenic as well as antifibrinolytic properties of the Lp(a) particles may be of pathogenic importance. Normal plasma Lp(a) concentration reported for western population is less than 20 mg/dl.8 Most of the studies on Lp(a) have been done on Whites and data on other ethnic groups are scant. In a comparative study on different ethnic groups, South Asians settled in North America were reported to have high Lp(a) levels compared to Caucasians, Chinese and Malays.9

The phenotypic forms of Lp(a) have been found to be correlated to their plasma levels and probably also atherogenicity. The larger isoforms (S3, S4 and >10 PN repeats) of apo(a) are considered less atherogenic compared to smaller (S1,S2 and 6-9 PN repeats) isoforms. The smaller isoform is associated with higher plasma Lp(a) levels whereas

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larger isoforms with lower Lp(a) levels. Levels in excess of 30 mg/dl (usually considered as a threshold for therapeutic decisions) are found to be more prevalent in Asian Indians compared to several other ethnic groups. 

Dietary management is generally accepted as an initial step in the management of hyperlipidemia. For individuals at high risk of CAD due to hyperlipidemia, the need for lowering plasma lipids is obvious. The effect of dietary fat on Lp(a) has not been studied very well particularly in the Indian population. Hence the present study was undertaken to evaluate the potential of Lp(a) along with other lipids and lipoproteins as risk factors of CAD and also to understand the influence of dietary fat on these lipoproteins, Lp(a) and CAD.

**Material and Methods**

Angiographically assessed male CAD patients (n = 20, age = 45.9 ± 10.5 yrs) were selected from the Out Patient Department of the Cardio-Thoracic and Neuro-Sciences Centre of All India Institute of Medical Sciences. Age and sex matched controls (n = 20, age = 42.6 ± 8.1 yrs) comprised of healthy volunteers. The questionnaire-cum-interview schedule formulated was used to collect information regarding general profile, lifestyle variables and dietary habits. Twenty-four hours dietary recall method was used to study the dietary practices and to assess the average daily food intake of the subjects.

Overnight fasting blood samples were drawn by venipuncture. Informed consent was obtained from each of the subjects included in the study. Four ml blood was collected in a plain tube and 2 ml in EDTA vials for serum and plasma separation, respectively. The lipid and lipoprotein profile was assayed for the study subjects. Lp(a) was estimated by using commercially available immunoturbidimetric (Human, Germany) kits. The TC and TG levels were analyzed by fully enzymatic method using commercial kits (Randox, UK) on a Beckman CX5 autoanalyzer. LDL-C in serum was determined by the dual precipitation procedure of Wilson and Spiger. Serum very low density lipoproteins (VLDL) were selectively precipitated by 10% sodium dodecyl sulphate (SDS) leaving LDL and HDL in the supernatant. HDL-C present was estimated by the method of Burstein et al. The significance of difference between the groups was analyzed using Student’s 't' test. The correlation coefficient (Pearson) was obtained to assess the association of Lp(a) with other lipoproteins.

**Results**

The body mass index (BMI) of patients (23.34 ± 4.11 g/m²) and controls (22.94±3.47 g/m²) fell in the upper part of the normal range (18-25 kg/m²). The average daily energy intake for a day in both patients and controls was calculated and found to be marginally lower (statistically insignificant) than the Recommended Dietary Allowances (RDA). The total energy percent from dietary fat was as high as 34.7% in patients and 32% in controls (Table 1) as against 15-20% of RDA. Recommended daily allowances.

**Discussion**

The present investigation was undertaken with the aim of understanding the effect of dietary fat on Lp(a) and other lipoprotein levels in CAD patients and apparently healthy volunteers. There was no significant difference in the BMI between patients and controls. BMI of the entire study group (patients and controls) fell in the upper part of the normal range (18-25kg/m²) indicating an increased susceptibility towards disease.

**Table 1: Mean daily percent contribution of energy from proximate principles**

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Patients (n=20)</th>
<th>Controls (n=20)</th>
<th>RDA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate</td>
<td>50.7</td>
<td>51</td>
<td>55-75</td>
</tr>
<tr>
<td>Protein</td>
<td>14.6</td>
<td>16.5</td>
<td>10-15</td>
</tr>
<tr>
<td>Fat</td>
<td>34.7</td>
<td>32</td>
<td>15-20</td>
</tr>
</tbody>
</table>

RDA: Recommended daily allowances.

**Table 2: Lipid and lipoprotein profile of patients and controls**

<table>
<thead>
<tr>
<th>Lipid (mg/dl)</th>
<th>Patients (n=20)</th>
<th>Controls (n=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lp(a)</td>
<td>59.1 ± 11.9</td>
<td>42.6± 12.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TC</td>
<td>196.6 ± 30.4</td>
<td>1676 ± 33.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C</td>
<td>117.2 ± 26.8</td>
<td>88.4 ± 29.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>33.0 ± 12.1</td>
<td>31.6 ± 17.2</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-C</td>
<td>39.5 ± 6.9</td>
<td>42.0 ± 6.5</td>
<td>NS</td>
</tr>
<tr>
<td>LDL/HDL-C</td>
<td>2.8 ± 0.9</td>
<td>2.2 ± 0.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TG</td>
<td>157.8 ± 65.6</td>
<td>151.0 ± 78.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

All the values are Mean (mg/dl) ± SD recommended by the Indian Council of Medical Research (ICMR), 1990. The distribution of cholesterol in the subjects showed that 65% of CAD patients and 80% controls were in the cholesterol range of less than 200 mg/dl. In the present study TC, LDL-C and LDL/HDL-C ratio were significantly higher in patients compared to controls indicating a higher atherogenic potential in the patients (Table 2). The mean Lp(a) concentration of the control group was much higher (42.6 ± 12.61 mg/dl) than reported elsewhere. The patients had 28% higher Lp(a) concentration (59.11 ± 11.92 mg/dl) than that of the control group (Table 2).

Based on the amount of dietary fat intake, the patient and control groups were further subdivided into two groups each: Group A subjects consuming fat providing > 30% energy; Group B subjects consuming fat providing ≤ 30% energy. Lp(a) levels of patients consuming high fat were significantly higher (p<0.05) than the patients consuming comparatively lower fat and controls consuming high fat. Interestingly high fat intake by controls did not alter Lp(a) levels significantly when compared to lower fat consuming patients or controls (Table 3). No significant correlation was found between Lp(a) and any of the studied lipoproteins.  

![Image](https://via.placeholder.com/150)
by about three-fold than those with low plasma Lp(a).

Subjects with Lp(a) levels above 25 or 30 mg/dl are commonly accepted cutoff points for categorizing high plasma Lp(a). Atherosclerosis and CAD. The TC in Indians has been singled out as being chiefly concerned with the incidence of heart disease in the general population. In the present study serum TC, VLDL-C and TG were significantly higher in patients consuming relatively lower fat (≤30%) than the controls consuming comparatively lower fat (≤30%). This observation clearly demonstrates the beneficial effect of reducing the fat in diet on the lipoprotein profile in normal population and thus having a preventive potential against CAD.

The Lp(a) levels were found to be significantly higher (p<0.01) in patients (59.1±11.9 mg/dl) compared to the controls (42.6±12.6 mg/dl) demonstrating a strong correlation between Lp(a) levels and CAD. No significant correlation was observed between Lp(a) and any of the studied lipid or lipoprotein suggesting Lp(a) to be an independent, genetic risk factor for CAD.

Moderate decrease in dietary fat has consistently resulted in lowering of both TC and LDL-C levels in normolipidemic subjects in several studies. There is consensus that dietary saturated fat and cholesterol should be reduced in the diet of the general population to decrease the risk of CAD. The National Cholesterol Education Program (NCEP, USA) and other health agencies have recommended that the intake of total fat, saturated fat and cholesterol should be reduced to <30%, <10% and <300 mg/day, respectively to reduce the risk of heart disease in the general population. In the present study serum TC, VLDL-C and TG were significantly higher in controls consuming high fat (>30%) than the controls consuming relatively lower fat (<30%).

The Lp(a) levels were found to be significantly higher (p<0.01) in patients (59.1±11.9 mg/dl) compared to the controls (42.6±12.6 mg/dl) demonstrating a strong correlation between Lp(a) levels and CAD. No significant correlation was observed between Lp(a) and any of the studied lipid or lipoprotein suggesting Lp(a) to be an independent, genetic risk factor for CAD.

Table 3: Comparison of lipid and lipoprotein profile in patients and controls consuming >30% and ≤30% fat of the total kcal/day

<table>
<thead>
<tr>
<th>Lipid (mg/dl)</th>
<th>Group A (n=5)</th>
<th>Group A (n=9)</th>
<th>Group B (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>197.0 ± 31.6</td>
<td>206.0 ± 32.2**</td>
<td>190.8 ± 42.3</td>
</tr>
<tr>
<td>LDL-C</td>
<td>112.4 ± 31.8</td>
<td>116.6 ± 32.1</td>
<td>112.4 ± 31.8</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>35.6 ± 13.8</td>
<td>49.4 ± 14.9***</td>
<td>35.6 ± 13.8</td>
</tr>
<tr>
<td>HDL-C</td>
<td>38.9 ± 7.6</td>
<td>41.0 ± 6.3</td>
<td>38.9 ± 7.6</td>
</tr>
<tr>
<td>LDL/HDL</td>
<td>3.1 ± 1.07</td>
<td>2.5 ± 0.4</td>
<td>3.1 ± 1.07</td>
</tr>
<tr>
<td>TG</td>
<td>174.0 ± 74.1</td>
<td>208.8 ± 29.6**</td>
<td>144.6 ± 57.9</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>68.3 ± 20.1^a</td>
<td>42.5 ± 14.7</td>
<td>47.4 ± 20.1</td>
</tr>
</tbody>
</table>

All values are Mean (mg/dl) ± S.D. Group A - Subjects consuming >30% of calories as fat. Group B - Subjects consuming <30% of calories as fat. *p<0.05 comparison of group A with group B within patient group. **p<0.01 comparison of group A with group B within control group. a(p<0.05) comparison of group A of patients with group A of controls.

Out of the serum lipids, cholesterol has most often been singled out as being chiefly concerned with the incidence of atherosclerosis and CAD. The TC in Indians has been observed to be lower than people in the Western countries. Further, majority of Indians follow a vegetarian lifestyle with cereal grain as their staple food. In spite of this, prevalence of CAD in Indians is as high as in Western population and is steadily increasing. This ‘Asian Indian Paradox’ needs to be investigated. The CAD patients of the present study showed increased TC, LDL-C levels and LDL-C/HDL-C ratio even while consuming total calories within the RDA. The above observation can be explained to a certain extent by analyzing the calories provided by individual macronutrients i.e. carbohydrate, protein and fat. The patients derived nearly 35% of their daily energy from fats (Table 1). Several other investigators have also demonstrated that fat intake higher than 30% of total energy is directly linked to hyperlipidemia and development of CAD.

Lp(a) is emerging as a strong candidate for CAD. Lp(a) levels above 25 or 30 mg/dl are commonly accepted cutoff points for categorizing high plasma Lp(a). Subjects with Lp(a) above these cutoff points have their risk of CAD increased by about three-fold than those with low plasma Lp(a). How ever control groups of this study had Lp(a) levels (43 mg/dl) higher than those reported in other investigations. Several studies on Indian population have also shown higher Lp(a) levels compared to other ethnic groups suggestive of inherently high Lp(a) levels in this genetic pool. Further the control group of the present study comprised of North Indians with a particularly high intake of fried foods and hydrogenated fats. These fats are rich in trans fatty acids which are known to affect the Lp(a) levels adversely.

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Announcement

14th Annual Conference of Bihar Chapter of API to be held on March 13-14, 2004 at Munger Club, Munger, Bihar.
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