LIPOPROTEIN(a) AND LIPID LEVELS IN CHILDREN WITH AND WITHOUT FAMILY HISTORY OF PREMATURE ISCHEMIC HEART DISEASE

Dr. Jusmita Dutta1*, Dr. Ummed Singh Solanki2

1Associate Professor, Department of Biochemistry, Peoples College of Medical Sciences and Research Centre, Bhopal (MP), India.
2Assistant Professor, Department of Biochemistry, Jhalawar Medical College, Jhalawar (Raj.)

ABSTRACT

Cardiovascular disease (CVD) is the number one cause of death globally. The incidence of Coronary Artery Disease (CAD) in the young has been reported to be 12%–16% in Indians. Half of the CVD-related deaths (ie 52% of CVDs) in India occur below the age of 50 years, and about 25% of acute myocardial infarction (MI) in India occurs under the age of 40 years. Multiple studies have demonstrated that atherosclerosis has its silent beginning during childhood. The importance of cardiovascular risk factors like hypertension, obesity and dyslipidemia in prediction of latent CAD in offspring of parents with Ischemic Heart Disease (IHD) are well known. New risk factor, such as lipoprotein (a) has been identified and is under further investigation. This study was aimed to identify the children with high risk of IHD in terms of dyslipidemia and Lp(a) levels so that appropriate measures can be taken early in life to prevent or delaying the IHD. Total 90 subjects (children) were included in the study. The subjects were divided into 2 groups, group A and group B. Group A consisted of 45 offspring of cases of premature ischemic heart disease and 45 age sex matched healthy children served as group B. Lp(a) levels were estimated by in vitro turbidometric immunoassay using a kit. It was seen that mean level of Total Cholesterol, Triglyceride, Very Low Density Lipoprotein-Cholesterol and Low Density Lipoprotein-Cholesterol were significantly higher in children with family history of premature ischemic heart disease as compared to group B children. Taking 30 mg/dl as the
cut off value of Lp(a), majority of children with familial history of IHD had significantly higher levels (P<0.001) when compared to group B children. We conclude that children of ischemic heart disease patients have significant incidence of dyslipidemia compared to age sex matched healthy children. Therefore, all these children should be screened for dyslipidemia, and dietary measures should be applied as a first step approach. The strong genetic component of lipoprotein (a) in association with its atherogenic potential favours its determination in children with a family history of premature ischemic heart disease.

Key Words: Lipoprotein (a), Ischemic heart disease, Lipids, Coronary artery disease.

INTRODUCTION

Cardiovascular disease (CVD) is the number one cause of death globally and is projected to remain the leading cause of death. An estimated 17.5 millions people died from CVD in 2005, representing 30% of all global deaths\(^1\). Projections show that CVD has reached epidemic proportions in many developing countries. In India, mortality attributable to CVD is expected to rise by 103% in men and by 90% in women from 1985 to 2015. More importantly, the disease catches Indians young\(^2\). The incidence of Coronary Artery Disease (CAD) in the young has been reported to be 12%–16% in Indians\(^3\). Half of the CVD-related deaths (ie 52% of CVDs) in India occur below the age of 50 years, and about 25% of acute myocardial infarction (MI) in India occurs under the age of 40 years\(^4\).

Multiple studies have demonstrated that atherosclerosis has its silent beginning during childhood. Fatty streaks are the earliest grossly visible arterial lesions of the atherosclerotic process\(^5\). Dyslipidemias are disorder of lipoprotein metabolism which may result in hyperlipidemia or hypolipidemia. Among the dyslipidemias, hyperlipidemia is the most common and world wide problem. Epidemiologic studies in children establish a strong statistical association between childhood overweight and hyperlipidemia\(^6\). The importance of cardiovascular risk factors like hypertension, obesity and dyslipidemia in prediction of latent CAD in offspring of parents with Ischemic Heart Disease (IHD) are well known. New risk factor, such as lipoprotein (a) has been identified and is under further investigation\(^7\).

Lipoprotein (a) particles, Lp(a), were first described by Berg in 1963, and are a genetic variant of low-density lipoprotein particles linked via apoB-100 to apolipoprotein(a) [apo(a)]\(^8\). The apo(a) glycoprotein shows considerable homology with the kringle IV domain of plasminogen. Because of this homology, Lp(a),through its apo(a) part, competes with plasminogen for binding with fibrinogen or fibrin and thus attenuates fibrinolysis\(^9\). Since
being identified, numerous studies have reported that high plasma Lp(a) concentrations are associated with atherosclerotic/thrombotic disease, as comprehensively reviewed by others. A few studies have evaluated the serum concentration of Lp(a) and other lipoproteins in offspring of patients with premature ischemic heart disease in India.

This study was aimed to identify the children with high risk of IHD in terms of dyslipidemia and Lp(a) levels so that appropriate measures can be taken early in life to prevent or delaying the IHD.

MATERIAL AND METHODS
This study was performed from December 2011 to June 2013 at Peoples College of Medical Sciences and Research Centre Bhopal. Total 90 subjects (children) were included in the study. The subjects were divided into 2 groups, group A and group B. Group A consisted of 45 offspring of cases of premature ischemic heart disease (age <55 years for male and <65 years for female). The cases of IHD were taken from intensive cardiac care unit & their IHD status was obtained from medical case sheet. Offspring from these patients aged between 5 to 18 years, irrespective of their sex, were included in the study. Only one child from each family was selected randomly. 45 age sex matched healthy children served as group B. They were selected from the outpatient and inpatient department who came to hospital along with their parents with no reason or to see their relatives.

Children with the following conditions were excluded from the study. Children with diabetes mellitus, obesity, renal failure, liver failure, endocrine disorders, DM, or hypertension, taking systemic drugs especially lipid lowering agents, β blockers and diuretics, smoking and alcohol users. Children below 5 years were also excluded.

Informed consent was taken from the parents of group A and group B subjects. 5ml of venous sample was collected from the subjects after an overnight fast of 10-12hrs. The samples were centrifuged, separated and analyzed immediately. A urine sample was collected and analyzed immediately. Total cholesterol (TC), High Density Lipoprotein-Cholesterol (HDL-C) and Triglycerides (TG) in serum were measured by enzymatic methods using commercially available kits (Biosystems S.A. Barcelona).

Serum Very Low Density Lipoprotein-Cholesterol (VLDL-C) was calculated. Low-Density Lipoprotein-Cholesterol (LDL-C) was also calculated by Friedewald’s formula. Lp(a) levels
were estimated by in vitro turbidometric immunoassay using a kit (AGAPPE DIAGNOSTIC Ltd). Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters and a value of >30 is considered as measure of obesity.

Statistical analyses were performed by the SPSS software program using Student’s unpaired ‘t’ test. P-values less than 0.05 were considered as significant.

RESULTS
In children and adolescents, dyslipidemia were defined as TC ≥ 200 mg/dl, LDL-C ≥ 130 mg/dl according to National Cholesterol Education Program (NCEP) Expert Panel on Blood Cholesterol Levels in Children and Adolescents, TG levels > 150 mg/dl and HDL-C levels < 40 mg/dl. For children in general, borderline levels of TC and LDL-C are defined as 170-199 and 110-129 mg/dl, respectively.

The values of age, gender, body mass index, systolic and diastolic blood pressure in group A and group B are presented in Table 1. The two groups did not differ significantly with respect to age, sex, BMI, systolic and diastolic blood pressure.

The result of lipid and Lp(a) measurements have shown in Table 2. Mean levels of total cholesterol, low density lipoprotein cholesterol, and Lp(a) were significantly higher in the children with positive family history of premature ischemic heart disease (ie. group A) compared to the children without positive family history (ie. Group B). There was a significant difference as well between the two groups in terms of HDL-C also.

Table 1: Characteristics of study population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group A</th>
<th>Group B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs) (m ± SD)</td>
<td>11.8±2.5</td>
<td>11.5±2.1</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>Male: Female</td>
<td>29:15</td>
<td>31:13</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>BMI (kg/m²) (m±SD)</td>
<td>22.1±3.9</td>
<td>21.8±4.1</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>Systolic BP (mmHg) (m±SD)</td>
<td>109±9.7</td>
<td>108±8.9</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>Diastolic BP (mmHg) (m±SD)</td>
<td>71±7.6</td>
<td>69±7.3</td>
<td>P&gt;0.05</td>
</tr>
</tbody>
</table>

BMI: Body Mass Index
Table 2: Mean distribution of Lp(a) and lipid levels in group A and group B subjects

<table>
<thead>
<tr>
<th>Biochemical Parameter</th>
<th>Group A (m±SD)</th>
<th>Group B (m±SD)</th>
<th>Significance (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>201.15±51.05</td>
<td>155.24±18.66</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>138.26±20.48</td>
<td>123.75±14.31</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>37.77±6.53</td>
<td>41.30±5.18</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>135.22±17.98</td>
<td>94.37±17.38</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>VLDL (mg/dl)</td>
<td>27.65±4.02</td>
<td>24.70±2.58</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Lp(a) (mg/dl)</td>
<td>31.97±9.38</td>
<td>24.02±5.13</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

DISCUSSION

Atherosclerosis begins in childhood and progresses to coronary artery disease in adults. Coronary artery disease is multifactorial and caused by the interaction of genetic and environmental factors. The genetic component is believed to be more predominant than the environmental when coronary atherosclerosis presents early in life.

Several studies have showed that the offspring of patients with premature coronary artery disease are at increased risk for atherosclerosis so it is important to pay more attention to its risk factors from an early age. Dyslipidemia is a conventional risk factor for CAD. Family history of parental dyslipidemia is one of the major factors to be considered in the decision of assessing the lipid profile in children and adolescents. Lp(a) is a genetic variant of low-density lipoprotein (LDL) in which apolipoprotein B100 is linked by a disulfide bond to apo(a). Apo(a) is structurally similar to plasminogen and renders Lp(a) uniquely atherogenic and thrombogenic.

Serum Lp(a) levels account for much of the genetic component of atherosclerosis not expressed through any of the standard risk factors. Because of its strong heritability, Lp(a) is widely recognized as a biological marker for premature CAD. Several studies have shown that Lp(a) levels are two to three times higher in 3- to 18-year-old children with a parental or grandparental history of premature CAD than in those without such a history. Thus, measurement of Lp(a) in children may help to identify families with an increased risk of CAD. The aim of our study was to study the lipid and Lp(a) levels in children with and without family history of premature ischemic heart disease.
In our study we found that there were increased levels of TC, LDL-C in children with family history of premature ischemic heart disease. In a study by Blumenthal, et al. of the 72 children whose fathers had myocardial infarction, 13.8% had cholesterol levels greater than 230 mg% whereas there was no significant difference between mean triglyceride levels\(^\text{17}\). This observation is consistent with the finding in our study. Analysis from the Bogalusa Heart Study has shown that antemortem levels of total cholesterol and low density lipoprotein cholesterol were associated with coronary artery fatty streaks at autopsy in 150 persons aged 6 to 30 years\(^\text{18}\). Savitha MR et al 2011 also reported hypercholesterolemia in 66% children with family history of CAD\(^\text{10}\).

Though we found a significant difference in TG level between the two group but the absolute values of TG in group A children were within the normal range for age. We also found that there was a significant difference in HDL-C level between the two group. Lee, et al. studied 173 progeny from 63 families in which father had angiographically diagnosed coronary artery disease by 50 years of age. Age group of studied progeny ranged from 6 to 31 years. 65% of the affected fathers and 51% of progeny had elevated triglyceride, elevated low density lipoprotein cholesterol, decreased high density lipoprotein or combinations thereof\(^\text{19}\). These observations were in consistent with the finding in our study.

In our study we also found significantly higher level of LP(a) in children with family history of premature ischemic heart disease. An elevated Lp(a) level is an independent risk factor for premature CAD in both sexes. Lp(a) concentrations are largely genetically determined through autosomal dominant transmission. Lp(a) levels stabilize by age 2 and remain constant throughout life. Individuals with high levels of Lp(a) develop MI or stroke in their 40s and 50s, about 10 to 20 years earlier than those who develop MI or stroke attributable to other risk factors\(^\text{16}\). The Framingham Offspring Study found that a high Lp(a) level (>30 mg/dL) was an independent risk factor for the development of CAD in men aged<55 years, with risk comparable in magnitude to a total cholesterol level of >240 mg/dL or an HDL-C level of <35 mg/dL\(^\text{20}\).

Risk potentiation occurs with concomitant elevations of Lp(a) and LDL-C. A high Lp(a) level increased CAD risk threefold in the Prospective Cardiovascular Munster (PROCAM) Study and fourfold in the PRIME Study, when LDL-C was>160 mg/dL. The risk from Lp(a) excess is also markedly increased with low HDL-C\(^\text{16}\). In the PROCAM Study, the risk associated
with high Lp(a) levels was eightfold greater with low HDL-C compared to threefold greater risk with high LDL-C\(^{21}\).

**CONCLUSION**

We conclude that children of ischemic heart disease patients have significant incidence of dyslipidemia compared to age sex matched healthy children. Therefore, all these children should be screened for dyslipidemia, and dietary measures should be applied as a first step approach. The strong genetic component of lipoprotein (a) in association with its atherogenic potential favours its determination in children with a family history of premature ischemic heart disease.

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