Lipoprotein Lp(a)
A Risk Factor for Myocardial Infarction

Gerald Hoefler, Franz Harmoncourt, Eduard Paschke, Wolfgang Mirtl, Karl H. Pfeiffer, and Gerhard M. Kostner

The aim of this study was to test plasma lipoprotein Lp(a) and other lipid and lipoprotein levels for association with the incidence of myocardial infarction. Total plasma cholesterol, triglycerides, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, and Lp(a) were measured in 1486 men at the age of 18 years. In addition, the Broca Index (a measure of relative body weight) and other data were recorded. The sample was divided into probands whose mothers or fathers suffered a myocardial infarction (case group, n=52) and into probands whose parents had no myocardial infarction (control group, n=1434). In the case group, 32% had Lp(a) plasma concentrations greater than 25 mg/dl, but only 13.4% of the control group had this level of concentration, a highly significant difference (p<0.01). In addition, there was a statistically significant difference in the ratio of LDL cholesterol/HDL cholesterol (p<0.05) and the Broca Index (p<0.01) between cases and controls. The parents of the case group were significantly older than the parents of the control group; however, when a control group was matched for parents’ age, the results were similar. These data suggest that parents of male children with Lp(a) plasma concentrations greater than 25 mg/dl have a 2.5-fold higher incidence of myocardial infarction. Considering the familial aggregation of elevated Lp(a) levels, we conclude that increased levels of this lipoprotein may be a significant risk factor for myocardial infarction. (Arteriosclerosis 8:398–401, July/August 1988)

According to current concepts, increased plasma concentrations of atherogenic lipoproteins play an important role in the development of atherosclerosis leading to premature myocardial infarction (MI) and stroke. This has been shown in many case-control studies. The results from prospective studies are scarce and, in most instances, they include only the measurements of lipids and lipoprotein lipids, despite the fact that individual lipoprotein levels seem to be of greater predictive value in the assessment of atherosclerosis risk. One particular fraction, which is important in that respect, is Lp(a), a lipoprotein that is inherited as a quantitative genetic trait (reviewed by Kostner). Albers et al. demonstrated that plasma Lp(a) levels were not correlated with apolipoprotein B levels. We have shown in previous reports that Lp(a) is synthesized independently of other cholesterol ester-rich apo B-containing lipoproteins. Furthermore, the rate of Lp(a) synthesis is the determinant of plasma Lp(a) concentration, which may vary considerably among individuals and may range from <1 to >150 mg/dl. Lp(a) catabolism, on the other hand, proceeds via routes that resemble those of LDL.

A link between increased plasma Lp(a) concentrations and premature atherosclerosis, MI, and stroke has been postulated on the basis of case-control studies. We chose to study the association between an inherited marker and the familial aggregation of certain diseases because the results of this model are nearly as reliable as those of a prospective trial.

Methods

Study Design

We studied 1486 male probands, 18 ±0.5 years old, who had routine physical examinations for the Austrian military service. The cases were consecutive and included nearly all young men in that age group in the county of Styria who were called for military service. The examinations were performed between June and September, 1986. Only severely physically or mentally handicapped men were excluded. All procedures were approved by the Medical Director of the Draft Commission.

The family histories and personal data were assessed by one physician using a standardized questionnaire to avoid differences in the formulation of questions. The following variables were noted by the physician: 1) MI of father or mother, 2) MI of blood relatives, 3) cases of diabetes mellitus in the family, 4) cerebral atherosclerosis or stroke in family members, 5) age of father and mother, 6) smoking habits of parents, 7) dietary habits of the family especially with respect to saturated fat and cholesterol intake, and 8) physical activity.

In addition, the probands’ weights and heights were measured, and the Broca Index was calculated according to the formula: weight(kg)/height(cm) – 100.
The group of probands with fathers or mothers who suffered from MI will be referred to as the case group as opposed to those whose parents had no MI (control group).

**Lipid and Lipoprotein Measurements**

Lipids and lipoproteins were measured in nonfasting plasma obtained in the morning approximately 5 to 6 hours after breakfast. The usual breakfast in this country is a light meal of coffee or tea, one or two pieces of bread, butter, and marmalade. Only a few men had ham, eggs, or cheese for breakfast. Triglycerides and total cholesterol were measured enzymatically (PAP method) on a Cobas-Bio with reagents from Bio-Merieux, France. High density lipoprotein cholesterol (HDL-C) was quantified by the same enzymes after precipitation of very low density lipoprotein + low density lipoprotein (VLDL + LDL) with polyethylene glycol.\(^{19}\) LDL cholesterol (LDL-C) was calculated according to the Friedewald equation:

\[ \text{LDL-C} = \text{total cholesterol} - \text{triglycerides}/5 - \text{HDL-C} \]

\(\text{Lp(a)}\) was assayed by counterimmunoelectrophoresis with polyclonal antibodies and the Rapidophor System (Immuno Bio, Vienna). This particular assay discriminates between samples with less than 25 mg/dl of \(\text{Lp(a)}\) from those with more.\(^{20}\) For the present study, this semiquantitative method was standardized with plasma samples of known \(\text{Lp(a)}\) concentration to distinguish further between samples with an \(\text{Lp(a)}\) content of 25 to 35 mg/dl (weak +), 35 to 50 mg/dl (medium +), and more than 50 mg/dl (strong +).

This yielded a grading scale of 0 to 3. Since this classification did not improve the predictive value of our test in the final statistical evaluation of our data, the probands were classified as \(\text{Lpa+}\) when \(\text{Lp(a)}\) was more than 25 mg/dl and as \(\text{Lpa-}\) when \(\text{Lp(a)}\) was less than 25 mg/dl.

**Statistical Analysis**

Groups were selected by different criteria combined by logical "and" and "or". Because a Kolmogoroff-Smirnov test showed significant deviations from the normal distribution for some biochemical variables, the nonparametric method, Wilcoxon's U test, and Spearman's rank correlation coefficients were used to analyze the continuous variables as has been described in detail previously.\(^{3,9,16,18}\) For the analysis of frequency distributions, the chi-square statistic was applied.

**Results**

Table 1 summarizes the plasma \(\text{Lp(a)}\) levels and the parental prevalence of MI. A total of 1486 probands were included in this study: 52 (3.5%) of them reported that a parent had suffered MI (42 fathers and 10 mothers); 1278 of the probands were \(\text{Lpa-}\) and 208 were \(\text{Lpa+}\), a prevalence of 14%.

Table 2 displays the median values of plasma lipids and lipoproteins separately for probands with parents with a positive or negative history of MI. There was no significant difference in the plasma concentration of total cholesterol, triglycerides, LDL-C, or HDL-C. Children whose parents suffered from MI, however, had significantly higher LDL-C/HDL-C values \((p<0.05)\). A greater difference between the case and the control group was found in the Broca Index \((p<0.01)\).

Dividing the case group into those whose mothers or fathers suffered from MI gave no difference in results. In both instances, only the LDL-C/HDL-C ratio and the Broca Index differed significantly from the control group, whereas the other parameters listed in Table 2 were not significantly different.

![Figure 1. Prevalence of Lpa+ in the control group (MI-, parents free of myocardial infarction) and in the case group (MI+, father or mother suffered from myocardial infarction).](attachment:image.png)
Table 4. Correlation of Broca Index and Lp(a) with Other Lipid Parameters by Spearman's Rank Correlation Coefficient

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cases (Lp(a) +) (n = 208)</th>
<th>Controls (Lp(a) +) (n = 1278)</th>
<th>Lp(a) (n = 208)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broca Index</td>
<td>0.231*</td>
<td>0.192*</td>
<td>0.067 ns</td>
</tr>
<tr>
<td>TC</td>
<td>0.182†</td>
<td>0.239*</td>
<td>-0.060 ns</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-0.142†</td>
<td>-0.116*</td>
<td>0.069 ns</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>-0.064 ns</td>
<td>0.022 ns</td>
<td>-</td>
</tr>
</tbody>
</table>

* p<0.001, † p<0.01, * p<0.05.
Abbreviations are explained in Table 2 legend.

Discussion

The biological function of Lp(a) is unknown and there are no indications whatsoever that individuals with very low Lp(a) concentrations or even those who lack this lipoprotein may suffer from any metabolic diseases. On the basis of metabolic studies, we have postulated that Lp(a) may be secreted directly by the liver, and that it is not derived from triglyceride-rich precursors in contrast to LDL.12 This could explain the observation that plasma Lp(a) concentrations remain stable for months or even years and are hardly influenced by low fat and low calorie diets.11,12

A similar study design for the assessment of coronary risk factors was used in two recent reports. De Backer et al.6 reported that offspring of patients with MI differed significantly from control offspring in their plasma concentrations of apo A-I, apo A-II, and the non-HDL-C/apo B ratio. In another study including a few individuals who underwent coronary angiography, the sons of patients with atherosclerosis had significantly higher apo B and apo B/apo A-I values than did the sons of patients without atherosclerosis; there was no difference in the lipid and lipoprotein values of daughters.7

The present study included 1486 men in a very restricted age group, i.e., all men who consecutively underwent medical examination for induction into the military service (military service in Austria is compulsory) within a certain time period. Thus, we believe that there were no biases with respect to proband selection, and that this study may be representative for the chosen geographic area. Considering the fact that increased Lp(a) concentrations have been associated with atherosclerosis and MI in many ethnic groups,10,17,18 we believe that this study may be generally applicable.

Some of our measurements may have been biased by the fact that nonfasting samples were tested. It is known that triglycerides measured postprandially are significantly higher than those measured in the fasting state and also...
that HDL may be somewhat lower. The emphasis of this study, however, was on Lp(a) levels, which are independent of dietary status.\textsuperscript{11,19} Our results confirm the well-recognized relationship between increased plasma LDL-C and the LDL-C/HDL-C ratio with premature MI. In addition, the Broca Index was significantly higher in the case group as compared to the control group. Since the Broca Index correlated significantly with plasma total cholesterol, triglycerides, and HDL-C (Table 4), we believe that these parameters may be more environmentally determined than genetically segregated. In contrast, Lp(a) plasma concentrations measured by our standardized assay correlated neither with the Broca Index nor with any of the measured plasma lipids or lipoproteins (Table 4). Thus, its independence from other lipoprotein concentrations was confirmed.\textsuperscript{16,17}

Except for the Broca Index, plasma Lp(a) was the MI risk indicator with the highest significance in this study. In previous case-control studies, we used a cut-off level for Lp(a) of 20 to 30 mg/dl to discriminate between MI + individuals and controls.\textsuperscript{16} Similar threshold values have been reported in other studies.\textsuperscript{17} By counterimmunoelectrophoresis, a simple technique which can be installed in any laboratory, Lp(a) may be determined from 50 or more samples within 1 hour. Samples may even be frozen and stored for 2 months before assay.\textsuperscript{20} Our test indicated a 2.5-fold relative risk for parents with sons whose Lp(a) level was greater than 25 mg/dl ($p<0.01$). We also calculated a sensitivity of 86.6% and a positive predictive value of 71.3% for the Lp(a) assay. Considering the fact that atherosclerosis is a multifactorial disease, we believe that any additional risk indicator may help to improve the predictive value of a discriminant function assessed in a multivariate analysis.\textsuperscript{3,9}

Finally, it is worth noting that we found no associations between smoking habits, diabetes mellitus, physical activity, or other recorded demographic data and MI in this study. Similarly, no association of Lp(a) level with cerebrovascular insults or stroke was observed. However, the accuracy of the probands' knowledge about these complex diseases in their parents may be limited. In addition, the prevalence of these conditions in the parents of the study group was low, consistent with the known prevalence for their age group.

In summary, our results suggest that there is an association between elevated Lp(a) levels and the risk for MI. Since there are only a few drugs on the market that may reduce plasma Lp(a) levels,\textsuperscript{22} the treatment of coinciding risk factors in Lp(a) + individuals must be considered seriously.

Acknowledgments

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