Racial (Black-White) Differences in Serum Lipoprotein (a) Distribution and Its Relation to Parental Myocardial Infarction in Children

Bogalusa Heart Study

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Larry S. Webber, PhD; and Gerald S. Berenson, MD

Background. The value of lipoprotein (a) [Lp(a)] in the prediction of coronary artery disease risk very early in life remains to be established in different racial groups.

Methods and Results. Serum Lp(a) distribution and its relation to parental histories of myocardial infarction were examined in 2,438 children (8–17 years old) from a biracial community. Parental myocardial infarction was used as a surrogate measure of future risk of disease in the offspring. Lp(a) levels averaged 1.7-fold higher in blacks than in whites ($p<0.0001$). A small but significant sex difference (females greater than males, $p<0.05$) was seen in both races. Race was the only independent variable that contributed appreciably (9%) to the variability of Lp(a) in serum. White children with parental myocardial infarction ($n=90$) had increased levels of Lp(a) compared with those without parental myocardial infarction (22.4 versus 17.1 mg/dl, $p<0.01$). Furthermore, among white children, the prevalence of parental myocardial infarction was higher in those with Lp(a) levels of more than 25 mg/dl than in those with values of 25 mg/dl or less (9.5% versus 5.4%, $p<0.01$). In contrast, the relation of Lp(a) to parental myocardial infarction was not seen in black children. No associations were observed between parental myocardial infarction and serum levels of any of the lipids or lipoprotein cholesterol classes in children of either race.

Conclusions. Serum Lp(a) levels may prove valuable in the assessment of coronary artery disease risk early in life among white populations. These findings also emphasize the need to evaluate the atherogenic potential of Lp(a) in different racial groups. (Circulation 1991;84:160–167)

Serum lipoprotein (a) [Lp(a)] is a cholesterol-rich lipoprotein with structural features of low density lipoprotein (LDL) and plasminogen that provides a link between atherosclerosis and thrombosis.$^{1,2}$ The apolipoprotein (apo) moiety of Lp(a) includes apo B and apo(a), the latter being the antigenic determinant.$^{3,4}$ Structurally, apo(a) subunit contains multiple copies of kringle 4, a single copy of kringle 5, and a protease domain, which are highly homologous to their plasminogen counterparts.$^{5,6}$ Furthermore, it exhibits genetic-size polymorphism that can be related to Lp(a) concentration in serum.$^7$ Although Lp(a) is synthesized independently of other apo B-containing lipoproteins, its catabolism appears to follow the LDL pathway.$^{2,8,9}$

Although Lp(a) contributes less than 15% to serum total cholesterol, clinical studies of adults have shown that elevated levels of this lipoprotein are strongly associated with coronary artery disease (CAD)$^{10-13}$ and stenosis of carotid and cerebral arteries$^{14,15}$ and saphenous vein bypass grafts.$^{16}$ However, it is not known whether the relation of this putatively atherogenic lipoprotein to CAD is the same in different racial groups. In the United States, the incidence of premature CAD is relatively lower in blacks, especially in black males, than in whites.$^{17-19}$ Although extensive prevalence data on Lp(a) are available in white populations,$^2$ such information in the black population is limited to a few studies involving small samples.$^{20,21}$ The pathological precursors of CAD begin in childhood.$^{22}$ Prospective studies are needed to deter-
mine the value of Lp(a) in the prediction of CAD risk early in life. This, however, requires years of continuous investigation. Relevant information concerning the future risk of disease can be obtained by comparing the relation of Lp(a) levels in children with the incidence and history of cardiovascular disease in their parents. Because Lp(a) is inherited as a quantitative genetic trait, studies relating an inherited marker such as Lp(a) to the familial association of CAD can provide results that are akin to those of a prospective study. In the present population-based study, we demonstrate that although Lp(a) levels were markedly higher in black children than in white children, the increased levels of Lp(a) were significantly related to parental history of myocardial infarction in whites but not in blacks.

Methods

Population

The Bogalusa Heart Study is a long-term epidemiological study of cardiovascular disease risk factors from birth through young adulthood in the biracial community (65% white and 35% black) of Bogalusa, La. Children (n=2,666) in grades 3–12, representing 85% of all eligible individuals, were examined during the school year 1984–1985. Half of the children in grades 3–6 were examined between September and December, and the remainder were examined between March and May. Children in grades 7 or 8 and 9–12 were examined between December and February and February and March, respectively. Children less than 8 years old or more than 17 years old were excluded (n=107) because they were not representative of those attending grades 3–12. The sample size for analysis involving Lp(a) distribution by race, age, and gender was 2,438; this represented 78% of all eligible children.

Parental History of Myocardial Infarction

Immediately before the survey, a self-reported parental history of myocardial infarction was obtained through questionnaires completed by each child’s parent or guardian, as shown in Table 1. The percentages of incomplete (or “don’t know”) responses to the presence of parental histories among white and black children in whom Lp(a) data were obtained were 13% (n=202) and 28% (n=245), respectively. Among the children included in these analyses, 90 (7%) white children and 37 (6%) black children had parental histories of the disorder.

The data on parental history were not verified through examinations of case records. Associations of self-reported parental histories of myocardial infarction, diabetes mellitus, and stroke with levels of serum lipids, lipoprotein cholesterol, and apolipoproteins among children from this community have been reported previously.

Anthropometric and Lifestyle Examinations

Sexual maturation was determined by visual assessment of secondary sex characteristics during a physical examination, according to the method of Tanner. 29 The ratings for sexual maturation ranged from 1 (no development) to 5 (complete development) according to the stages of female breast or male genitalia development. Subscapular skinfold thickness was used as a measure of adiposity.

Information on lifestyle characteristics was obtained by questionnaires concerning smoking (number of cigarettes per week, grades 3–12), alcohol intake (ml/wk, grades 7–12), and oral contraceptive use (girls, grades 7–12).

Collection of Blood Specimens

Children were instructed to fast for 12–14 hours, and compliance was determined by interview on the morning of examination. Serum samples were obtained from antecubital venous blood and were sent in a cold-packed box to New Orleans for lipid and lipoprotein cholesterol analyses on the following day; the remaining samples were kept frozen at −70°C and sent to Umea, Sweden (G.H.D.), for Lp(a) measurements.

A second independent blind duplicate blood sample was collected at each screening day on an approximate 10% random subsample of the children to estimate measurement error.

Determination of Serum Lipids and Lipoprotein Cholesterols

Cholesterol and triglycerides were measured in a Technicon Auto-Analyzer II according to the protocols developed by the Lipid Research Clinics. 31 The laboratory is monitored by a surveillance program of the Centers for Disease Control in Atlanta, Ga. Serum levels of very low density lipoprotein (VLDL) cholesterol, high density lipoprotein (HDL) cholesterol, and LDL cholesterol were analyzed by a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis. A detailed description of

### Table 1. Questionnaire Providing Parental History of Myocardial Infarction

<table>
<thead>
<tr>
<th></th>
<th>Child's true father</th>
<th></th>
<th>Child's true mother</th>
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</thead>
<tbody>
<tr>
<td>High blood pressure</td>
<td>□ Yes □ No □ Don't know</td>
<td></td>
<td>□ Yes □ No □ Don't know</td>
<td></td>
</tr>
<tr>
<td>Heart attack</td>
<td>□ Yes □ No □ Don't know</td>
<td></td>
<td>□ Yes □ No □ Don't know</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>□ Yes □ No □ Don't know</td>
<td></td>
<td>□ Yes □ No □ Don't know</td>
<td></td>
</tr>
<tr>
<td>Sugar diabetes</td>
<td>□ Yes □ No □ Don't know</td>
<td></td>
<td>□ Yes □ No □ Don't know</td>
<td></td>
</tr>
<tr>
<td>Tumor or cancer</td>
<td>□ Yes □ No □ Don't know</td>
<td></td>
<td>□ Yes □ No □ Don't know</td>
<td></td>
</tr>
</tbody>
</table>
the method, including measurement errors, has been previously reported.32

Determination of Lp(a)

Lp(a) was determined by an enzyme-linked immunosorbent assay using sheep polyclonal monospecific antibodies against purified human Lp(a) (Biopool AB, Umeå, Sweden). The measurements were completed within 6 weeks. Plasminogen in the range of 0–50 mg/dl and LDL in the range of 0–250 mg/dl had no impact on the assay result. The detection limit was 1.0 mg/dl. Inter assay and intra-assay coefficients of variation at Lp(a) concentrations of 4 and 30 mg/dl were 8.5% and 3.6% and 3.8% and 2.1%, respectively.

On the basis of 316 pairs of blind duplicate determinations on the study sample, the coefficient of variation and SD for measurement errors were 10% and 2.3 mg/dl, respectively. Furthermore, the intraclass correlation coefficient for the blind duplicate values was 0.99, reflecting a high degree of reliability of measurements.

Statistical Analysis

Race and sex differences in levels of Lp(a) were examined by t tests. The relations of Lp(a) to age and sexual maturation (Tanner stage) were examined using Spearman (rank-order) correlation coefficients within each race-sex group. A polynomial regression model (including age, age², and age³ terms as predictor variables) was used to estimate the relation of levels of Lp(a) to age.33 Because Lp(a) did not show a linear relation to age, a nonlinear model was considered appropriate. Significant predictors of Lp(a) were identified using a stepwise regression procedure;34 the independent variables included age, race, sex, Tanner stage, subcapular skin thickness, cigarette smoking, alcohol consumption, and oral contraceptive use.

The relation of Lp(a) levels in children to parental histories of myocardial infarction was analyzed by race. Mean levels of Lp(a) were compared in children with reported parental histories of myocardial infarction and in those without such a history after appropriately controlling for several covariates by analysis of covariance. (Comparisons involving either unadjusted or adjusted levels yielded similar results.) Similarly, the prevalence of parental disease was compared according to children’s Lp(a) levels. All probability values are based on two-sided statistical tests.

Results

Distribution and Mean Levels

The frequency distribution of serum Lp(a) in black and white children are shown in Figure 1; mean levels as well as selected percentiles by race and sex are listed in Table 2. Overall, Lp(a) levels were markedly higher in black children than in white children, irrespective of sex. Fifty-two percent of the white children had Lp(a) levels of 5 mg/dl or less; in contrast, only 14% of black children fell into this category. The frequency distributions were continuous but highly skewed to the right in both races, reflecting the wide difference between the median and the mean values for each race-sex group. A small but significant male/female difference in Lp(a) was seen in both racial groups, with females having higher values than males.

Mean levels and both race- and sex-related differences of the major serum lipids and lipoprotein cholesterol levels remained essentially the same as previously noted in children from this community35–36 (data not shown). In particular, black children had significantly higher levels of total cholesterol and HDL cholesterol and lower levels of triglycerides and VLDL cholesterol compared with white children.

Relation to Age and Sexual Maturation

Race- and sex-specific levels of Lp(a) in children between the ages of 8 and 17 years were estimated by a polynomial regression model to examine the age-related trends (Figure 2). Overall, Lp(a) levels tended to decrease in younger children (8–10 years)

**TABLE 2. Serum Levels of Lipoprotein (a) in Children by Race and Sex in the Bogalusa Heart Study**

<table>
<thead>
<tr>
<th>Race</th>
<th>Mean lipoprotein (a) (mg/dl)</th>
<th>5th</th>
<th>25th</th>
<th>50th</th>
<th>75th</th>
<th>95th</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White†</td>
<td>767</td>
<td>16.4</td>
<td>16.8</td>
<td>2.2</td>
<td>4.7</td>
<td>9.2</td>
</tr>
<tr>
<td>Black‡</td>
<td>431</td>
<td>20.3</td>
<td>28.7</td>
<td>15.3</td>
<td>13.9</td>
<td>21.4</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White†</td>
<td>786</td>
<td>17.9</td>
<td>18.4</td>
<td>2.1</td>
<td>5.0</td>
<td>9.5</td>
</tr>
<tr>
<td>Black‡</td>
<td>454</td>
<td>30.0</td>
<td>21.1</td>
<td>15.4</td>
<td>14.4</td>
<td>26.6</td>
</tr>
</tbody>
</table>

*Sex difference (all children), p<0.05.
†Race difference (all children), p<0.0001.
and to increase in older children (11–17 years). However, the correlation analysis by age group showed that the small age-related trend was significant only in older white females ($r=0.16, p<0.001$); furthermore, the Lp(a) levels also showed a weak but significant positive association with the Tanner stage ($r=0.07, p<0.05$).

Measures (Predictors) of Lp(a)

The predictor variables that were related independently to Lp(a) are listed in Table 3. Race was the predominant predictor variable, accounting for 9% of the variability in Lp(a) levels. Although sexual maturation (Tanner stage) and sex were also independently related to Lp(a), their contribution was not appreciable. Other covariates such as age, subscapular skinfold thickness (measure of adiposity), cigarette smoking, oral contraceptive use, and alcohol consumption did not contribute to the variation of Lp(a) levels.

Relation to Parental Myocardial Infarction

Selected characteristics of the children, listed according to history of myocardial infarction in their parents, are shown in Table 4. Race and sex as well as lifestyle behaviors such as cigarette smoking, alcohol drinking, and oral contraceptive use remained similar in groups of children with and without parental histories of myocardial infarction. However, children whose parents reported a myocardial infarction were relatively older and more obese than those whose parents did not report the disorder. In subsequent analysis that examined association of Lp(a) to parental histories, adjustments were made for these characteristics.

The association of Lp(a) with parental myocardial infarction was examined by race, according to parental histories of the disorder (Figure 3, left panel). White children with parental histories of the disease had increased levels of Lp(a) compared with those without parental histories of the disorder (mean±SD, 22.4±18.0 versus 17.1±17.8 mg/dl; $p<0.01$). In addition, the levels of Lp(a) in white children who turned in “don’t know” responses to the presence of parental histories were not significantly different from those in children without parental histories of myocardial infarction (15.7±18.0 versus 17.1±17.8 mg/dl). Among black children, the levels of Lp(a) remained similar, irrespective of the status of parental histories of myocardial infarction (yes, 27.7±18.3 mg/dl; no, 30.3±21.0 mg/dl; don’t know, 28.4±20.3 mg/dl). The significant race-related difference in Lp(a) levels persisted in each of the categories.

Because Lp(a) levels of more than 20–30 mg/dl have been associated with increased risk of CAD, a cutoff level of 25 mg/dl was used to determine the variability in the prevalence of myocardial infarction in parents (Figure 3, right panel). Among the white children, the percentage of offspring with parental disease was higher in those with Lp(a) levels of more than 25 mg/dl than in those with Lp(a) levels of 25 mg/dl or less (9.5% versus 5.4%, $p<0.01$). In contrast, the above trend was not seen among black children. Furthermore, black and white children with parental histories of myocardial infarction had similar levels of serum lipids and lipoprotein cholesterol fractions compared with those without parental histories of the disease (data not shown).

![Figure 2. Plots of relation of serum lipoprotein (a) [Lp(a)] to age in children by race and sex, estimated by a polynomial regression model, in the Bogalusa Heart Study.](image-url)
The prevalence of parental myocardial infarction was further examined in relation to a range of selected levels (quintiles) of Lp(a) in children of both races (Figure 4). Among white children, although the percentage of offspring with parental disease remained more or less the same between the first and fourth quintiles, the prevalence of parental disease increased 1.9-fold between the fourth and fifth quintiles, whereas no consistent pattern has emerged over the quintiles among black children.

**Discussion**

The present community-based study provides race-, sex-, and age-specific levels of serum Lp(a) in children and examines the relation of Lp(a) levels in offspring to parental myocardial infarction. Black children of both sexes showed markedly higher levels of Lp(a) than their white counterparts, with the frequency distribution highly skewed in both races. It appears that this pattern continues through adulthood, because similar black/white differences in Lp(a) have been noted in adult populations of both the United States and the Congo. In addition, females of both races showed slightly higher Lp(a) values than males.

In the present study, race was the only independent variable that contributed appreciably to the variability of Lp(a) in serum. Other variables such as children's age, sex, sexual maturation, adiposity, cigarette smoking, alcohol intake, and use of oral contraceptives contributed very little to Lp(a) levels. This is in contrast to the marked influences that these covariates have on LDL levels of children and adolescents, suggesting divergent metabolic pathways in the regulation of Lp(a) and LDL.

Because serum levels of Lp(a) show a strong heritability and remain rather constant individually, it is quite likely that the race-related difference in Lp(a) levels is a result of genetic rather than environmental factors. Recent studies have demonstrated that genetic variations at the apo(a) gene locus controls apo(a) protein size and Lp(a) levels, and in a given individual, apo(a) size correlates inversely with Lp(a) levels. The extent to which the black/white difference in Lp(a) levels is mediated by variation at the apo(a) gene locus remains to be determined.

The present study underscores the association of Lp(a) levels with CAD risk early in life. Children of white parents who reported having had a myocardial infarction tended to have increased levels of Lp(a) compared with those without the parental history, independent of several potentially confounding variables. Conversely, among the white children, the prevalence of parental myocardial infarction was higher in those with Lp(a) levels of more than 25 mg/dl than in those with values below this cutoff level.

**FIGURE 4.** Plots of prevalence of myocardial infarction (MI) in parents of children by race, assessed according to selected levels (quintiles) of lipoprotein (a) [Lp(a)] in serum, in the Bogalusa Heart Study. Prevalence per 100=\[\text{yes}^+ (\text{yes}^+ \text{no})\]100.

**FIGURE 3.** Bar graphs of relation of serum lipoprotein (a) [Lp(a)] in children to parental myocardial infarction (MI) by race, assessed according to parental histories of the disease (left panel) or selected Lp(a) cutoff level (right panel), in the Bogalusa Heart Study. Prevalence per 100=\[\text{yes}^+ (\text{yes}^+ \text{no})\]100.
level. Furthermore, the percentage of white offspring with parental myocardial infarction tended to increase above the 75th percentile levels of Lp(a); others have suggested a “threshold” concentration in this relation.13,40

In white populations, increased levels of Lp(a) similar to those found in the present study have been reported in adult first-degree relatives of patients with premature CAD.13,41–43 A similar trend was also noted in Hawaiians of Japanese ancestry in whom Lp(a) levels were similar to those found in white populations.12 Clinical studies in adults have shown association of premature CAD with increased levels of Lp(a).10–13 Taken together, it appears that the adverse levels of Lp(a) may be evident long before clinical symptoms begin.

The present study, we believe, was free of biases with respect to proband selection. Although self-reported parental histories were not verified in the present study, others have found that 73–81% of self-reported myocardial infarction can be confirmed by reviews of medical records and death certificates.44,45 Furthermore, nonsystematic misclassification generally reduces the risk estimate. Despite any possible misclassification of the disease, our results clearly show that white children with elevated Lp(a) levels tended to have increased prevalence of parental myocardial infarction.

In contrast to the findings in white children, there was a lack of a relation between childhood Lp(a) levels and prevalence of parental myocardial infarction in black children. It is likely that the high rate of “don’t know” responses to parental histories in blacks (versus whites) might have influenced the results. However, the levels of Lp(a) among black children remained similar irrespective of the status (yes, no, or don’t know) of parental histories. Although parents and guardians were instructed to provide information on true fathers and mothers, it is difficult to determine whether parents providing histories of myocardial infarction were biologically related to the children and whether information on this aspect differed between the races. Furthermore, parents with a history of myocardial infarction are likely to be older than those without, implying higher parity and/or late child bearing, which might relate to other risk variables. In the present study, as expected, parents with histories of myocardial infarction were significantly older than those without in both races; however, there was no significant age difference between the races within each category.

It is of interest that although the putatively atherogenic Lp(a) levels are markedly higher in blacks than in whites, corresponding black excess in CAD is not seen among the US adult population. Studies have shown that, in general, atherosclerotic fibrous plaque lesions in the coronary artery develop much later in blacks than in whites.46,47 Furthermore, the incidence of premature CAD for black males is relatively lower than that for whites, although the results are not consistent in black females.17–19 It has been suggested that the increased levels of antiatherogenic HDL in blacks (versus whites) may counteract the atherogenic potential of Lp(a).20,48,49 Further detailed studies regarding the relation of childhood Lp(a) levels and prevalence of myocardial infarction in black parents from other populations are needed to confirm the generality of these findings.

The relation of risk factor levels in childhood to subsequent CAD in adulthood is uncertain. Furthermore, there is no consensus regarding the best methods of identifying children at risk for CAD. The present study as well as our previous studies26,27 on the total population of children from this community showed that the levels of lipids and lipoprotein cholesterol fractions in children of either race remained similar between those with and without parental histories of myocardial infarction. However, observations from the Bogalusa Heart Study28 and others50–52 showed a significant relation between childhood levels of lipoprotein cholesterol fractions and prevalence of parental myocardial infarction among children with dyslipoproteinemia. For example, we found that high levels (95th percentile or more) of childhood LDL cholesterol related significantly to parental myocardial infarction in whites, whereas low levels (5th percentile or less) of childhood HDL cholesterol related significantly to parental disease in blacks.51 It appears that childhood Lp(a) levels may be a better marker for CAD risk than lipoprotein cholesterol levels in the general population of white children.

A family history of premature heart attack has been shown to be an independent predictor of CAD in first-degree relatives.53 However, in children, parental history may not be useful in identifying those who are at risk, especially when both children and parents are still quite young. It has been shown recently that serum Lp(a) levels could be substituted for a knowledge of parental history of premature CAD in distinguishing patients from controls.41 The results of the present study favor the concept that Lp(a) may be valuable in the assessment of CAD risk early in life among white populations. They also emphasize the need to evaluate the atherogenic potential of Lp(a) in different racial groups.

Acknowledgments

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