Relation of Cholesterol to Apolipoprotein B in Low Density Lipoproteins of Children

The Bogalusa Heart Study

Sathanur R. Srinivasan, Wendy Wattigney, Larry S. Webber, and Gerald S. Berenson

Cholesterol and apolipoprotein (apo) B contents and their relationship within serum low density lipoprotein (LDL) were examined in 2018 children, ages 8 to 17 years, from a biracial community. The levels of LDL cholesterol and LDL apo B showed significant race-related differences (blacks > whites) in both boys and girls and gender-related differences (girls > boys) in white children. These LDL measures associated inversely and significantly with both age and Tanner stage, more so in boys than in girls. The black-white differences in LDL measures persisted after adjusting for the covariates (sexual maturation, age, adiposity, oral contraceptive use, cigarette smoking, and alcohol use). The distribution of LDL cholesterol for a given range of LDL apo B varied considerably, despite a strong correlation (r = 0.91) between these variables, indicating that measuring LDL cholesterol alone does not accurately reflect LDL composition. The ratio of cholesterol to apo B in LDL ranged from 1.01 (5th percentile) to 1.42 (95th percentile) among the four race-gender groups, suggesting marked interindividual variation in composition. That this ratio was significantly elevated in black children indicates the occurrence of relatively larger, less dense, and cholesterol-enriched LDL particles in blacks. Significant independent associations were noted between LDL cholesterol/apo B ratios and the levels of serum total cholesterol (positive) and triglycerides (negative), suggesting the influence of pool size of different lipoproteins on LDL composition. These observations may help identify a subgroup of children with apo B-enriched LDL particles who are potentially at risk for coronary artery disease.

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Serum lipoproteins are important risk factor variables for coronary heart disease (CHD), with low density lipoproteins (LDL) and high density lipoproteins (HDL) showing positive and inverse risk associations, respectively. Recent studies by Sniderman and colleagues indicate that many patients with CHD have elevated levels of LDL apolipoprotein (apo) B but normal levels of LDL cholesterol. Kesaniemi and Grundy reported that some patients with CHD (apo B) have increased ratios of apo B to cholesterol in LDL and abnormalities in LDL apo B metabolism despite normal concentrations of LDL.

That the LDL particles are heterogeneous in terms of both size and composition even in normal individuals is now well recognized. However, no population-based data are currently available regarding the variability in LDL. Although the LDL particles differ in size and lipid content, they contain one molecule of apo B per particle. The larger LDL particles with less density have a higher cholesterol/apo B ratio than the smaller and denser particles. Therefore, measurements of cholesterol and apo B in LDL offer one of the means by which variability in LDL can be examined on a population basis.

Since CHD risk factor variables are related to initial stages of atherosclerosis in the young, it is important to study the serum lipoproteins in children. Serum lipoprotein lipid and apolipoprotein distributions in U.S. children from population-based studies are currently available. Of these, the Bogalusa Heart Study provides data on a biracial (black-white) pediatric population. In addition to the race, gender, and puberty-related differences in certain lipoproteins, our studies show that variability in lipoprotein composition occurs in a general population of children. For example, a marked interindividual variation was found in the composition of HDL, with the ratio of cholesterol to apo A-I in HDL ranging from 1.4 to 1.2 between the 10th and 90th percentiles. Similar variability in the relation of cholesterol to apo B in LDL might be expected.

The objective of the current study was to examine the variability in the relation of apo B to cholesterol in LDL of children from a biracial community. Factors that influence LDL composition were also determined.

Methods

Population

The Bogalusa Heart Study is a long-term epidemiologic study of cardiovascular disease risk factors from birth.
through early adulthood in the biracial community (65% white, 35% black) of Bogalusa, Louisiana. During 1984 and 1985, 2666 children in grades 3 to 12 representing 85% of all eligible individuals were examined. Children younger than 8 years old or older than 17 years were excluded (n=107) because they were not representative of those attending grades 3 to 12. In addition, 345 non-living participants and 214 children with any missing laboratory data (primarily due to lack of adequate serum samples for LDL apo B and LDL cholesterol measurements) were excluded from the analysis, yielding a final sample size of 2018. In this group, there were 66% whites and 34% blacks, 49% boys, and 51% girls, reflecting the race-gender distribution of the community.

**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. 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 measured and used as a measure of adiposity.

Information on lifestyle characteristics was obtained by questionnaire concerning smoking (number/week, grades 3 to 12), alcohol intake (ml/week, grades 7 to 12), and oral contraceptive use (girls, grades 7 to 12).

**Collection of Blood Specimens**

Children were instructed to fast for 12 to 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 the New Orleans Core Lipid Laboratory where they were kept at 4°C. Laboratory analyses were performed on the following day.

A second blood sample (blind duplicate) was collected on each screening day (an approximate 10% random subsample) to estimate measurement error.

**Serum Lipids**

Cholesterol and triglyceride were determined in a Technicon Auto-Analyzer II (Technicon Corporation, Tarrytown, NY) according to the laboratory manual of the Lipid Research Clinics Program. The laboratory has been designated as standardized by the Centers for Disease Control (CDC) in Atlanta, Georgia, and currently is in the surveillance phase of its quality control program.

### Table 1. Measurement Error for Serum Low Density Lipoprotein Cholesterol and Apolipoprotein B Determinations. The Bogalusa Heart Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of pairs (blind)</th>
<th>Mean</th>
<th>Measurement error</th>
<th>Intraclass correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>SD (mg/dl)</td>
<td>CV (%)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>260</td>
<td>96.5</td>
<td>97.1</td>
<td>5.6</td>
</tr>
<tr>
<td>LDL apo B</td>
<td>260</td>
<td>89.4</td>
<td>89.8</td>
<td>5.2</td>
</tr>
</tbody>
</table>

LDL = low density lipoprotein, SD = standard deviation, CV = coefficient of variation, apo = apolipoprotein.

**Low Density Lipoprotein Cholesterol and Apolipoprotein B**

The cholesterol and apo B contents of serum LDL were measured directly by selectively precipitating this lipoprotein with heparin at pH 5.11 according to the method of Wieland and Seidel, which was based on the original observation by Burstein. Briefly, 200 μL of the sample is added to 2 ml of buffered heparin (0.064 M trisodium citrate, 50 000 U/l heparin) and vortexed. After 10 minutes of standing at room temperature, the insoluble LDL fraction is sedimented by centrifugation at 1000 g for 10 minutes. The precipitate is dissolved in phosphate-buffered isotonic saline (pH 7.4), and aliquots are taken for assay of cholesterol and apo B. The determination of LDL cholesterol by this procedure showed an excellent agreement with results obtained by ultracentrifugation in combination with polyanionic precipitation (cholesterol content of d>1.006 g/ml infranate fraction minus cholesterol content of heparin-Mg++ supemate). Therefore, we considered this method practical for large epidemiologic studies such as ours.

Apo B in LDL was determined by the electroimmunoassay procedure of Laurell as described elsewhere in detail. Antibodies to LDL (d=1.03 to 1.05 g/ml) raised in a goat were used. The candidate international standard serum pool for apo B quantitation was obtained from the CDC and was used to standardize an in-house secondary standard serum pool. The laboratory is participating in the apolipoprotein standardization program of the International Union of Immunological Societies, CDC, and the National Heart, Lung, and Blood Institute.

The measurement errors for LDL cholesterol and LDL apo B are given in Table 1. Because two independent samples were collected from each of 260 individuals, the measurement errors include errors associated with collection, processing, and analysis of the samples, as well as with data processing. Both LDL cholesterol and LDL apo B had equally high intraclass correlation coefficients, reflecting the same degree of reliability of measurement.

**Statistical Analyses**

Race and gender differences in levels of LDL measures were examined by t tests. The relation of LDL measures to age and sexual maturation (Tanner stage) were assessed with Spearman (rank-order) correlation coefficients within each race-gender group. Analysis of covariance was used to determine if black-white differences in mean levels of LDL measures persisted after appropriately controlling for Tanner stage, age, age², age³, subscapular skinfold thickness, cigarette smoking, alcohol consumption, and oral contraceptive use.
Spearman correlation coefficients were computed to examine the interrelationships among serum lipids and LDL measures separately for whites and blacks. Variability in the mean LDL cholesterol/apo B ratio among different strata of serum lipid levels (quintiles) were examined by analysis of variance; Duncan's method was used to test all pairwise differences among quintile means. Significant predictors of LDL cholesterol/apo B ratio were identified using a stepwise regression procedure; the independent variables included serum lipids, age, race, gender, Tanner stage, subscapular skinfold thickness, cigarette smoking, alcohol consumption, and oral contraceptive use.

The levels of LDL cholesterol and LDL apo B were divided into quintiles, and these categories were then cross-tabulated to examine separately the percent distribution of LDL cholesterol quintiles within each LDL apo B quintile.

**Results**

**Distribution and Mean Levels**

The race- and gender-specific cumulative frequency distributions of LDL apo B, LDL cholesterol, and LDL cholesterol/apo B ratio are shown in Figure 1; the mean levels by race and gender are given in Table 2. The median and mean values for these variables were almost identical. Overall, the values for these LDL measures were significantly higher in black children than in white children, irrespective of gender. A significant male-female difference in LDL apo B and LDL cholesterol levels, with girls showing higher values than boys, was noted only among white children. No such gender-related difference in LDL cholesterol/apo B ratio was apparent in either black or white children. The ratio of cholesterol to apo B in LDL ranged from 1.01 (5th percentile) to 1.42 (95th percentile) among the four race-gender groups.

**Distribution of Low Density Lipoprotein Cholesterol Relative to Apolipoprotein B**

In view of the wide range in the ratio of cholesterol to apo B in LDL, the prevalence of variability in LDL cholesterol levels for a given range of LDL apo B was examined by tabulating frequency distribution of LDL cholesterol quintiles according to LDL apo B quintiles (Table 3). The values across each row represent percentages of the children within a given LDL apo B quintile (shown on the left) having different LDL quintiles (shown at the top). If the stoichiometric relation between the cholesterol and apo B constituents of LDL remained constant, one would expect a 100% frequency within cells representing identical LDL apo B and LDL cholesterol quintiles (e.g., quintiles 1-1, 2-2, 3-3, etc.). Instead, the children within each LDL apo B quintile were distributed among different LDL cholesterol quintiles. Of the children belonging to the first, second, third, fourth, and fifth LDL apo B quintiles, only 79.3%, 51.5%, 41.0%, 52.7%, and 78.9%, respectively, remained in the corresponding LDL cholesterol quintiles. Of the children belonging to the first, second, third, fourth, and fifth LDL apo B quintiles, only 79.3%, 51.5%, 41.0%, 52.7%, and 78.9%, respectively, remained in the corresponding LDL cholesterol quintiles. Furthermore, children in the extreme LDL apo B quintiles showed relatively higher concordance with corresponding LDL cholesterol quintiles; the opposite was true for children in the middle LDL apo B quintile.

**Relation to Age and Sexual Maturation**

Race-, gender-, and age-specific mean levels of LDL apo B, LDL cholesterol, and LDL cholesterol/apo B ratio are shown in Figure 2. The levels of LDL apo B and LDL cholesterol showed a decrease with age, especially between the ages of 10 and 14 years in boys and 8 and 13 years in girls of both racial groups; afterwards, the levels tended to fluctuate towards higher values. By comparison, the levels of LDL cholesterol/apo B ratio by age showed no discernible trend in the four race-gender groups, except that the values remained remarkably low in white boys compared to other race-gender groups between the ages of 15 and 17 years. Overall, the cross-sectional correlations of LDL apo B and LDL cholesterol to age were negative and significant in all the race-gender groups, with boys \(r = -0.20\) to \(-0.24\), \(p < 0.001\) showing relatively higher correlations than girls \(r = -0.12\) to \(-0.17\), \(p < 0.01\), whereas the correlation of LDL cholesterol/apo B ratio to age was not significant in all the cases \(r = -0.08\) to \(0.08\).

Because adolescents of a given age express wide variations in their stage of sexual maturation, the serum variables were also related to various Tanner stages, an index of physiologic development during adolescence. The results were similar to those noted above with age.
Table 2. Serum Levels of Low Density Lipoprotein (LDL) Apolipoprotein (Apo) B, LDL Cholesterol, and LDL Cholesterol/Apo B Ratio in Children by Race and Gender. The Bogalusa Heart Study

<table>
<thead>
<tr>
<th></th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White (n=646)</td>
<td>Black (n=342)</td>
</tr>
<tr>
<td>LDL apo B (mg/dl)</td>
<td>80±18</td>
<td>84±18</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>93±23</td>
<td>102±23</td>
</tr>
<tr>
<td>LDL cholesterol/apo B</td>
<td>1.16±0.12</td>
<td>1.18±0.11</td>
</tr>
<tr>
<td>Race difference</td>
<td>p&lt;0.01</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Gender difference</td>
<td>p&lt;0.01*</td>
<td>NS†</td>
</tr>
<tr>
<td></td>
<td>Black (n=683)</td>
<td>Black (n=347)</td>
</tr>
<tr>
<td>LDL apo B (mg/dl)</td>
<td>83±17</td>
<td>87±18</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>96±22</td>
<td>102±23</td>
</tr>
<tr>
<td>LDL cholesterol/apo B</td>
<td>1.16±0.11</td>
<td>1.18±0.11</td>
</tr>
<tr>
<td>Race difference</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Gender difference</td>
<td>p&lt;0.01*</td>
<td>NS†</td>
</tr>
</tbody>
</table>

*Whites only; †Not significant.

Both LDL cholesterol and LDL apo B associated inversely with Tanner stage, more so in boys (r = -0.26 to -0.29, p<0.001) than in girls (r = -0.11 to -0.16, p<0.01). On the other hand, no significant correlation was noted between Tanner stage and LDL cholesterol/apo B ratio (r = -0.08 to 0.07).

Evaluation of Black-White Differences

Black-white differences in LDL apo B and LDL cholesterol levels were examined for boys and girls separately, controlling for potential confounding covariates (sexual maturation, age, adiposity, cigarette smoking, alcohol use, and oral contraceptive use) (Figure 3). The observed differences in LDL apo B and LDL cholesterol were independent of the above confounding factors, with covariant-adjusted values for LDL apo B showing 8.2% and 4.7% higher in black boys (p<0.001) and black girls (p<0.001), respectively, than their white counterparts. The covariate-adjusted levels of LDL cholesterol remained higher in black boys (11.6%, p<0.001) and black girls (6.2%, p<0.001). Black-white differences in LDL cholesterol/apo B ratio also persisted in both boys (3.0%, p<0.001) and girls (1.6%, p<0.05) after adjusting for the covariates (data not shown).

Influence of Serum Lipids on Low Density Lipoprotein/Apolipoprotein B Ratio

Serum total cholesterol correlated positively and significantly to LDL cholesterol/apo B ratio in both races (r = -0.33 to 0.38, p<0.001); in contrast, serum triglycerides showed an inverse relationship (r = -0.13 to -0.17, p<0.001). As expected, LDL apo B showed a strong positive correlation to LDL cholesterol in both races (r = 0.90 to 0.91, p<0.001). The ratio of LDL cholesterol to LDL apo B correlated to LDL cholesterol (r = 0.37 to 0.40, p<0.001) but did not correlate to LDL apo B (r = -0.01 to 0.01) even though the ratio contains both the original variables. This suggests that cholesterol, rather than apo B, varies within LDL.

Since serum total cholesterol and triglycerides showed opposing relations to LDL cholesterol/apo B ratio, the variability in the mean levels of this ratio was examined in relation to a range of levels (quintiles) of serum lipids (Figure 4). Gradients in the levels of LDL cholesterol/apo B ratio were evident over quintiles of both serum total cholesterol (a positive trend, p<0.001) and triglycerides (an inverse trend, p<0.001). Furthermore, mean levels of LDL cholesterol/apo B ratio among various total cholesterol and triglyceride quintiles were significantly different from each other (p<0.05), with the exception of a lack of difference in values noted between second and third triglyceride quintiles. The mean values for LDL cholesterol/apo B ratio ranged from 1.11 to 1.22 among total cholesterol quintiles, and from 1.14 to 1.19 among triglycerides quintiles.

A stepwise regression procedure was then used to identify covariates (including serum total cholesterol and triglycerides) that were all independently related to LDL cholesterol/apo B ratio (Table 4). Serum total cholesterol and triglycerides accounted for 16% of the variability in LDL cholesterol/apo B ratio. Other covariates such as age, race, gender, Tanner stage, subscapular skinfold thickness, cigarette smoking, and oral contraceptive and alcohol use contributed less than 2% to the variations of the ratio.

Discussion

The present community-based study provides race-, gender-, and age-specific levels of cholesterol and apo B
and their relative proportion within LDL in children and adolescents. Our findings that small, but consistent, black-white differences in both LDL cholesterol and LDL apo B occur, with blacks showing higher values than whites, indicate relatively higher LDL particle numbers in blacks. Earlier studies by us14 and Morrison et al.25 did not detect black-white differences in LDL cholesterol, probably because cholesterol measurements were not performed directly on isolated LDL fractions, as in the present study. Furthermore, we did not find black-white differences in fasting serum total apo B,14 which represents all the lipoproteins except HDL. This is to be expected, in view of the present finding, because serum levels of very low density lipoproteins (VLDL) are relatively lower in blacks as compared with whites.11,26 The opposing trends in LDL and VLDL levels between the two racial groups might result in similar total apo B values.

The black-white divergences in LDL cholesterol and LDL apo B persisted even after adjusting for the confounding covariates such as sexual maturation, age, adiposity, oral contraceptive use, cigarette smoking, and alcohol use. The possibility exists, however, that the observed black-white differences may be partly due to lipoprotein Lp(a), the serum levels of which have been found to be higher in black individuals.29 Lipoprotein Lp(a), which includes apo B, apo (a), and cholesterol, is known to interact with heparin, but the extent of precipitation of Lp(a) by heparin is negligible in the absence of Ca++.27 Since lipoprotein Lp(a) represents less than 3% and 5% of serum total cholesterol in white and black individuals, respectively,26 any contribution of lipoprotein Lp(a) in quantitative terms to LDL measures in the precipitation procedure devoid of Ca++ should be minimal.

The present data show a gender differential (girls>boys) in both LDL cholesterol and LDL apo B only among white children. Furthermore, the cross-sectional associations of LDL measures with age and sexual maturation remained negative, more so in boys than in girls. These findings in conjunction with earlier observations in children26,29 and adults30,31 indicate that the characteristic adult pattern of elevated levels of LDL in men versus women emerges after completion of sexual maturation.
Of particular interest is our finding that marked interindividual variations in the composition of LDL particles exists among children. The variability in LDL is evaluated in terms of cholesterol to apo B ratio within LDL because, with decreasing ratio, the particles become smaller and denser and carry less core lipid.8,32,33,34 In children, the ratio of cholesterol to apo B within LDL varied from 1.01 to 1.42 between the 5th and 95th percentiles. Furthermore, this ratio was significantly higher in black children than in white children, suggesting that LDL particles are relatively larger, less dense, and more cholesterol-enriched in the former group. It appears that the black-white difference in LDL is not only quantitative, but qualitative as well.

Despite a strong correlation between LDL apo B and LDL cholesterol (r=0.91), the distribution of LDL cholesterol for a given range of LDL apo B varied considerably. For example, of the 385 children who belonged to the third LDL apo B quintile, only 158 (41%) remained in the same LDL cholesterol quintile. It is, therefore, obvious that, even in a general population of children, measuring LDL cholesterol alone does not accurately reflect LDL concentration (particle number). Moreover, as Teng et al.8 pointed out, important differences in composition may be missed if only LDL cholesterol is measured.

The interrelationships of serum lipids and LDL measures noted in the present study support the hypothesis that serum triglyceride (VLDL) concentration influences the characteristics of LDL.33,36,37 Our results show that graded changes in the relative proportions of cholesterol to apo B within LDL are inversely and continuously related to serum triglyceride levels and positively to serum total cholesterol levels. Moreover, both serum total cholesterol and triglycerides remained as the predominant significant predictor variables for the LDL cholesterol/apo B ratio. Deckelbaum et al.30 reported a strong inverse association (r=-0.64) between serum triglyceride levels and the ratio of cholesterol ester to protein in LDL; however, the study subjects (n=43) varied from individuals with extremely low triglyceride levels (abetalipoproteinemia) to those with hypertriglyceridemia (Types I and IV). It is noteworthy that serum triglyceride level is a significant determinant of LDL cholesterol/apo B ratio in a free-living population of children with a median triglyceride level of 56 mg/dl. That the divergence in LDL cholesterol/apo B ratio between the racial groups (blacks>whites) reflects difference in serum triglyceride levels between the two groups (white>blacks) further demonstrates the influence of serum triglycerides on LDL composition.

Recently Barter et al.38 demonstrated that exchange of cholesteryl ester between lipoproteins is a function of the pool size of different lipoprotein fractions. In a related study, we found that children with low VLDL triglycerides had a higher ratio of cholesterol to triglycerides in lipoprotein fractions (VLDL, LDL, and HDL) and vice versa.15 Taken together, it appears that increased serum triglyceride levels (VLDL) would result in decrease in cholesterol as compared with apo B in LDL particles. By comparison, increased serum total cholesterol levels (LDL) under conditions of low serum triglyceride levels would produce an opposite effect.

The alterations in LDL size, density, and composition are considered to be due to the bidirectional transfer of triglycerides and cholesteryl ester between VLDL and LDL mediated by lipoprotein transfer protein.30,40 The triglyceride-loaded LDL is then subject to hydrolysis by hepatic lipase and lipoprotein lipase, resulting in smaller and denser particles with lower cholesterol/apo B ratio. It was recently suggested that the ratio of cholesterol to apo B in LDL could be a reflection on the turnover rates of LDL.41 The observed variability in LDL cholesterol/apo B ratio, although relatively modest, may nevertheless reflect the heterogeneity of LDL metabolism on a population basis.

Recently, it was reported that genetic polymorphism in apo B is reflected in the general population.42,43,44 The structural differences in apo B, probably resulting from an alteration in its amino acid sequence, may influence the LDL composition in normal individuals. It is unclear how much of the variability in LDL seen in the current study is due to genetic heterogeneity. It should be noted, however, that only 18.8% of the variability in LDL cholesterol/apo B ratio is explained by the independent variables listed in Table 4.

Our observation that variability in LDL composition occurs among free-living, healthy children may have a bearing on CHD risk. Earlier we showed that the LDL cholesterol/total apo B ratio was significantly higher in children with paternal myocardial infarction.44 With technological advances allowing routine measurement of apo B in a reliable manner, information on the relative proportion of cholesterol to apo B within LDL can have practical merit. For example, a subgroup of children with disproportionate increase in apo B relative to cholesterol in LDL may be at an increased risk because of the atherogenic potential of such LDL particles.44,45 Furthermore, it is likely that the preponderance of early coronary artery disease in white men compared to other race-gender groups47 may be due in part to characteristic difference in LDL. It is of interest that LDL particles are relatively apo B-enriched in white children (especially in adolescent white boys) compared to black children, although particle numbers are higher in the latter. If the compositional difference in LDL continues through adulthood, this may confer additional CHD risk on white men because the levels of antiatherogenic HDL (cholesterol and apo A-I) are relatively low in this group compared to other race-gender groups.11,14,25,48 Further studies in this direction are obviously needed.
Acknowledgments

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References


Index Terms: low density lipoprotein composition • LDL cholesterol • LDL apolipoprotein B • white children • black children
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