Divergent Levels of High Density Lipoprotein Cholesterol and Apolipoprotein A-I in Children

The Bogalusa Heart Study

David S. Freedman, Sathanur R. Srinivasan, Larry S. Webber, and Gerald S. Berenson

Clinical studies indicate that levels of apolipoprotein A-I (apo A-I), the major protein moiety of the high density lipoprotein (HDL) particle, may provide more information concerning the risk of future cardiovascular disease than do levels of HDL cholesterol (HDL-C). Therefore, the relationship of HDL-C to apo A-I levels was examined in a biracial sample of 2849 5- to 17-year-olds. The mean HDL-C to apo A-I ratio, a measure of HDL composition, was 0.42. However, marked interindividual variation was found: HDL-C/apo A-I levels varied from 0.27 (10th percentile) to 0.57 (90th percentile). Furthermore, only 26% of the variation in HDL-C levels was explained by concomitant variation in apo A-I. Increasing levels of triglyceride (and very low density lipoprotein cholesterol) were related to decreases in both the HDL-C/apo A-I ratio and the magnitude of the correlation between HDL-C and apo A-I. Low density lipoprotein cholesterol, race, and age were also related to the HDL-C/apo A-I ratio, but influenced HDL composition less strongly than did triglyceride levels. These observations may be explained by the bidirectional transfer of cholesteryl esters and triglycerides between HDL and triglyceride-rich lipoproteins. The current study documents the influence of triglyceride levels on HDL composition in a general population of children and adolescents, and emphasizes the interrelationships between the various lipoprotein fractions. (Arteriosclerosis 7:347-353, July/August 1987)

Elevated levels of cholesterol in the high density lipoprotein (HDL) fraction are inversely related independently of other serum lipoprotein cholesterol fractions to the extent of atherosclerosis and incidence of cardiovascular disease.1-4 Apolipoprotein A-I (apo A-I), the principal protein moiety of HDL, is also inversely associated with angiographically documented coronary artery disease,5-8 and decreased levels of apo A-I have been found in first-degree relatives of persons with cardiovascular disease.9, 10, 11 Although there is opposing evidence,12 levels of apo A-I probably provide additional information, as compared with HDL cholesterol (HDL-C), concerning the risk of future cardiovascular disease.9, 12-15 Differences in the relationship of cardiovascular disease to levels of HDL-C and apo A-I may be due to variation in HDL structure and composition. HDL particles are derived, in part, from the lipolysis of triglyceride-rich lipoproteins.16 However, decreased amounts of cholesteryl ester are seen in the HDL core in the presence of elevated plasma triglyceride levels17, 18, 19 possibly due to the bidirectional transfer of triglycerides and cholesteryl esters between lipoprotein fractions. Levels of both triglyceride and very low density lipoprotein cholesterol (VLDL-C) are inversely related to HDL-C levels,20, 21, 22 whereas only weak associations between levels of serum triglyceride and apo A-I have been observed.23, 24 Therefore, although only limited population data are available,24, 25, 26 a less than perfect correlation between levels of HDL-C and apo A-I might be expected.

The purpose of the current study was to quantify the variability in levels of HDL-C and apo A-I in a biracial (black-white) sample of 2849 5- to 17-year-olds. Previous analyses of apo A-I levels in this population have examined race, sex, and age differences22 and compared the relationships of offspring levels of HDL-C and apo A-I to parental histories of cardiovascular disease.11 The present study describes the joint distribution of HDL-C and apo A-I and contrasts their relationships with other serum lipids and lipoproteins, especially triglyceride. Factors that influence HDL composition are also identified.

Methods

Population

The Bogalusa Heart Study is a long-term epidemiologic study of cardiovascular disease risk factors from birth through early adulthood.27 The target population (70% white, 30% black) includes all residents up to age 26 of
Bogalusa, Louisiana. In 1980, the population of Bogalusa was approximately 20,000.

Five cross-sectional examinations of school-aged children have been conducted in Bogalusa since 1973, and data collected from 3312 5- to 17-year-olds in the fourth (1981-1982) examination are used in the current analyses. The overall participation rate was 80.2%. Nonfasting participants (n = 391, 11.8%) and children with any missing lipid, lipoprotein cholesterol, or apolipoprotein determinations (n = 72, 2.5%) were excluded from the analyses, yielding a final sample size of 2849 children and adolescents. (Nonfasting participants, however, were used to assess the influence of postprandial lipemia on levels of HDL-C and apo A-I.)

**General Examinations**

Children fasted for 12 hours before examination, and compliance was determined from an interview with the child. As previously described, the examination procedure included venipuncture, a menstrual history interview, anthropometric measurements, a physical examination, nine blood pressure measurements, and questionnaires concerning smoking and alcohol use.

Levels of serum total cholesterol and triglyceride were measured with an AutoAnalyzer II using protocols developed by the Lipid Research Clinics. (The Core Lipid Laboratory has been standardized by the Centers for Disease Control in Atlanta, and is monitored by a surveillance program.) Serum lipoprotein cholesterol fractions were analyzed by a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis. Levels of apo A-I in whole serum were assayed by the electroimmunoassay procedure of Laurell as previously reported. A 10% random sample of the participants was selected daily to assess the reproducibility of all laboratory analyses. Intraclass correlation coefficients for the serum lipids and lipoprotein cholesterol fractions, based on 377 pairs of blind duplicate determinations, ranged from 0.89 (HDL-C) to 0.99 (triglyceride). The reproducibility of apo A-I measurements was 0.84.

**Statistical Methods**

The mean levels of HDL-C and apo A-I were plotted by age for each race and sex group. The mean levels and selected percentiles (10th, 50th, and 90th) of the HDL-C/apo A-I ratio were then calculated for each race, sex, and age group (5 to 9, 10 to 14, and 15 to 17 years of age). Levels of HDL-C and apo A-I were cross-tabulated, and the number of children within each cell were calculated. Pearson correlation coefficients (and corresponding linear regression analyses) were used to describe the relationship of HDL-C levels to apo A-I within each race, sex, and age group. (Spearman correlations yielded almost identical results.) Differences among the correlation coefficients were tested for statistical significance after applying Fisher's Z-transformation. These transformed correlation coefficients were also used in weighted least squares regression (weighted according to the inverse of the variance, N-3) to assess the linear trends in the magnitudes of the correlations according to age and triglyceride level (see below).

The associations of HDL-C, apo A-I, and the HDL-C/apo A-I ratio with the other lipids and lipoprotein cholesterol classes were also assessed using Pearson correlation coefficients. In addition, the association between levels of HDL-C and apo A-I was also evaluated within categories defined by serum triglyceride levels. Significant predictors of HDL-C/apo A-I levels were identified using a backward elimination procedure; the initial independent variables included race, sex, age, and the other serum lipids and lipoprotein cholesterol fractions. Standardized regression coefficients, expressing the predicted change (in standard deviation units) in HDL-C/apo A-I from a one-standard deviation change in the independent variables, were calculated.

**Figure 1.** Mean levels of HDL cholesterol and apo A-I in children by race, sex, and age. The Bogalusa Heart Study.
The mean levels of HDL-C and apo A-I according to race, sex, and age are shown in Table 1. In general, blacks had elevated levels of HDL-C as compared with whites, but these racial differences increased with age in boys and decreased with age among girls. Black-white differences in apo A-I levels were seen only in boys. Male-female differences in levels of both HDL-C and apo A-I showed an interaction (crossover) with age. Whereas younger (<13 years of age) boys had higher levels than did girls, the mean levels of both HDL components in older children were either higher in females (whites) or showed no male-female difference (blacks). The levels of HDL-C and apo A-I were most strongly associated with age in white males: as compared with 5- to 9-year-olds, mean levels were 13 mg/dl (21%) and 9 mg/dl (15%) higher, respectively, in the 15- to 17-year-olds.

Although previously reported, the mean levels of selected serum lipids and lipoprotein cholesterol fractions are shown in Table 1 as background information. Whites had higher mean levels of triglyceride and VLDL-C as compared with blacks, opposite to the racial differences observed for HDL-C and apo A-I. In addition, white males showed the strongest association between age and levels of both triglyceride and VLDL-C. The median levels of these two variables in 15- to 17-year-old white males were 18 mg/dl (34%) and 6 mg/dl (15%) higher, respectively, than were levels in 5- to 9-year-olds.

The HDL-C/apo A-I ratio, a measure of HDL composition, showed marked between-person variation: the 10th, 50th, and 90th percentiles were 0.27, 0.43, and 0.57, respectively (Table 2). Differences according to race, sex, and age were also observed. The 5- to 9-year-old white boys had higher HDL-C/apo A-I levels than did similarly aged white females, and 10- to 14-year-old blacks had higher levels than did whites. Furthermore, the proportion-

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**Table 1. Mean Levels of Selected Lipids and Lipoproteins in Children by Race, Sex, and Age Group. The Bogalusa Heart Study**

<table>
<thead>
<tr>
<th>Race and sex</th>
<th>Age (years)</th>
<th>No.</th>
<th>TC</th>
<th>LDL-C</th>
<th>TG</th>
<th>VLDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>5-17</td>
<td>2849</td>
<td>161 (158) ± 27</td>
<td>93 (90) ± 25</td>
<td>64 (56) ± 32</td>
<td>8 (5) ± 7</td>
</tr>
<tr>
<td>White males</td>
<td>5-9</td>
<td>393</td>
<td>160 (157) ± 25</td>
<td>92 (89) ± 22</td>
<td>59 (53) ± 27</td>
<td>6 (4) ± 6</td>
</tr>
<tr>
<td></td>
<td>10-14</td>
<td>409</td>
<td>156 (154) ± 27</td>
<td>92 (89) ± 26</td>
<td>66 (58) ± 37</td>
<td>8 (6) ± 8</td>
</tr>
<tr>
<td></td>
<td>15-17</td>
<td>122</td>
<td>150 (145) ± 28</td>
<td>88 (82) ± 27</td>
<td>81 (71) ± 72</td>
<td>12 (10) ± 9</td>
</tr>
<tr>
<td>White females</td>
<td>5-9</td>
<td>409</td>
<td>165 (163) ± 25</td>
<td>100 (97) ± 26</td>
<td>67 (59) ± 32</td>
<td>7 (4) ± 7</td>
</tr>
<tr>
<td></td>
<td>10-14</td>
<td>398</td>
<td>155 (154) ± 26</td>
<td>93 (91) ± 25</td>
<td>77 (67) ± 42</td>
<td>11 (8) ± 10</td>
</tr>
<tr>
<td></td>
<td>15-17</td>
<td>99</td>
<td>156 (153) ± 24</td>
<td>87 (84) ± 23</td>
<td>67 (61) ± 26</td>
<td>9 (7) ± 7</td>
</tr>
<tr>
<td>Black males</td>
<td>5-9</td>
<td>211</td>
<td>165 (163) ± 26</td>
<td>92 (91) ± 23</td>
<td>52 (48) ± 18</td>
<td>5 (3) ± 5</td>
</tr>
<tr>
<td></td>
<td>10-14</td>
<td>194</td>
<td>163 (161) ± 26</td>
<td>91 (89) ± 23</td>
<td>52 (50) ± 19</td>
<td>6 (5) ± 4</td>
</tr>
<tr>
<td></td>
<td>15-17</td>
<td>73</td>
<td>163 (154) ± 36</td>
<td>93 (87) ± 31</td>
<td>66 (54) ± 56</td>
<td>8 (6) ± 7</td>
</tr>
<tr>
<td>Black females</td>
<td>5-9</td>
<td>236</td>
<td>168 (167) ± 28</td>
<td>97 (94) ± 25</td>
<td>54 (50) ± 18</td>
<td>5 (4) ± 5</td>
</tr>
<tr>
<td></td>
<td>10-14</td>
<td>198</td>
<td>163 (161) ± 28</td>
<td>94 (93) ± 24</td>
<td>60 (56) ± 24</td>
<td>8 (6) ± 7</td>
</tr>
<tr>
<td></td>
<td>15-17</td>
<td>107</td>
<td>165 (164) ± 30</td>
<td>94 (90) ± 27</td>
<td>63 (60) ± 25</td>
<td>8 (6) ± 6</td>
</tr>
</tbody>
</table>

Values are mean (median) ± standard deviation.

TC = serum total cholesterol; LDL-C = low density lipoprotein cholesterol; TG = serum triglycerides; VLDL-C = very low density lipoprotein cholesterol.

**Table 2. Mean and Selected Percentiles of HDL Cholesterol/Apolipoprotein A-I in Children by Race, Sex, and Age Group. The Bogalusa Heart Study**

<table>
<thead>
<tr>
<th>Race and sex</th>
<th>Age (years)</th>
<th>No.</th>
<th>Mean</th>
<th>STD</th>
<th>10</th>
<th>50</th>
<th>90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>5-17</td>
<td>2849</td>
<td>0.42</td>
<td>0.13</td>
<td>0.27</td>
<td>0.43</td>
<td>0.57</td>
</tr>
<tr>
<td>White males</td>
<td>5-9</td>
<td>393</td>
<td>0.44</td>
<td>0.12</td>
<td>0.31</td>
<td>0.45</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td>10-14</td>
<td>409</td>
<td>0.41</td>
<td>0.13</td>
<td>0.25</td>
<td>0.42</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>15-17</td>
<td>122</td>
<td>0.37</td>
<td>0.13</td>
<td>0.19</td>
<td>0.38</td>
<td>0.52</td>
</tr>
<tr>
<td>White females</td>
<td>5-9</td>
<td>409</td>
<td>0.42</td>
<td>0.13</td>
<td>0.26</td>
<td>0.42</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>10-14</td>
<td>398</td>
<td>0.37</td>
<td>0.14</td>
<td>0.18</td>
<td>0.39</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>15-17</td>
<td>99</td>
<td>0.43</td>
<td>0.11</td>
<td>0.27</td>
<td>0.43</td>
<td>0.54</td>
</tr>
<tr>
<td>Black males</td>
<td>5-9</td>
<td>211</td>
<td>0.47</td>
<td>0.12</td>
<td>0.33</td>
<td>0.47</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>10-14</td>
<td>194</td>
<td>0.46</td>
<td>0.11</td>
<td>0.31</td>
<td>0.45</td>
<td>0.60</td>
</tr>
<tr>
<td></td>
<td>15-17</td>
<td>73</td>
<td>0.42</td>
<td>0.11</td>
<td>0.26</td>
<td>0.43</td>
<td>0.55</td>
</tr>
<tr>
<td>Black females</td>
<td>5-9</td>
<td>236</td>
<td>0.47</td>
<td>0.12</td>
<td>0.33</td>
<td>0.47</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>10-14</td>
<td>198</td>
<td>0.44</td>
<td>0.12</td>
<td>0.28</td>
<td>0.45</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>15-17</td>
<td>107</td>
<td>0.43</td>
<td>0.11</td>
<td>0.30</td>
<td>0.42</td>
<td>0.57</td>
</tr>
</tbody>
</table>

STD = standard deviation.
Table 3. Cross-tabulation of HDL Cholesterol and Apolipoprotein A-I Levels in Children. The Bogalusa Heart Study

<table>
<thead>
<tr>
<th>HDL cholesterol (mg/dl)</th>
<th>Apolipoprotein A-I (mg/dl)</th>
<th>&lt;100</th>
<th>100-119</th>
<th>120-139</th>
<th>140-159</th>
<th>160-179</th>
<th>£180</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td></td>
<td>0.7</td>
<td>0.7</td>
<td>1.2</td>
<td>0.8</td>
<td>0.2</td>
<td>0.1</td>
<td>3.6</td>
</tr>
<tr>
<td>20-39</td>
<td></td>
<td>1.5</td>
<td>2.8</td>
<td>3.5</td>
<td>2.4</td>
<td>0.9</td>
<td>0.1</td>
<td>11.1</td>
</tr>
<tr>
<td>40-59</td>
<td></td>
<td>1.1</td>
<td>6.1</td>
<td>14.7</td>
<td>9.9</td>
<td>3.4</td>
<td>0.2</td>
<td>35.2</td>
</tr>
<tr>
<td>60-79</td>
<td></td>
<td>0.1</td>
<td>1.7</td>
<td>10.9</td>
<td>12.9</td>
<td>8.9</td>
<td>0.5</td>
<td>35.1</td>
</tr>
<tr>
<td>80-99</td>
<td></td>
<td>0.1</td>
<td>0.1</td>
<td>2.1</td>
<td>3.5</td>
<td>5.2</td>
<td>1.5</td>
<td>12.4</td>
</tr>
<tr>
<td>£100</td>
<td></td>
<td>—</td>
<td>—</td>
<td>0.3</td>
<td>0.6</td>
<td>1.0</td>
<td>0.7</td>
<td>2.5</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>3.6</td>
<td>11.4</td>
<td>32.6</td>
<td>29.9</td>
<td>19.5</td>
<td>3.0</td>
<td></td>
</tr>
</tbody>
</table>

All values are percent of total sample (n = 2849). Because of rounding, table entries do not sum exactly to totals.

Table 4. Pearson Correlations between HDL Cholesterol and Apolipoprotein A-I in Children. The Bogalusa Heart Study

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>White males</th>
<th>White females</th>
<th>Black males</th>
<th>Black females</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-9</td>
<td>0.50 (393)</td>
<td>0.43 (409)</td>
<td>0.49 (211)</td>
<td>0.52 (236)</td>
<td>0.48 (1249)</td>
</tr>
<tr>
<td>10-14</td>
<td>0.47 (409)</td>
<td>0.49 (398)</td>
<td>0.51 (194)</td>
<td>0.56 (198)</td>
<td>0.50 (1199)</td>
</tr>
<tr>
<td>15-17</td>
<td>0.85 (122)</td>
<td>0.46 (99)</td>
<td>0.60 (73)</td>
<td>0.63 (107)</td>
<td>0.62 (401)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.52 (924)</td>
<td>0.47 (906)</td>
<td>0.51 (478)</td>
<td>0.55 (541)</td>
<td>0.51 (2849)</td>
</tr>
</tbody>
</table>

Values are r (n).

The levels of HDL-C and apo A-I are cross-tabulated in Table 3. Within each cell is the percentage of the 2849 children having that particular combination of levels of HDL-C (indicated on the left) and apo A-I (indicated at the top). A clustering around the mean levels of both variables (60 mg/dl, HDL-C; 141 mg/dl, apo A-I) was observed, with almost one-half of the children having HDL-C levels ranging from 40 to 79 mg/dl and apo A-I levels ranging from 120 to 159 mg/dl. However, there was much variation in the joint distribution of HDL-C and apo A-I levels. For example, ately larger decrease in levels of HDL-C with age in white males, as compared with apo A-I (21% vs. 6%), resulted in low HDL-C/apo A-I levels in 15- to 17-year-old white males. Smaller decreases with age were observed in blacks, but white females showed no consistent relationship between HDL-C/apo A-I and age.

The levels of HDL-C and apo A-I are cross-tabulated in Table 3. Within each cell is the percentage of the 2849 children having that particular combination of levels of HDL-C (indicated on the left) and apo A-I (indicated at the top). A clustering around the mean levels of both variables (60 mg/dl, HDL-C; 141 mg/dl, apo A-I) was observed, with almost one-half of the children having HDL-C levels ranging from 40 to 79 mg/dl and apo A-I levels ranging from 120 to 159 mg/dl. However, there was much variation in the joint distribution of HDL-C and apo A-I levels. For example,
levels below the 20th percentile (data not shown).

As assessed by linear regression, the correlation between apo A-l levels and HDL-C was 0.51 (Table 4). (The addition of squared and cubed apo A-l terms did not improve the prediction of HDL-C.) In general, a 1 mg/dl increase in apo A-l was associated with a 0.49 mg/dl predicted increase in HDL-C. Although there were only small differences in the association between levels of apo A-l and HDL-C among the race-sex groups, the magnitude of the association tended to increase with age (p = 0.06). Apo A-l levels accounted for only 23% (0.48^2) of the variation in HDL-C levels among 5- to 9-year-olds, whereas 38% of the variation in HDL-C could be explained by apo A-l levels in 15- to 17-year-olds. These age-related increases in the association between HDL-C and apo A-l levels paralleled decreases in the HDL-C/apo A-l ratio with age (Table 2).

The associations of HDL-C, apo A-l, and HDL-C/apo A-l with various lipids and lipoprotein cholesterol fractions are shown in Figure 2. (With the exception of the correlation between apo A-l and LDL-C, all correlation coefficients are statistically significant at the 0.001 level.) As compared with apo A-l, HDL-C showed stronger negative associations with LDL-C (r = -0.30 vs. -0.04), serum triglycerides (-0.52 vs. -0.09), and VLDL-C (-0.60 vs. -0.12). These differing associations were reflected in the associations with HDL-C/apo A-l: levels of both triglyceride and VLDL-C were strongly (inversely) related to this ratio. The HDL-C/apo A-l ratio was inversely related to levels of both triglyceride and VLDL-C in all race-sex groups, even though the (inverse) associations of HDL-C with both triglyceride and VLDL-C were stronger in whites than in blacks (data not shown).

The influence of serum triglyceride levels, which ranged from 20 to 492 mg/dl (median = 56 mg/dl), on HDL composition is shown graphically in Figure 3. The overall correlation between HDL-C and apo A-l decreased from 0.77 at low (20 to 29 mg/dl) triglyceride levels to 0.43 at high (≥100 mg/dl) triglyceride levels; this decreasing linear relationship was statistically significant (p = 0.01). Also shown in Figure 3 are mean levels of both HDL-C and apo A-l. As triglyceride levels increased from <30 mg/dl to ≥100 mg/dl, reductions in HDL-C levels (from 71 to 33 mg/dl, a 54% decrease) were more striking than were reductions in mean levels of apo A-l (from 150 to 137 mg/dl, a 9% decrease).

A backward elimination procedure was then used to identify a subset of predictor variables that were all (independently) related to the HDL-C/apo A-l ratio. The four variables shown in Table 5 accounted for 35% of the variation in levels of HDL-C/apo A-l, with levels of triglyceride alone accounting for most of this variability. Increases in triglyceride, LDL-C, and age were all associated with a decrease in the HDL-C/apo A-l ratio. Furthermore, as compared with whites, blacks had elevated levels of this ratio, irrespective of differences in the other variables. (Because levels of triglyceride and VLDL-C were highly correlated (r = 0.84), VLDL-C levels were not included in the regression model.)

### Discussion

Marked interindividual variation exists in the composition of HDL particles. In the current study of children and adolescents, the ratio of HDL-C to apo A-l varied from approximately 1:4 to 1:2 between the 10th and 90th percentiles, with only 26% of the variation in HDL-C levels explainable by concomitant variation in levels of apo A-l. Increasing levels of triglyceride (and VLDL-C) were related to: 1) decreases in the HDL-C/apo A-l ratio, and 2) decreases in the magnitude of the correlation between HDL-C and apo A-l. LDL-C, race, and age were also related to HDL-C/apo A-l levels, but these factors were less important in influencing HDL composition than were levels of triglyceride or VLDL-C.

Abnormal HDL composition has been observed in hypertriglyceridemic patients, and changes in core and surface constituents of HDL particles (decreases in cholesteryl ester relative to apo A-l) have been related to increasing plasma triglyceride levels in adults. However, several of these studies examined HDL composition in nonrandomly selected persons, including patients with noninsulin-dependent diabetes and various lipoprotein disorders. For example, although Deckelbaum et al. reported a strong inverse correlation (r = -0.58) between plasma triglyceride levels and the ratio of cholesteryl ester to protein in the HDL particle, levels of plasma triglyceride ranged from 31 to 2820 mg/dl. The current study documents an almost identical, inverse association in a free-living population of children and adolescents with a median triglyceride level of 56 mg/dl.

Alterations in HDL composition may be mediated by plasma proteins, which transfer triglyceride from VLDL to HDL (and transfer cholesteryl ester in the opposite direction) in response to an expanded pool of triglyceride-rich lipoproteins. In vitro, HDL particles can be modified by incubation with high levels of VLDL and transfer proteins toward smaller (and denser), triglyceride-enriched particles containing decreased amounts of cholesteryl ester. Clinical studies have reported a strong negative association (r = -0.71) between levels of HDL triglyceride and

<table>
<thead>
<tr>
<th>Table 5. Characteristics Related to the HDL-C/Apo A-l Ratio in Children. The Bogalusa Heart Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Independent variable</strong></td>
</tr>
<tr>
<td>TG (mg/dl)</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
</tr>
<tr>
<td>Race (0 = whites)</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
</tbody>
</table>

All variables were independently related to HDL-C/apo A-l at the 0.001 level. 
*Estimated from partial coefficients.
HDL-C, after taking into account the varying number of HDL particles, plasma triglyceride levels have been positively related to levels of HDL triglyceride. It is likely that VLDL triglyceride would have been even more strongly (inversely) related to levels of HDL-C in the current study than were levels of serum triglyceride (which includes triglyceride in all lipoprotein fractions). In contrast to the transfer of lipids between lipoprotein particles, apo A-I is not redistributed by the transfer process. Therefore, increased triglyceride levels result in a proportionately larger decrease in cholesterol, as compared with protein, in HDL particles. Schönfeld and Pfleger have described hypertriglyceridemic adults who have normal apo A-I levels, and only weak correlations between levels of triglyceride and apo A-I have been reported by others.

The differing relationships of HDL-C and apo A-I with triglyceride levels may explain the only moderate (r = 0.51), currently observed correlation between HDL-C and apo A-I levels. Comparable associations have been reported in adults, although many of these studies examined persons with clinical cardiovascular disease. Tyrold et al. reported correlations between HDL-C and apo A-I ranging from 0.35 (white females) to 0.44 (black males) in a free-living sample of 318 adults. Stronger correlations ranging up to r = 0.85 have been reported in other recently selected samples of adults. Variability in the relationship between HDL-C and apo A-I may reflect interindividual differences in the relative proportions of HDL2-C and HDL3-C: HDL2 carries about twice as much cholesteryl ester per mole of apo A-I as does HDL3.

Although neither HDL-C nor apo A-I levels were measured with perfect reproducibility in the current study, the observed correlation (r = 0.51) is substantially lower than the two intraclass correlation coefficients of 0.89 and 0.84, respectively. (The reproducibility of the HDL-C/apo A-I ratio in the present study was 0.80.) In addition, variations in levels of both HDL-C and apo A-I may reflect physiologic differences: Patscht et al. have shown that levels of both HDL-C and apo A-I are inversely related to the magnitude of postprandial lipemia, and that physical exercise may lead to improved fat tolerance. The 391 nonfasting participants in the current study had decreased levels of both HDL-C (–2 mg/dl) and apo A-I (–1 mg/dl) as compared to fasting subjects, but showed a similar correlation between HDL-C and apo A-I.

Unfortunately, no information on the stability of the HDL-C/apo A-I ratio is available from the current cross-sectional analyses. Nevertheless, the current study demonstrates that, even in a general population of children, HDL-C measurements do not accurately reflect plasma levels of HDL in the presence of elevated plasma triglyceride levels. This may be important in evaluating lipoprotein levels in early life; the ratio HDL-C/ (LDL-C + VLDL-C) has been shown to be negatively related to the initial stages of atherosclerosis.

In addition, HDL compositional alterations may account for the reported differences in the relationships of HDL-C and apo A-I with cardiovascular disease in adults. Kukita et al. found that among normotriglyceridemic patients, the extent of angiographically defined coronary artery disease was inversely related to levels of both HDL-C and apo A-I, but that only apo A-I was related to disease in hypertriglyceridemic patients.

Because apo A-I levels are less influenced by levels of triglyceride than are HDL-C levels, apo A-I may be more stable over time. The current results emphasize the importance of considering the interrelationships of the different lipid and lipoprotein fractions in the prediction of cardiovascular disease. For example, even if triglyceride levels are not directly related to clinical disease, they are important determinants of HDL composition. Because of metabolic interconversions of the different lipoprotein fractions, attempting to hold one variable constant while assessing the "independent" contribution of other fractions can be misleading.

Acknowledgments

The Bogalusa Heart Study is a joint effort involving many people. The authors thank Bettye Seal, the staff of the Bogalusa Heart Study, and the children and parents whose cooperation made this study possible.

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Index Terms: child • lipids • HDL cholesterol • apolipoprotein A-I

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Divergent levels of high density lipoprotein cholesterol and apolipoprotein A-I in children.
The Bogalusa Heart Study.
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Arterioscler Thromb Vasc Biol. 1987;7:347-353
doi: 10.1161/01.ATV.7.4.347
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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