LDL Size in African Americans, Hispanics, and Non-Hispanic Whites

The Insulin Resistance Atherosclerosis Study

Steven M. Haffner, Ralph D’Agostino, Jr, David Goff, Barbara Howard, Andreas Festa, Mohammed F. Saad, Leena Mykkänen

Abstract—The prevalence of cardiovascular disease (CVD) and atherosclerosis varies among several minority ethnic groups in the United States. Recently, small, dense low density lipoprotein (LDL) particle size has been recognized as a risk factor for CVD. We examined LDL size as a possible explanation for differences in CVD rates in 1571 subjects from the Insulin Resistance Atherosclerosis Study (IRAS), a multiethnic study of insulin resistance and cardiovascular risk factors. LDL size (Å) was significantly different by ethnic group (African Americans 262.1 ± 0.6, Hispanics 257.6 ± 0.6, and non-Hispanic whites 259.2 ± 0.4, P < 0.001). Ethnic differences in LDL size continued to be statistically significant after adjustment for upper body adiposity, insulin resistance, and glucose tolerance status. However, after further adjustment for other cardiovascular risk factors, especially ethnic differences in triglyceride and high density lipoprotein (HDL) cholesterol levels, the ethnic differences in LDL size were markedly attenuated and in general no longer statistically significant. The relation of triglyceride, HDL cholesterol, insulin resistance, and adiposity to LDL size in each ethnic group was similar. LDL size differs by ethnic group, which is independent of obesity or insulin resistance. These ethnic differences appear to be due to ethnic variations in dyslipidemia (especially differences in triglyceride levels); ethnic differences in LDL size are not consistent with previously reported ethnic dissimilarities in CVD or atherosclerosis. (Arterioscler Thromb Vasc Biol. 1999;19:2234-2240.)

Key Words: Hispanics ■ non-Hispanic whites ■ African Americans ■ LDL size ■ coronary heart disease ■ insulin resistance

Differences in the prevalence of coronary heart disease (CHD) and cardiovascular disease (CVD) have been reported in the United States between ethnic groups. Hispanics have been reported to have rates of CHD1–5 or CVD6 similar to or lower than those of non-Hispanic whites, although a few recent reports have not supported this position.7–9 African Americans have increased CVD relative to non-Hispanic whites.10–12 We have reported recently that African Americans have a significantly greater intima-media wall thickness than do non-Hispanic whites in the common carotid artery in nondiabetic subjects in the Insulin Resistance Atherosclerosis Study (IRAS).13 In the IRAS, ethnic differences in the common carotid artery intima-media wall thickness could not be explained by conventional cardiovascular risk factors. (No ethnic differences were observed in internal carotid artery wall thickness in the IRAS.13)

Considerable information has been gathered on cardiovascular risk factors to explain ethnic differences in CVD. Hispanics have increased obesity,14 higher triglyceride and lower HDL cholesterol levels,15,16 and an increased prevalence17,18 and incidence19 of type 2 diabetes. The above ethnic differences in cardiovascular risk factors suggest a higher risk of CVD in Hispanics. However, Hispanics have been reported to have a lower prevalence of hypertension than do non-Hispanic whites.20,21 The risk of CVD predicted from the Framingham model is higher in Hispanics than in non-Hispanic whites.21 African Americans have an increased prevalence of both hypertension22 and type 2 diabetes23,24 relative to non-Hispanic whites, which might increase the risk of CVD in the former group. In contrast, African Americans have lower levels of triglyceride and higher levels of HDL cholesterol (especially in males) than do non-Hispanic whites.25,26

Increased levels of small, dense LDL (LDL subgroup pattern B) have been identified as a risk factor for the prevalence27–31 and incidence32–34 of CHD. The epidemiological correlates of small, dense LDL include increased triglyceride and decreased HDL cholesterol levels, male sex, hyperinsulinemia, insulin resistance, and type 2 dia-
betes. Of these variables, decreased HDL and especially increased triglyceride levels are the strongest predictors of small, dense LDL. We have previously shown that Mexican Americans have increased small, dense LDL relative to non-Hispanic whites in the San Antonio Heart Study, but these findings were no longer significant after adjustment for the greater dyslipidemia in Mexican Americans (increased triglyceride and decreased HDL cholesterol levels).

LDL size has not been previously examined in African Americans. On the basis of previous studies showing increased HDL cholesterol and decreased triglyceride levels relative to non-Hispanic whites in African Americans, one might expect a larger LDL size (less atherogenic) in the latter group. However, considering the greater obesity and diabetes and increased insulin resistance in African Americans, the effects of which might decrease LDL size, it is difficult to predict whether LDL size would be smaller or larger in African Americans compared with non-Hispanic whites.

In this report, we examine LDL size in a triethnic population (African Americans, Hispanics, and non-Hispanic whites) in the IRAS. We also examine whether the relation of traditional correlates of LDL size (hyperinsulinemia, obesity, and dyslipidemia) affect LDL size in a similar fashion across ethnic groups.

Methods
A detailed description of the design and methods of the IRAS has been published. In brief, this study was conducted at 4 centers: Oakland and Los Angeles, Calif; San Antonio, Tex; and San Luis Valley, Colo. Diabetic subjects receiving insulin were not eligible for the IRAS. Diabetic subjects with a fasting glucose level $\geq 300$ mg/dL (16.7 mmol/L) were also excluded. A total of 1625 individuals participated in the IRAS (56% women). Individuals with normal glucose tolerance composed the largest segment of the study sample (44%: non-Hispanic whites, n = 291; African Americans, n = 187; and Hispanics, n = 241), followed by diabetes (37%: non-Hispanic whites, n = 177; African Americans, n = 187; and Hispanics, n = 241) and persons with impaired glucose intolerance (23%: non-Hispanic whites, n = 145; African Americans, n = 101; and Hispanics, n = 123).

Height, weight, and girths (minimum waist and hips) were measured by following a standardized protocol. Body mass index (BMI; weight/height$^2$ [kg/m$^2$]) was used as an estimate of overall adiposity. Waist circumference was taken as the minimum circumference between the thorax and the hips. The waist circumference was used as an estimate of body fat distribution.

The IRAS examination required 2 visits (approximately 1 week apart [range 2 to 28 days]), each lasting $\sim$4 hours. An oral glucose tolerance test and a frequently sampled intravenous glucose tolerance test (FSIGT) were performed during the first and second visits, respectively. Glucose tolerance was classified according to World Health Organization criteria. Insulin sensitivity was assessed by the FSIGT with minimal model analyses. The protocol has been previously described in detail.

Plasma lipid concentrations were obtained from fasting, single, fresh plasma samples by using Lipid Research Clinics methods. VLDL was isolated by preparative ultracentrifugation, and the VLDL (top) and bottom fractions were measured for cholesterol and triglyceride concentrations. HDL cholesterol was measured after precipitation of apo B-containing lipoproteins with MnCl$_2$ and heparin. The cholesterol content in the supernatant was measured in a separate autoanalyzer channel set to measure low cholesterol values. LDL cholesterol was calculated as the difference between the HDL cholesterol and the bottom cholesterol. Triglycerides were measured enzymatically after correction for free glycerol. Direct measurement of VLDL cholesterol by preparative ultracentrifugation was done for all subjects.

LDL size distribution (ie, distribution of diameters of the major LDL peaks for all participants) was determined using the method of Krauss and Burke. Gradient gels were obtained from Isolab. Measurement of the size of the predominant peak was calibrated using LDL fractions whose molecular diameters were determined by analytical ultracentrifugation (courtesy of Dr Ronald Krauss, Donner Laboratories, Berkeley, Calif). The LDL size of the predominant peak for an individual was defined as that person’s LDL size.

In the IRAS, the coefficient of variance was 2%.

Mean values of the cardiovascular risk factors were compared according to ethnic group by ANCOVA (SAS version 6.08, SAS Institute). Logarithmic transformations (for statistical testing) were used for triglyceride values. Further adjustment was made for variables previously shown to affect LDL size (Table 3). Because waist circumference and BMI were highly correlated ($r=0.82$), they were not included in the same regression model. Spearman correlations were used to describe the relationship of LDL size to possible confounding variables separately in the ethnic groups (Table 2). The LDL size by ethnic group is also shown stratified by possible confounding variables (the Figure) by using ANCOVA. Because the non-Hispanic whites were sampled at all 4 locations, whereas African Americans and Hispanics were sampled at only 2 areas, we examined whether the reference group (non-Hispanic whites) was similar in all 4 areas with respect to key variables (triglyceride, HDL cholesterol, and LDL size). Non-Hispanic whites were similar with respect to these variables, and therefore, we compared the ethnic groups by adjusting for clinic location.

Results
Table 1 shows the clinical and biochemical characteristics of the population. Obesity (BMI) was greater in Hispanics and African Americans than in non-Hispanic whites. Insulin concentrations were higher and insulin sensitivity lower in Hispanics and African Americans relative to non-Hispanic whites. African Americans had the highest blood pressure, and Hispanics had the lowest blood pressure. The proportion of subjects on lipid-lowering medications was very low in all ethnic groups (8.0%) and did not differ by ethnic group. Because the results for subsequent analyses were similar with and without these subjects (on lipid treatment), we report data including these subjects. As might be expected from previous studies, African Americans had lower triglyceride and higher HDL cholesterol levels than did non-Hispanic whites. Hispanics had the opposite pattern, with higher triglyceride and lower HDL cholesterol levels than non-Hispanic whites. LDL size ($\Delta$) differed significantly $(P<0.001)$ by ethnic group (African Americans 262.1 $\pm$ 0.6, Hispanics 257.6 $\pm$ 0.6, and non-Hispanic whites 259.2 $\pm$ 0.4). In pairwise comparisons, African Americans had a significantly greater LDL size than did non-Hispanic whites $(P<0.001)$ or Hispanics $(P<0.001)$. Hispanics had a slightly smaller LDL size than did non-Hispanic whites $(P=0.039)$.

Table 2 shows the correlations between LDL size and selected variables. In the overall population, LDL size was significantly correlated with obesity (BMI) $(r=-0.09)$.
waist circumference \((r = -0.19)\), fasting glucose \((r = -0.17)\), 2-hour glucose \((r = -0.20)\), fasting insulin \((r = -0.18)\), insulin sensitivity \((S_I)\) \((r = 0.21)\), HDL cholesterol \((r = 0.38)\), and triglyceride \((r = -0.47)\). However, LDL size was not significantly related to systolic \((r = -0.01)\) or diastolic \((r = 0.04)\) blood pressure. These associations were similar in each ethnic group. After further adjustment for diabetic status (data not shown), LDL size continued to be significantly related to triglyceride, HDL cholesterol, and insulin sensitivity, although the magnitude of the association was somewhat attenuated.

The Figure shows LDL size by ethnic group stratified by selected variables by use of a 2-way ANOVA. Male sex, type 2 diabetes, high triglyceride levels, and low HDL cholesterol levels were associated with smaller LDL size. African Americans continued to have a higher LDL size after adjustment for sex or diabetic status compared with non-Hispanic whites. Hispanics had a smaller LDL size than did non-Hispanic whites after adjustment for sex or diabetic status. However, after adjustment for triglyceride or HDL levels, the ethnic differences in LDL size were attenuated, especially in the groups with low triglyceride or high HDL cholesterol values.

Table 3 shows ethnic differences in LDL size after sequential adjustment in possible confounding variables. Ethnic differences in LDL size remained statistically significant after further adjustment for demographic variables or the following variables: obesity, body fat distribution, glucose levels, or insulin sensitivity. However, adjustment for triglyceride and HDL cholesterol attenuated the ethnic differences in LDL size, although there remained modestly lower LDL size in Hispanics than in African Americans (model 5 or 6).

**Discussion**

We have confirmed earlier data that African Americans have decreased triglyceride and increased HDL cholesterol levels compared with non-Hispanic whites. In this report, for the first time, we have shown that LDL size is significantly higher in African Americans than in non-Hispanic whites. These differences are not the result of the greater adiposity, diabetes, or insulin resistance in African Americans. However, after controlling for the lower triglyceride and higher HDL cholesterol levels in African Americans, the ethnic differences in LDL size are no longer significant, except for possibly a smaller LDL size in Hispanics than in African Americans (Table 3, models 5 and 6).

We have also shown that Hispanics have a smaller LDL size than do non-Hispanic whites, as has been reported previously from the San Antonio Heart Study. As in that report, Hispanics and non-Hispanic whites had similar LDL size after adjustment for dyslipidemia and lipoproteins. In the current report, Hispanics had lower HDL cholesterol and higher triglyceride levels than did non-Hispanic whites, which is consistent with a number of previous studies.

In previous articles, LDL size was associated with increased triglyceride levels, decreased HDL cholesterol levels, hyperinsulinemia, insulin resistance, obesity, and an unfavorable body fat distribution. With the exception of a few studies, those studies were done in...
TABLE 1. Clinical and Biochemical Description of Subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>African Americans, n (%)</th>
<th>Hispanics, n (%)</th>
<th>Non-Hispanic Whites, n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>462 (27)</td>
<td>546 (34)</td>
<td>612 (38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>199 (43.1)</td>
<td>225 (42.1)</td>
<td>293 (47.9)</td>
<td>0.062</td>
</tr>
<tr>
<td>Type 2 diabetes, n (%)</td>
<td>175 (37.8)</td>
<td>184 (35.7)</td>
<td>177 (28.9)</td>
<td>0.008</td>
</tr>
<tr>
<td>Age, years</td>
<td>55.5±0.4</td>
<td>55.1±0.4</td>
<td>56.3±0.3</td>
<td>0.048</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.2±0.4</td>
<td>29.4±0.5</td>
<td>28.8±0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>94.0±0.8</td>
<td>94.4±0.8</td>
<td>93.3±0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>122.5±3.1</td>
<td>129.8±2.9</td>
<td>118.7±2.0</td>
<td>0.007</td>
</tr>
<tr>
<td>2-h Glucose, mg/dL</td>
<td>182.1±6.4</td>
<td>203.7±6.1</td>
<td>174.5±4.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Fasting insulin, μU/mL</td>
<td>18.8±0.7</td>
<td>19.9±0.7</td>
<td>16.7±0.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>(42.2)</td>
<td>(44.3)</td>
<td>(44.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Past</td>
<td>(40.7)</td>
<td>(34.3)</td>
<td>(43.4)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>(16.9)</td>
<td>(21.4)</td>
<td>(12.4)</td>
<td></td>
</tr>
<tr>
<td>Sₐ ×10⁻⁴/μU/mL</td>
<td>1.26±0.12</td>
<td>1.65±0.11</td>
<td>1.93±0.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>212.5±2.7</td>
<td>211.1±2.5</td>
<td>213.2±1.8</td>
<td>0.782</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>143.8±2.2</td>
<td>139.4±2.1</td>
<td>140.7±1.5</td>
<td>0.410</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>47.0±0.8</td>
<td>42.3±0.8</td>
<td>44.0±0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>102.1±1.0</td>
<td>147.7±1.0</td>
<td>134.0±1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL size, Å</td>
<td>262.1±0.6</td>
<td>257.6±0.6</td>
<td>259.2±0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>129.3±0.8</td>
<td>122.8±0.8</td>
<td>123.3±0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>79.2±0.5</td>
<td>77.7±0.4</td>
<td>76.7±0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Subjects on lipid-lowering</td>
<td>(8.7)</td>
<td>(6.2)</td>
<td>(9.2)</td>
<td>0.15</td>
</tr>
<tr>
<td>medication (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects on antihypertensive</td>
<td>(30.2)</td>
<td>(21.2)</td>
<td>(24.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>medications (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sₐ indicates insulin sensitivity; BP, blood pressure. Data are mean±SEM. P values are for ANOVA or χ² test.

cant. The correlations, however, of LDL size with triglyceride and HDL were strong as in other studies.) Although it might be expected that similar relations between LDL size and other variables among different ethnic groups might exist, this is not always true of all associations. In the IRAS, insulin resistance was related to atherosclerosis in Hispanics and non-Hispanic whites but not in African Americans.49 Insulin resistance has been related to blood pressure in whites but not in African Americans in 1 study50; however, in another study, insulin resistance was related to blood pressure in African Americans.51

Previous studies have suggested increased CVD in African Americans.10–12 Because our data suggest that LDL size is actually higher in African Americans than in non-Hispanic whites, this observation cannot explain the ethnic difference in CVD rates. Hispanics were initially reported to have lower CVD rates than non-Hispanic whites,1–6 although recent findings have shown higher rates of CVD in Hispanics.7–9,52 In the IRAS, common carotid artery intima-media wall thickness was highest in African Americans and lowest in Hispanics,13 which is the opposite pattern observed for LDL size in this respect.

The reason for the higher LDL size in African Americans is not well understood. Cohen et al53 have suggested that the human hepatic lipase gene is a major determinant of HDL cholesterol levels, although Mahaney et al,44 in a Mexican-
American population, have found a major gene linked to HDL cholesterol and apoA1 but excluded the possibility of linkage to the human hepatic lipase locus. African Americans have been found to have a high frequency of the A allele at the human hepatic lipase locus, which is associated with lower hepatic triglyceride lipase levels and thus, could be an explanation for the higher LDL size in this ethnic group, although further work is needed in this area.

We have shown that LDL size is greater in African Americans than in non-Hispanic whites or Hispanics after adjustment for upper body adiposity, fasting glucose, and insulin resistance (Table 3, model 4). After further adjustment for triglyceride and HDL cholesterol (models 5 and 6), the higher LDL size in African Americans was markedly attenuated. However, adjustment for triglyceride or HDL cholesterol in regression models in which LDL size is a dependent variable can be problematic because of the strong correlations (possible “statistical issue” of multicollinearity) and because one variable can be problematic because of the strong correlations (possible “statistical issue” of multicollinearity) and because one variable may be opposite the CVD risk differences by ethnic group.

In conclusion, we have found an ethnic difference in the LDL size distribution, with African Americans having the highest LDL size (“less atherogenic”) and Hispanics having the lowest LDL size; these ethnic differences in LDL size, however, appear to be primarily due to differences in triglyceride and HDL cholesterol among the ethnic groups. Similar variables (triglyceride, HDL cholesterol, insulin resistance, etc.) appear to be related to LDL size in these ethnic groups. Last, ethnic differences in LDL size are not consistent with previously reported differences in their risk of CVD or atherosclerosis; in fact, the ethnic differences in LDL size may be opposite the CVD risk differences by ethnic group.

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References


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