Low-Density Lipoprotein Triglycerides Associated With Low-Grade Systemic Inflammation, Adhesion Molecules, and Angiographic Coronary Artery Disease

The Ludwigshafen Risk and Cardiovascular Health Study

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Background—Markers of systemic inflammation and LDL cholesterol (LDL-C) have been considered independent risk factors of coronary artery disease (CAD). We examined whether alterations of LDL metabolism not reflected by LDL-C were associated with low-grade inflammation, vascular injury, and CAD.

Methods and Results—We studied 739 subjects with stable angiographic CAD and 570 matched control subjects in which CAD had been ruled out by angiography. The association of LDL triglycerides (LDL-TGs) (odds ratio [OR], 1.30; 95% CI, 1.19 to 1.43; \( P < 0.001 \)) with CAD was stronger than that of LDL-C (OR, 1.10; 95% CI, 1.00 to 1.21; \( P = 0.047 \)). The predictive value of LDL-TG for CAD was independent of LDL-C. “Sensitive” C-reactive protein (CRP), serum amyloid A, fibrinogen, intercellular adhesion molecule-1 (ICAM-1), and vascular adhesion molecule-1 (VCAM-1) increased in parallel to LDL-TG. CRP, ICAM-1, and VCAM-1 were inversely related to LDL-C. To examine whether LDL-TGs were associated with the distribution of LDL subfractions, we studied 114 individuals with impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes mellitus. In subjects with high LDL-TG, LDLs were depleted of cholesteryl esters (CEs), and VLDLs, IDLs, and dense LDLs were significantly elevated.

Conclusions—Alterations of LDL metabolism characterized by high LDL-TG are related to CAD, systemic low-grade inflammation, and vascular damage. High LDL-TGs are indicative of CE-depleted LDL, elevated IDL, and dense LDL. LDL-TG may better reflect the atherogenic potential of LDL than LDL-C. (Circulation. 2004;110:3068-3074.)

Key Words: cholesterol ▪ triglycerides ▪ lipoproteins ▪ inflammation

Elevated LDL cholesterol (LDL-C) is among the strongest predictors of coronary artery disease (CAD). Lowering LDL-C reduces vascular events. The majority of CAD patients, however, present with fairly normal LDL-C. In these patients, nontraditional risk factors, such as low-grade systemic inflammation, have been advocated to explain the development of CAD.1,2

Little is known about factors that initiate and maintain low-grade systemic inflammation. At least in part, the variation of circulating C-reactive protein (CRP) levels may be attributed to conventional risk factors such as smoking, age, obesity, dyslipidemia, elevated blood pressure, or impaired glucose metabolism.3,4 However, CRP concentrations correlate only minimally with LDL-C, and the predictive value of CRP has been largely independent of LDL-C,5 suggesting that disorders of LDL metabolism and inflammatory processes promote atherogenesis by distinct pathways. LDL, however, is a complex mixture of particles. In addition to cholesterol, its lipid moiety is made up primarily of phospholipids and triglycerides (TGs). We therefore examined whether constituents of LDL other than cholesterol were associated with markers of systemic inflammation, circulating adhesion molecules, and angiographically verified CAD.

Methods

Study Design
We studied 1309 clinically stable participants of the Ludwigshafen Risk and Cardiovascular Health (LURIC)® study not taking lipid-lowering drugs. Among these, 739 individuals had angiographic CAD (≥20% stenosis); 570 subjects served as control subjects. Comparing subjects with at least 1 stenosis ≥50% (n=556) and those with stenoses <20% (n=570) did not materially affect our

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An online-only Appendix and online-only Figures are available at http://www.circulationaha.org.

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3068
results (for details regarding the design of this study, see online Appendix 1).

To examine the relationship between lipid constituents of LDL and the distribution of LDL subfractions in detail, we studied another 114 patients (not included in the LURIC study) with fasting plasma glucose between 1.1 and 2.0 g/L, established impaired glucose tolerance, or type 2 diabetes mellitus (T2DM) < 75 years of age and not receiving oral antidiabetics, insulin, or lipid-lowering agents (LDL-C > 1.3 g/L, TG > 1.0 g/L).

**Laboratory Procedures**

**Lipoproteins**

In the comparison of CAD patients with control subjects, lipoproteins were separated by a combined ultracentrifugation-precipitation method (β-quantification). 5-9 Cholesterol, TGs, and phospholipids were measured with enzymatic reagents (Wako) and apolipoprotein B (apoB) by turbidimetry (Greiner). 6 In this method, the LDL fraction includes particles with densities of 1.006 through 1.063 g/L and thus comprises IDLs (1006 to 1.019 g/L).

**LDL Subfractions**

VLDLs (d < 1.006 kg/L), IDLs (1.006 < d < 1.019 kg/L), LDLs (1.019 < d < 1.063 kg/L), and HDLs (1.065 < d < 1.21 kg/L) were isolated by preparative ultracentrifugation. Total LDLs (1.019 < d < 1.063 kg/L) were fractionated into 6 density classes by equilibrium density-gradient centrifugation; particle radii and the molar ratios of lipids to apoB in VLDL, IDL, LDL, and LDL subfractions were calculated as described.10 The interassay coefficient of variation of the determination of apoB in each of the LDL subfractions was ≤ 5%.11 LDL constituents quantified by the β-quantification method corresponded well with the sums of IDL and LDL derived from sequential ultracentrifugation (see online Appendix 2).

**Other Methods**

“Sensitive” CRP and serum amyloid-A (SAA) were measured by immunonephelometry (N Latex CRP mono, Dade Behring). 5 Fibrinogen was measured according to Clauss (Dade Behring). Interleukin (IL)-6 (high-sensitivity), intercellular adhesion molecule-1 (ICAM-1), and vascular cellular adhesion molecule-1 (VCAM-1) were determined with commercial enzyme immunoassays (R&D Systems). 6 Glucose was determined enzymatically (Roche Diagnostics).

**Statistical Analysis**

CRP, SAA, and IL-6 were transformed logarithmically before being used in parametric statistical procedures. Continuous clinical and biological variables were compared between CAD patients and control subjects by univariate ANOVA with adjustment for sex. Associations between categorical variables were examined by logistic regression analysis. We established tertile or quartile ranges according to the values in control subjects, and we obtained odds ratios (ORs) by comparing the prevalences of clinically relevant CAD across the quartiles of LDL-TG, LDL-C, and HDL-C or across subgroups having different levels of predictors, as indicated. Sex and CAD status, age, body mass index (BMI), hypertension, smoking, and a variable metabolic syndrome (MS)/diabetes mellitus (DM) (derived by coding DM8 as 2, the presence of the MS12 as 1, and the absence of both as 0) were included in the models as categorical variables; TG, HDL-C, LDL-C, LDL-TG, and CRP were included as continuous variables when used as covariables. Nonparametric

| TABLE 1. Clinical and Biochemical Characteristics of CAD Patients and Control Subjects |
|-----------------------------------------------|-----------------|-----------------|-----------------|
|                                | Control Subjects |                     | CAD                     |
|                                | Male (n=310)     | Female (n=260)   | Male (n=550)            | Female (n=189) |
|                                |                  |                  |                            |                |
| Age, y                         | 55 ± 12          | 61 ± 11          | 64 ± 10                  | 67 ± 9        | < 0.001 |
| BMI, kg/m²                     | 27.4             | 27.5             | 28.4 ± 4                 | 27.5           | NS      |
| Smoker (former and current)    | 202 (65%)        | 77 (30%)         | 424 (77%)                | 61 (32%)      | < 0.001 |
| Diabetes mellitus              | 54 (17%)         | 47 (18%)         | 198 (36%)                | 79 (42%)      | < 0.001 |
| Systemic hypertension          | 177 (57%)        | 173 (67%)        | 435 (79%)                | 150 (79%)     | < 0.001 |
| Systolic blood pressure, mm Hg | 135 ± 21         | 138 ± 24         | 148 ± 23                 | 147 ± 25      | < 0.001 |
| Diastolic blood pressure, mm Hg| 81 ± 12          | 79 ± 11          | 84 ± 12                  | 82 ± 11       | < 0.001 |
| Fasting blood glucose, mg/dL   | 106 ± 32         | 103 ± 21         | 117 ± 37                 | 122 ± 48      | < 0.001 |
| Cholesterol, mg/dL             | 197 ± 36         | 202 ± 33         | 198 ± 37                 | 212 ± 38      | 0.043   |
| LDL-C, mg/dL                   | 119 ± 29         | 126 ± 30         | 123 ± 32                 | 132 ± 37      | 0.011   |
| LDL triglycerides, mg/dL       | 28 ± 9           | 30 ± 12          | 31 ± 12                  | 35 ± 12       | < 0.001 |
| LDL phospholipids, mg/dL       | 82 ± 21          | 95 ± 21          | 89 ± 22                  | 99 ± 21       | 0.017   |
| LDL apoB, mg/dL                | 86 ± 19          | 86 ± 20          | 89 ± 20                  | 93 ± 24       | < 0.001 |
| HDL-C, mg/dL                   | 40 ± 11          | 47 ± 12          | 37 ± 10                  | 44 ± 11       | < 0.001 |
| Triglycerides, mg/dL, median   | 145 (103–199)    | 122 (90–164)     | 144 (106–197)            | 140 (112–196) | NS      |
| C-reactive protein, mg/L, median| 1.5 (0.8–5.0)   | 2.5 (1.2–6.3)   | 3.0 (1.3–7.4)            | 3.7 (1.6–8.7) | < 0.001 |
| Serum amyloid A, mg/L, median  | 3.4 (2.1–6.7)    | 4.9 (3.1–8.2)   | 4.5 (2.5–9.2)            | 6.1 (3.6–11.5)| < 0.001 |
| Fibrinogen, mg/dL, median      | 334 (288–394)    | 346 (301–396)   | 367 (314–430)            | 376 (322–436) | < 0.001 |
| Interleukin 6, mg/L, median     | 2.7 (1.4–4.7)    | 2.9 (1.6–5.2)   | 3.4 (2.1–6.4)            | 3.5 (2.0–6.9)| 0.0044  |
| ICAM-1, mg/L                   | 246 ± 91         | 247 ± 81         | 264 ± 96                 | 253 ± 64      | 0.035   |
| VCAM-1, mg/L                   | 776 ± 265        | 733 ± 254        | 853 ± 319                | 823 ± 254     | < 0.001 |

Values are mean ± SD, n (%), or as indicated.

*ANOVA or logistic regression, respectively, adjusted for sex.

†ANOVA or logistic regression, respectively.

‡ANOVA of logarithmically transformed values.
between-group comparisons of LDL composition and LDL subfraction distributions were performed with the Mann-Whitney U test. A value of \( P < 0.05 \) was considered statistically significant. The SPSS 11.0 statistical package (SPSS Inc) was used for all analyses.

### Results

#### Characteristics of Stable CAD Patients Versus Control Subjects

Patients with stable CAD were significantly older than control subjects (Table 1). Current or past smoking, DM, and hypertension were more prevalent in stable CAD compared with control subjects. After adjustment for sex, systolic and diastolic blood pressure, fasting glucose, cholesterol, LDL-C, LDL-TG, LDL phospholipids (LDL-PL), LDL-apoB, CRP, SAA, fibrinogen, IL-6, ICAM-1, and VCAM-1 were higher in stable CAD patients than in control subjects; HDL-C was lower. BMI and TG did not differ significantly between groups.

#### Lipoproteins in Stable CAD and Control Subjects

We examined the prevalences of angiographic CAD by increasing quartiles of LDL-C, LDL-TG, and HDL-C. Each variable was broken down into quartiles and treated as an ordinal variable; ORs represent increments in prevalences of CAD between 2 consecutive quartiles. Solid squares indicate unadjusted ORs; solid circles, ORs adjusted for age and sex; solid triangles, ORs additionally adjusted for smoking, BMI, MS/DM, hypertension; open squares, ORs additionally adjusted for TG and LDL-C; (in case of LDL-C as predictor variable); open circles, ORs additionally adjusted for LDL-TG (in case of LDL-C as predictor variable) or LDL-C (in case of LDL-TG as predictor variable); open triangles, additionally adjusted for sensitive CRP.

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** OR (±95% CI) for angiographic CAD by LDL-C, LDL-TG, and HDL-C. Each variable was broken down into quartiles and treated as an ordinal variable; ORs represent increments in prevalences of CAD between 2 consecutive quartiles. Solid squares indicate unadjusted ORs; solid circles, ORs adjusted for age and sex; solid triangles, ORs additionally adjusted for smoking, BMI, MS/DM, hypertension; open squares, ORs additionally adjusted for TG and LDL-C; (in case of LDL-C as predictor variable); open circles, ORs additionally adjusted for LDL-TG (in case of LDL-C as predictor variable) or LDL-C (in case of LDL-TG as predictor variable); open triangles, additionally adjusted for sensitive CRP.

We wished to substantiate that LDL-TG predicted CAD independently of LDL-C. We generated nested strata of individuals according to increasing quartiles of LDL-C and LDL-TG but not after inclusion of CRP (Figure 1). HDL-C was significantly associated with CAD independently of age, sex, risk factors, TG, HDL-C, and LDL-C (Figure 1). The prevalence of angiographic CAD was also significantly greater at increasing quartiles of LDL-PL and LDL-apoB; both, however, were no longer predictive after adjustment for LDL-C and therefore were not examined further.

We examined the relationship of LDL-C and LDL-TG to established cardiovascular risk factors using factors not under consideration as covariables (Table 2). Most interestingly, LDL-C was low in patients with the MS or T2DM, whereas LDL-TGs were increased and thus behaved reciprocally to LDL-C. To confirm that LDL-TGs were predictive independently of the MS and DM, we divided the study sample into 9 strata according to the variable MS/DM and tertiles of LDL-TGs using the group without MS or DM and the lowest tertile of LDL-TG as reference. Within each tertile of LDL-C, LDL-TG in the highest tertile was significantly predictive of CAD. The highest OR of CAD was encountered in the layer with the highest tertiles of both LDL-C and LDL-TG.

### LDLs and Established Cardiovascular Risk Factors

We examined the relationship of LDL-C and LDL-TG to established cardiovascular risk factors using factors not under consideration as covariables (Table 2). Most interestingly, LDL-C was low in patients with the MS or T2DM, whereas LDL-TGs were increased and thus behaved reciprocally to LDL-C. To confirm that LDL-TGs were predictive independently of the MS and DM, we divided the study sample into 9 strata according to the variable MS/DM and tertiles of LDL-TGs using the group without MS or DM and the lowest tertile of LDL-TG as reference. Within each group of individuals, in particular among individuals with DM, LDL-TG remained predictive of CAD (online Appendix 3).

### LDLs and Low-Grade Inflammation

Adjustment for CRP weakened the association between LDL-TG and CAD (Figure 1). We therefore examined whether LDL-TGs were associated with markers of low-grade systemic inflammation. ANOVA revealed that CRP,
SAA, fibrinogen, and IL-6 increased in parallel to LDL-TG. This relationship was independent of conventional coronary risk factors. In contrast, SAA, fibrinogen, and IL-6 were not different across the quartiles of LDL-C, and CRP was significantly lower even in the highest quartile of LDL-C compared with the lowest quartile (Figure 3).

**LDL Triglycerides and CRP in Stable CAD**

In view of the apparent association of LDL-TG with CRP, we examined whether LDL-TG added to CRP in predicting CAD. We divided the study sample into 9 strata according to tertiles of both CRP and LDL-TG using the group with the lowest tertile of both CRP and LDL-TG as reference. Across all tertiles of CRP, crude ORs indicated an increased prevalence of CAD in the third tertile of LDL-TG (Figure 4). In the second and third tertiles of CRP, a significantly increased OR of CAD was also seen in the second tertile of LDL-TG. Adjustment for risk factors, TG, and HDL-C produced borderline significance in some cases, but the association between the highest tertile of LDL-TG and CAD remained stable in the second and third tertiles of CRP. These findings suggest that LDL-TG, although positively related to systemic markers of inflammation, is an independent risk factor of CAD.

**LDL Triglycerides, CRP, and Vascular Adhesion Molecules**

Mediators of the acute-phase reaction have been shown to decrease lipoprotein lipase and hepatic lipase. Downregulation of lipases partially explains the elevation of TGs during the acute phase. Low-grade systemic inflammation might thus produce rather than be a consequence of elevated LDL-TG. We therefore sought to determine whether LDL-TGs not only increased the OR of CAD independently of CRP but also were directly associated with biochemical indicators of vascular damage. We examined the relationship between LDL-C or LDL-TG on the one hand and ICAM-1 and VCAM-1 on the other across 3 tertiles of CRP. This revealed statistically significant positive relationships between LDL-TGs and both ICAM-1 and VCAM-1 regardless of CRP. The association was robust against adjustment for risk factors and CAD status. Intriguingly, both ICAM-1 and VCAM-1 decreased significantly as LDL-C increased (see online Appendix 4).

**LDL Triglycerides and LDL Subfractions**

We also wished to examine whether LDL-TGs were related to the distribution of LDL subfractions. Because LDL subfractions have not been determined in the LURIC cohort,
we chose 114 individuals with high LDL-TGs, namely, with impaired fasting glucose, impaired glucose tolerance, or T2DM (LDL-C \(\leq 1.3 \text{ g/L}\)) who received neither lipid-lowering nor glucose-lowering drugs. To match for the lipoprotein methodology used in the LURIC cohort, we used the sum of TGs in IDL (1.006 \(\leq d <1.019 \text{ kg/L}\)) and in the narrow LDL range (1.019 \(\leq d <1.063 \text{ kg/L}\)) as an estimate for LDL-TG. We stratified individuals according LDL-TGs above and below the median (0.54 g/L). Because apoB-containing particles contain 1 molecule of apoB, we considered the apoB contents to reflect the number of particles in each of the density fractions. Subjects with LDL-TGs above the median had significantly higher concentrations of VLDL, IDL, and dense LDL (LDL-5 and LDL-6). In contrast, buoyant LDL (LDL-1 and LDL-2) and intermediate LDL (LDL-3 and LDL-4) were not different (Figure 5).

Figure 3. Estimated marginal means (±95% CI) of concentrations of inflammatory markers by quartiles of LDL-C and LDL-TG. A, CRP; B, SAA; C, fibrinogen; D, IL-6. Squares, unadjusted; circles, adjusted for CAD status, sex, age, smoking, BMI, MS/DM, and hypertension. *\(p<0.05\) in post hoc pairwise comparisons, which are reported only in case of significant between-subjects effects in general linear model.

We also found significant differences in the composition of LDL subfractions between individuals with low or high LDL-TG. In the presence of high LDL-TG, LDL-1 through LDL-6 contained fewer molecules per particle of nonesterified cholesterol and of phospholipids (Table 3). These lipid classes reside on the surface of LDL particles. Consistently, each of the LDL subfractions tended to be smaller in high–LDL-TG than in low–LDL-TG subjects (Table 3). Furthermore, in each of the LDL subfractions, the number of TG molecules per particle was significantly greater in high–LDL-TG compared with low–LDL-TG subjects (Table 3). Thus, none of the LDL subfractions were specifically enriched in TGs. LDL-2 through LDL-6 contained fewer cholesteryl ester (CE) molecules in high LDL-TG subjects. The opposite, however, was true as to VLDL, which contained significantly more CE in high–LDL-TG than in low–LDL-TG subjects (Table 3).

Discussion

The present study provides several unexpected findings. First, LDL-TG predicts stable CAD independently of LDL-C. Second, in the MS and DM, LDL-TGs increase while LDL-C decreases. Third, systemic markers of low-grade inflammation are elevated at high LDL-TG but not at high LDL-C. Fourth, LDL-TG but not LDL-C is positively related to vascular adhesion molecules. Fifth, high LDL-TG is associated with high concentrations of VLDL, IDL, and dense LDL.

Abnormalities of Lipoprotein Metabolism: Cause or Consequence of Systemic Inflammation?

Abundant evidence is now available that low-grade systemic inflammation is predictive of cardiovascular events. Knowledge, however, as to the noxious agents fueling inflammatory processes of the vessel wall is scanty. In particular, potential links between endogenous lipid metabolism and inflammatory pathways remain poorly defined. Disorders of LDL metabolism and low-grade inflammation have so far been conceived to be atherogenic by completely distinct pathways. By considering LDL-TG in addition to LDL-C, this study links LDL metabolism to low-grade inflammation, LDL-TG apparently being a better indicator for atherogenic alterations of LDL metabolism.
LDL-TG but not LDL-C was positively associated with 4 indicators of systemic inflammation and positively related to vascular adhesion molecules independently of CRP. This finding is in line with the negative association of LDL-C and the MS or T2DM (Table 2) and raises the possibility that the TG contents of LDL may be implicated in inflammation and atherogenesis. In humans, LDL-TGs are hydrolyzed primarily by hepatic lipase. Like lipoprotein lipase, hepatic lipase is subject to modulation by inflammatory cytokines. Downregulation of lipases is considered to explain, at least in part, the elevation of TG during the acute-phase response. Low-grade systemic inflammation could thus well be the cause rather than the consequence of high LDL-TG. The observation, however, that LDL-TG was associated with both CAD and circulating adhesion molecules independently of CRP is in favor of the contention that TG enrichment of LDL might itself be proinflammatory. This would also be in line with experimental work. 

LDL-Triglycerides Indicate Accumulation of IDLs and of Dense LDLs

The relative proportions of LDL subfractions are strongly influenced by the metabolism of TG-rich lipoproteins. Once plasma TGs increase, TGs from the core of TG-rich lipoproteins are transferred to LDL by the CE transfer protein (CETP). In exchange, CEs are delivered to TG-rich lipoproteins. The net effect is that LDLs become enriched in TGs and depleted in CEs. The TGs associated with LDL are hydrolyzed by hepatic lipase. As a result, the hydrophobic core of the LDL particle shrinks, and dense LDLs are generated. We were interested to see whether the concentration of LDL-TGs was related to the distribution of LDL subfractions. As expected, subjects with LDL-TGs above the median had higher concentrations of dense LDLs. Dense LDLs are generally considered more atherogenic than other LDL particles. However, other authors claim that buoyant particles may be atherogenic as well. In this investigation, high LDL-TGs were associated not only with dense LDL but also with high concentrations of remnant particles, ie, IDL. Dense LDL and elevated LDL may thus indicate the same atherogenic alteration in the metabolism of apoB-containing particles, both well reflected by LDL-TG. Yet, estimating the atherogenicity of LDL by measuring LDL-TG with the β-quantification method used here is technically demanding and limits the clinical applicability of our findings. Future investigations will therefore have to show whether enzymatic determination of LDL-TG after agarose gel electrophoresis will be an alternative.

Elevated LDL Triglycerides Reflect the Accumulation of Triglycerides in All LDL Subfractions

In normolipidemic individuals, the ratio of TG to CE has been reported to be lowest in intermediate LDL compared with buoyant and dense LDL. Here, this was true for individuals with both low and high LDL-TGs (Table 3). Furthermore, at high LDL-TGs, each of the LDL subfractions was enriched in TG and depleted in CE, an observation that has previously also been made in pregnant women. Interestingly, the opposite was true for VLDL, which contained more CEs per particle at high compared with low LDL-TG (Table 3), supporting the concept that enrichment of LDL with TG may be mediated by CETP, which exchanges CE with TG.

### Table 3: Composition of ApoB-Containing Lipoproteins in Patients With Impaired Fasting Glucose, Impaired Glucose Tolerance, or T2DM (n=114) According to LDL-TG (1.006 kg/L<d<1.063 kg/L).

<table>
<thead>
<tr>
<th>LDL-TG, mg/dL</th>
<th>Nonesterified Cholesterol, mol/mol</th>
<th>Cholesterol Esters, mol/mol</th>
<th>Triglycerides, mol/mol</th>
<th>Phospholipids, mol/mol</th>
<th>Calculated Particle Radii, nm</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;54.4</td>
<td>&gt;54.4</td>
<td>&gt;54.4</td>
<td>&gt;54.4</td>
<td>&gt;54.4</td>
<td>&gt;54.4</td>
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<tr>
<td>(n=57)</td>
<td>(n=57)</td>
<td>(n=57)</td>
<td>(n=57)</td>
<td>(n=57)</td>
<td>(n=57)</td>
</tr>
<tr>
<td>VLDL</td>
<td>973 (688–1100)</td>
<td>1002 (928–1068)</td>
<td>NS</td>
<td>933 (612–1054)</td>
<td>1062 (608–1219)</td>
</tr>
<tr>
<td>IDL</td>
<td>566 (500-675)</td>
<td>537 (494-671)</td>
<td>NS</td>
<td>757 (604-829)</td>
<td>796 (604-807)</td>
</tr>
<tr>
<td>LDL-1</td>
<td>431 (392–531)</td>
<td>380 (341–447)</td>
<td>&lt;0.001</td>
<td>683 (637–738)</td>
<td>688 (609–743)</td>
</tr>
<tr>
<td>LDL-2</td>
<td>364 (337–413)</td>
<td>316 (277–365)</td>
<td>&lt;0.001</td>
<td>664 (605–705)</td>
<td>615 (591–647)</td>
</tr>
<tr>
<td>LDL-3</td>
<td>323 (304–375)</td>
<td>286 (245–335)</td>
<td>0.001</td>
<td>632 (579–667)</td>
<td>575 (525–619)</td>
</tr>
<tr>
<td>LDL-4</td>
<td>311 (262–362)</td>
<td>258 (214–300)</td>
<td>&lt;0.001</td>
<td>602 (566–639)</td>
<td>564 (529–599)</td>
</tr>
<tr>
<td>LDL-5</td>
<td>272 (246–304)</td>
<td>221 (162–263)</td>
<td>&lt;0.001</td>
<td>569 (539–597)</td>
<td>551 (527–574)</td>
</tr>
<tr>
<td>LDL-6</td>
<td>233 (214–265)</td>
<td>206 (170–238)</td>
<td>&lt;0.001</td>
<td>516 (440–495)</td>
<td>495 (468–523)</td>
</tr>
</tbody>
</table>

Entries are median lipid-to-apoB molar ratios (25th through 75th percentiles in parentheses). The particle radii were calculated according to Baumstark et al. Entries are given as median lipid-to-apoB molar ratios (25th through 75th percentiles in parentheses). The particle radii were calculated according to Baumstark et al. *LDL-TG = 54.4 mg/dL vs LDL-TG >54.4 mg/dL by Mann-Whitney U test.*
underestimated once LDLs are rich in TG and depleted in cholesterol. This would be a simple explanation for the finding that correlations between LDL-C and inflammatory markers have hardly been detected so far.5

**Major Limitations**

Our study has 2 major limitations. First, it represents a cross-sectional comparison of cases and control subjects. It is hence possible that our hospital-based control subjects are not representative for a random population sample. However, the prevalence of hypertension in the control group is close to that found in a random probability sample from Germany,27 and the age-adjusted prevalence of DM is similar to that found in a random population sample. However, the cross-sectional comparison of cases and control subjects. It is

In conclusion, we show that disorders of LDL metabolism characterized by elevated LDL-TG rather than by elevated LDL-C might be a stronger risk factor than at high LDL-C. This possibility is unlikely, however, because the predictive power of LDL-TG was greatest in the highest tertile of LDL-C.

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