Antibodies to Oxidized Low-Density Lipoproteins and Angiographically Assessed Coronary Artery Disease in White Patients

Gian Paolo Rossi, MD; Maurizio Cesari, MD; Renzo De Toni, DBSc; Mario Zanchetta, MD; Giuseppe Maiolino, MD; Luigi Pedon, MD; Chiara Ganzaroli, MD; Pietro Maiolino, MD; Achille C. Pessina, MD, PhD

Background—Low-density lipoprotein (LDL) can be oxidatively modified by reactive oxygen species, thus generating oxLDL. The latter induce formation of specific antibodies (oxLDLAb), which are detectable in patients with atherosclerosis, in which they might play a pathogenic or a protective role. Thus, we aimed to investigate the association of antibodies with oxidized LDLs (oxLDL) (oxLDLAbs) with coronary artery disease (CAD) and acute coronary syndromes.

Methods and Results—In a cross-sectional study of 529 consecutive patients undergoing quantitative coronary angiography for suspected CAD, we measured the titer of IgG oxLDLAbs by ELISA. With regression analysis techniques, we also investigated the determinants of oxLDLAb titer and the association of oxLDLAbs with CAD severity. We found no significant differences of oxLDLAb titer between groups of patients without and with different CAD severity. The oxLDLAb titer was 18.6 enzyme units (EU) (11.5 to 25.7 EU/mL) (mean, 95% CI) in patients without CAD; 16.8 EU (9.6 to 24.2 EU) in patients with stenosis <50%; and 19.9 EU (15 to 24.8 EU), 17.2 (13.8 to 20.6 EU), and 14.7 EU (12.1 to 17.3 EU) in those with in 1-, 2-, or 3-vessel ≥50% stenosis, respectively. Similarly, no differences of oxLDLAb titer between patients without and with acute coronary syndrome were found. The oxLDLAb titer correlated weakly with aging and with serum total, LDL, and HDL cholesterol and plasma homocysteine levels; however, only age and HDL cholesterol remained significant predictors of the oxLDLAb titer at a stepwise regression analysis.

Conclusions—The results of this study, which was adequately powered from the statistical standpoint, provided no evidence for an association of IgG oxLDLAb titer with angiographically assessed CAD in whites. (Circulation. 2003;108:2467-2472.)

Key Words: coronary disease ■ lipoproteins ■ antibodies ■ atherosclerosis ■ risk factors

Received May 27, 2003; de novo received July 17, 2003; accepted August 20, 2003.

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Circulation is available at http://www.circulationaha.org DOI: 10.1161/01.CIR.0000097122.19430.48
anti-OxLDLAb titers was reported in the general population.20 However, oxLDLAbs were found to block the uptake of oxLDL by macrophages and localize to atherosclerotic plaques in vivo.21 More recently, it was reported that autoantibodies to oxLDL derived from “naive” atherosclerotic mice share complete genetic and structural identity with antibodies that protect against common infectious pathogens, including Streptococcus pneumoniae, and that immunization with this latter pathogen induced high circulating levels of oxLDL-specific IgM.22 These antibodies, which were cross-reactive with pneumococcal determinants, decreased the extent of atherosclerosis and localized to atherosclerotic lesions. Thus, oxLDLAbs have been contended both to play a mechanistic role, either protective or pathogenic, and to entail a marker of widespread atherosclerotic disease. However, despite a good deal of research, their true biological role in humans remains unclear, primarily because of the availability of only small-size studies, which are prone to selection biases and serendipitous findings, and because of the lack adequately powered studies. Accordingly, in the consecutive white patients of the GENICA (Genetic and ENVironmental factors In Coronary Artery disease) study23 who underwent coronary angiography, we sought to determine whether an association between the oxLDLAbs and the extent and severity of CAD existed.

Methods

The criteria for enrollment of the patients and control subjects in the GENICA study were reported previously.24 In brief, consecutive white patients of both sexes consecutively referred to the Division of Cardiology of the Cittadella General Hospital for coronary angiography for investigation of chest pain and/or suspected CAD were enrolled. The only exclusion criterion was the refusal to participate in this study. The Medical Ethics Committee of our university approved the study protocol, and a written consent, after explanation of the aims and details of the study, was obtained from each participant. Two groups served as control subjects: the first included patients with a prevalence of CAD expected to have a very low prevalence of asymptomatic CAD.25

Coronary Angiography

Angiography was performed and evaluated by experienced cardiologists who were blinded to the patient’s oxLDLAb titer. The severity of CAD was determined by the number of significantly stenosed coronary arteries.26 Patients were classified as follows: code 1, normal vessels; code 2, <50% stenosis; and codes 3, 4, and 5, stenosis ≥50% in 1, 2, or 3 major coronary arteries, respectively.21

Laboratory Measurements

Each patient was studied between 8:30 and 12:00 AM. Before coronary angiography, blood samples were taken from the femoral artery and were immediately centrifuged at 3000 × g for 10 minutes. Total cholesterol, HDL cholesterol, triglycerides, glucose, sodium, potassium, BUN, and creatinine levels were measured with conventional methods. IgG autoantibodies against malondialdehyde-modified LDL (α-oxLDL) were assayed by ELISA with a commercially available ELISA kit (Anti-oxLDL Antibody ELISA KIT; IMMCO Diagnostic Inc), as described by Craig et al27 and according to manufacturer’s specifications. This kit uses individually poached microplate strips that were coated with native or oxLDL; as a result, the antigen stability was shown to last for at least 4 months. Sera were diluted 1:101, and low- and high-titer samples were included in each assay. Furthermore, a standard curve with samples at known oxLDLAb titer was determined for each assay. In our hands, the intra-assay and interassay coefficients of variation of this method were 9% and 15%, respectively.

Statistical Analysis

One-way ANOVA followed by Bonferroni’s post hoc test was used to compare quantitative variables between CAD patients and control subjects. Serum triglycerides, homocysteine, and oxLDLAbs that showed a normal distribution were examined after log transformation. χ² analysis was used to compare the frequencies of the categorical coronary risk factors between the CAD and the control groups. To identify the determinants of oxLDLAb titer, we performed a stepwise regression analysis (PIN = 0.05, POUT = 0.10). Statistical significance was defined as a value of P < 0.05. All analyses were performed with SPSS 11.0 for Windows (SPSS Italy Inc).

Results

Sample Size Determination and Demographic Characteristics

We first measured the titer of IgG oxLDLAbs in a pilot study of patients belonging to the different coronary artery groups. On the basis of these results, we calculated (N-Query version 5.0) that at least 500 patients were needed to provide a statistical power of 99% to detect a difference in means characterized by a variance of means, V = σ²/5, at the 0.05 level, with a 1-way ANOVA, given the common SD that was observed. Thus, for the present study, we randomly enrolled 529 consecutive patients, of the 1271 originally recruited in the GENICA study, who had complete coronary angiography data. Of them, 16% (n = 84) had normal coronary arteries; 8% (n = 43) had stenosis <50%; 28% (n = 147), 27% (n = 145), and 21% (n = 110) had significant (≥50%) stenosis in 1, 2, or 3 major epicardial vessels, respectively. Table 1 depicts their main features. Overall, 20% of all these consecutive patients undergoing coronary angiography had an acute coronary syndrome. The proportion of patients with such complications in 1-, 2-, and 3-vessel CAD patients, along with main clinical features, is shown in Table 2.

Demographic and Clinical Measurements

The medical history of CV events, smoking habits, presence/absence of hypertension, diabetes, hypercholesterolemia, hypertriglyceridemia, and current medications were carefully ascertained.23 Body mass index was calculated as weight/height² (kg/m²). Criteria for defining current smokers, nonsmokers, and ex-smokers, diabetes mellitus (type I or II), impaired glucose tolerance, hypercholesterolemia, and hypertriglyceridemia were reported previously.23 Blood pressure was measured by mercury sphygmomanometer using Korotkoff phase V for diastolic, according to the WHO guidelines. Hypertension was defined as systolic pressure ≥140 mm Hg and/or diastolic pressure ≥90 mm Hg or use of any antihypertensive agents. Insulin resistance was also quantified by use of the homeostasis model assessment (HOMA).28
TABLE 1. Demographic and Clinical Features of the Whole Population, Classified According to the Angiographically Assessed Coronary Findings

<table>
<thead>
<tr>
<th>Coronary Angiography Findings</th>
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</thead>
<tbody>
<tr>
<td>Group 1, Normal (n=84)</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
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<tr>
<td>HDL cholesterol, mg/dL</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
</tr>
<tr>
<td>Glycemia, mg/dL</td>
</tr>
<tr>
<td>IR, HOMA index</td>
</tr>
<tr>
<td>Plasma folate, nmol/L</td>
</tr>
<tr>
<td>Plasma homocysteine, µmol/L</td>
</tr>
<tr>
<td>oxiLDLAb, EU/mL</td>
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</table>

Data are expressed as mean±SD or mean and 95% CI for insulin resistance (IR) index (homeostasis model assessment [HOMA] index), plasma folate, plasma homocysteine, and anti-oxLDLAb.  
*Statistically significant differences vs stenosis ≥50% in 1 and 3 epicardial vessels.  
†Statistically significant differences vs stenosis ≥50% in 2 and 3 epicardial vessels.

Antibodies to oxLDL

The titer of oxLDLAb in the group of healthy subjects was 11.5±0.8 enzyme units (EU)/mL (mean±SEM) (11.5 EU and 5.0 to 26.0 EU, median and range). The distribution of values was found to be skewed (skewness index=1.43±0.41; kurtosis index=3.23±0.80); therefore, the 90th percentile value was used as a cutoff for defining normal and high oxLDLAb titers in our population.

No significant differences of oxLDLAb titer between groups without and with CAD were observed. Figure 1 shows that although serum HDL cholesterol decreased stepwise (P<0.001 by ANOVA) along with increasing severity of CAD, no such relationship of oxLDLAb titer with severity of CAD was found. Furthermore, when patients were classified into those without and those with acute coronary syndromes, no significant differences in the titer of oxLDLAb between groups emerged (Figure 2). Among patients with acute coronary syndrome, those with unstable angina had significantly (P<0.05) higher HDL cholesterol levels than those with acute MI (46.6±1.7 versus 38.2±2.7 mg/dL); however,

TABLE 2. Age and Biochemical Features of the Patients With 1-, 2-, and 3-Vessel CAD Classified by the Presence or Absence of Acute Coronary Syndrome

<table>
<thead>
<tr>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable CAD (n=114)</td>
<td>Acute Coronary Syndrome (n=31)</td>
<td>Stable CAD (n=114)</td>
</tr>
<tr>
<td>Age</td>
<td>62±9</td>
<td>64±10</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>212±43</td>
<td>208±54</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>47±15</td>
<td>51±14</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>135±37</td>
<td>136±52</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.14±0.55</td>
<td>1.04±0.27</td>
</tr>
<tr>
<td>Glycemia, mg/dL</td>
<td>117±43</td>
<td>103±33</td>
</tr>
<tr>
<td>IR (HOMA)</td>
<td>2.5 (2.07–2.95)</td>
<td>2.19 (1.70–2.68)</td>
</tr>
<tr>
<td>Plasma folate, nmol/L</td>
<td>5.08 (4.66–5.50)</td>
<td>4.54 (3.98–5.10)</td>
</tr>
<tr>
<td>Plasma homocysteine, µmol/L</td>
<td>12.8 (11.4–14.3)</td>
<td>11.5 (9.8–13.2)</td>
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</table>

Abbreviations as in Table 1.
no differences of oxLDLAb titer were found (21.5±10.6 versus 44.1±27.3 EU/mL) because of the wide spread of the values. A bivariate correlation analysis (Table 3) showed that the oxLDLAb titer was weakly associated with some CV risk factors, eg, it was directly related to age, total serum cholesterol, LDL cholesterol, and plasma homocysteine levels and inversely related to HDL cholesterol. However, only age and HDL cholesterol remained in a stepwise linear regression model; they collectively explained only a minimal proportion of oxLDLAb titer (adjusted $R^2=0.005$, $P<0.001$).

**Discussion**

Atherosclerosis is characterized by vascular inflammation and associated with systemic and local immune responses to oxLDL and other antigens (reviewed by Ross28). To gather insight into the relevance of antibodies to oxLDL, we measured their titer in a relatively large sample of patients who underwent coronary angiography because of suspected CAD. These patients entail a population at high risk, eg, with a 20% or greater risk of CV events in the next 10 years, according to the NCEP criteria.29 as mirrored by the fact that the majority of them had already experienced a major CV event. Stable CAD was detected in most (80%) of these patients, and acute coronary syndromes were diagnosed in 20% of them (Table 3). Despite this atherosclerotic burden, we found no significant differences in oxLDL titer either between groups of patients without and with angiographically assessed CAD or between patients with different severity and extension of CAD (Figure 1). These negative findings differ from previous results. According to Inoue et al,9 the oxLDLAb titer was higher in 108 Japanese patients who had angiographically confirmed CAD than in 31 patients who had chest pain but no significant CAD. Because these authors also reported higher oxLDLAb titers in 39 patients with acute MI than in 24 patients with no CAD,14 they contended that the oxLDLAb titer would be higher in the patients with unstable angina and acute MI than in those with stable effort angina and therefore could allow discrimination between patients with these conditions. However, consistent with our present results, they also found no significant differences between the multivessel and single-vessel CAD groups and the control subjects.9 High plasma levels of oxLDLAbs have also been associated with carotid artery plaque instability in another study of Japanese patients, but conflicting results on the association with carotid atherosclerosis exist in whites.15,31 A more recent study, in which the ethnicity of case and control subjects was not specified, showed higher IgG oxLDLAb titer in 8 patients with acute MI, compared with 15 patients with unstable angina, 17 patients with stable CAD, or 8 subjects with normal coronary arteries.32 However, higher IgM oxLDLAb titers and higher IgM LDL immune complexes were observed in the normal subjects than the other groups. No such group differences could be confirmed in our study of white patients (Table 1, Figures 1 and 2).

The reasons for these divergent results are at present unclear, although both ethnicity and selection biases might play an important role. The latter explanation is likely to apply to at least 2 of the aforementioned studies in which the number of cases was small and largely exceeded that of control subjects.9,14 Equally important, it should be acknowledged that coronary angiography focuses on the arterial lumen, rather than on the arterial wall, whereas it has become widely recognized that plaques prone to rupture (“vulnerable plaques”) are not those that yield a high degree of stenosis, eg, the very advanced, fibrotic, and calcified atherosclerotic lesions.33 It has been established that lesion growth goes hand in hand with compensatory dilatation of the artery wall and that even relatively large lipid-rich vulnerable
lesions that might cause acute events, such as MI and ischemic stroke, often result in only minimal stenosis (“Glagov postulate”). Moreover, oxLDLs are most prominent in early lesions but are a minor component in calcified, fibrous, or complicated plaques. Indeed, oxLDL is a major promotor of macrophage activation and other proinflammatory events thought to weaken the fibrous cap. Accordingly, angiography may not be particularly suitable to detect atherosclerotic lesions rich in oxLDL that modulate antibody responses. These considerations might explain the lack of association of antibody titers to oxLDL of the number of the very advanced lesions causing >50% stenosis in this study. However, it should also be noticed that we could find no significant differences between CAD patients without and with acute coronary syndromes (Figure 2).

Whatever the underlying explanation might be, collectively, our present results conclusively ruled out the contention that IgG oxLDLAbs are associated with angiographically assessed CAD. Furthermore, they also make unlikely the hypothesis that they represent a marker for widespread atherosclerotic disease. Similar conclusions were reached in a 10-year study in Finnish type 2 diabetes mellitus patients in whom neither changes of intimal-medial thicknesses of the common carotid artery and carotid bifurcation nor, more importantly, CV events were found to be predicted by the oxLDLAbs titer measured at baseline.17 Results of a number of studies performed in patients with cardiovascular risk factors are also consistent with this conclusion. The oxLDLAbs titer was not raised in patients with heterozygous familial hypercholesterolemia compared with matched control subjects34; it was lower in smokers than in nonsmokers,35 and in patients with borderline arterial hypertension than in matched normotensive control subjects.31 Moreover, the oxLDLAbs titer did not show any differences between men with established hypertension in the ELSA study and normotensive control subjects, nor did it show any association with carotid atherosclerosis.36

Despite the evidence involving oxLDL in atherosclerosis,1,6 the mechanisms associated with formation of antibodies to oxLDL have not been widely investigated. Thus, to gain some further insight, we sought the determinants of oxLDLAbs titer. We found, with a correlation analysis, that only age, total and LDL cholesterol, HDL cholesterol, and plasma homocysteine levels showed statistically significant, albeit very weak, correlations with oxLDLAbs titer. Only age and HDL cholesterol remained in a stepwise regression model, thus being identified as significant predictors of oxLDLAbs titer; however, the proportion of oxLDL titer variance that was accounted for these 2 variables was negligible, eg, 5%. Therefore, although oxLDLAbs titer appears to increase with aging and to decrease with increasing HDL cholesterol levels, its association with these covariates does not seem to be a strong one.

The present finding of oxLDL in patients without CAD and in normal healthy subjects, which accords with previous reports,19,20,32 deserves some comment. A complete identity of oxLDLAbs and antibodies from the classic anti-phosphorylcholine B-cell clone T15, which protect against common infectious pathogens, has been unexpectedly found.22 The molecular mimicry between the phosphorylcholine moieties of microbial cell wall polysaccharide and oxLDL was suggested to explain this observation22 and could also account for the previous and present findings of oxLDLAbs in healthy individuals and of increased titer with aging.

Negative findings of a study, like the present ones, should always raise the possibility of inadequate statistical power. In this regard, we would like to point out that (1) our study was the largest ever performed to investigate the biological role of antibodies to oxLDL in patients with angiographically assessed CAD, to the best of our knowledge9,11–14,32,35; and (2) given its total sample size, it had 99% power to detect, with a 1-way ANOVA, an effect size (eg, the variance of the mean divided by the within-group variance) of 0.61, on the basis of the assumptions made earlier.

The lack of association of oxLDLAbs titer with CAD could be accounted for by several considerations. First, the assay used in this study measures total IgG antibodies to oxLDL, whereas the antibodies to oxLDL are highly heterogeneous antibodies that differ not only for Ig class but also for epitope specificity and affinity.35 Therefore, it might be that only some of them play a mechanistic role, as suggested by at least 3 lines of evidence. First, IgG and IgM antibodies, as well as immune complexes containing these 2 classes of antibodies, where the antibodies to oxLDL are highly heterogeneous class B cell clone T15, which protect against common infectious pathogens, has been unexpectedly found. The molecular mimicry between the phosphorylcholine moieties of microbial cell wall polysaccharide and oxLDL was suggested to explain this observation22 and could also account for the previous and present findings of oxLDLAbs in healthy individuals and of increased titer with aging.

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TABLE 3. Correlation Matrix Showing the Value of Pearson Correlation Coefficient and Significance (1 Tailed) Between oxLDLAbs Titer (Ln) and Other Biochemical Variables

<table>
<thead>
<tr>
<th></th>
<th>Ln oxLDL</th>
<th>Age</th>
<th>Homocysteine</th>
<th>Total Cholesterol</th>
<th>LDL Cholesterol</th>
<th>Creatinine</th>
<th>HDL Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ln oxLDL</td>
<td>1.000</td>
<td>0.119 (–0.005)</td>
<td>0.085 (–0.026)</td>
<td>–0.083 (–0.028)</td>
<td>–0.082 (–0.030)</td>
<td>0.070 (–0.054)</td>
<td>–0.067 (–0.063)</td>
</tr>
<tr>
<td>Age</td>
<td>1.000</td>
<td>0.103 (–0.01)</td>
<td>–0.066 (NS)</td>
<td>–0.076 (–0.05)</td>
<td>0.089 (–0.05)</td>
<td>0.122 (–0.005)</td>
<td></td>
</tr>
<tr>
<td>Homocysteine</td>
<td>1.000</td>
<td>–0.003 (NS)</td>
<td>–0.030 (NS)</td>
<td>–0.273 (NS)</td>
<td>–0.079 (–0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>1.000</td>
<td>0.856 (&lt;0.001)</td>
<td>–0.023 (NS)</td>
<td>0.344 (&lt;0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>1.000</td>
<td>–0.017 (NS)</td>
<td>0.129 (&lt;0.002)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.000</td>
<td>–0.106 (&lt;0.01)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.000</td>
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</table>

Pearson correlation coefficient and (significance, P).
epitopes and not against others play a major protective role. This contention is supported by a recent study in which oxLDL Abs directed to phosphorylcholine, e.g., a key epitope in the protective immune response, proved to be more potent from the standpoint of protection from atherosclerosis than those to malondialdehyde, which were measured in this study.22

As mentioned, this cross-sectional study comprised exclusively white individuals, and therefore, our findings might not apply to other ethnic groups. Furthermore, although we could not confirm the usefulness of the titer of antibodies to oxLDL as predictor of CAD either in men or in women, we cannot exclude the possibility that this study was underpowered to detect such an association in women, who composed only a minority of our patients.

In conclusion, our results showed no significant association of titer of IgG antibodies to oxLDL Abs and angiographically assessed CAD and acute coronary syndromes. Therefore, they provide no support for the contention of IgG oxLDL Abs to malondialdehyde playing a mechanistic role.

Acknowledgments

This study was supported by grants from the Italian Cabinet of Unindustria Treviso to Prof G.P. Rossi.

References


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_Circulation_. 2003;108:2467-2472; originally published online October 27, 2003;
doi: 10.1161/01.CIR.0000097122.19430.48
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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