Antibodies Against Oxidized LDL and Carotid Artery Intima-Media Thickness in a Healthy Population

Mariko Fukumoto, Tetsuo Shoji, Masanori Emoto, Takahiko Kawagishi, Yasuhisa Okuno, Yoshiki Nishizawa

Abstract—Oxidation of LDLs plays an important role in atherosclerosis, and immune response to oxidized LDL (oxLDL) may modulate atherogenesis. Although immunization with oxLDL is shown to suppress atherogenesis in animal models, the role of the immune response to oxLDL is not well established in humans. We investigated the relationship between the titer of anti-oxLDL antibody (oxLDL Ab) and arterial wall thickness in a healthy population with no clinical signs of atherosclerosis. Intima-media thickness of the carotid arteries (CA-IMT) was measured by high-resolution B-mode ultrasonography in 446 healthy subjects. The titer of IgG-class oxLDL Ab was measured by a solid-phase ELISA. In univariate analysis, CA-IMT correlated positively with age, systolic blood pressure, total cholesterol, triglyceride, LDL cholesterol, body mass index, and waist-to-hip ratio, whereas it correlated negatively with HDL cholesterol and oxLDL Ab titer. The inverse association between oxLDL Ab titer and CA-IMT remained significant in multiple regression analysis, which took other confounding variables into account. These results indicate an independent inverse relationship between oxLDL Ab titer and CA-IMT in healthy subjects, supporting the hypothesis that immune response to oxLDL may have a protective role at an early stage of human atherosclerosis. (Arterioscler Thromb Vasc Biol. 2000;20:703-707.)

Key Words: oxidized LDL ■ anti-oxidized LDL antibody ■ immunoglobulin ■ atherosclerosis ■ intima-media thickness

Oxidative modification of LDL is an important event in the development and progression of atherosclerosis.1 Oxidized LDL (oxLDL) is taken up by macrophages via the scavenger receptors,2 promoting foam cell formation and fatty plaque development. OxLDL acquires molecular epitopes that are cytotoxic for endothelial cells,3 stimulate chemotaxis and recruitment of monocytes,4 and induce macrophage proliferation.5

In addition, oxLDL is antigenic.6 Recent studies suggested that the immune response to oxLDL may modulate the process of atherogenesis.7,8 Immune-competent cells such as macrophages and T and B lymphocytes are present in atheromatous lesions. T cells in atherosclerotic plaques are often activated.9 Some of these T-cell clones are specifically stimulated by oxLDL.10 Immunoglobulin mRNA is abundantly expressed in atheromatous plaques,11 and antibodies recognizing oxLDL are detected in the lesions12 and also in human serum.13–21

It is reported that immunization with oxidatively modified LDL remarkably suppressed the development of atherosclerosis in animal models.22,23 suggesting that the immune response to oxLDL may be antiatherogenic. In contrast, the role of immunity against oxLDL is not well established in humans. The serum titer of anti-oxLDL antibodies (oxLDL Ab) has been measured in human studies. Some previous cross-sectional studies showed that the titer of oxLDL Ab was elevated in patients with advanced atherosclerosis of the carotid,13 coronary,14 and peripheral arteries.15 OxLDL Ab titer was reported to be predictive for the progression of carotid atherosclerosis.16 These studies suggest that a raised titer of oxLDL Ab is a marker of advanced atherosclerosis. Conversely, some reports failed to confirm such a raised titer of oxLDL Ab in patients with atherosclerotic diseases.17–19 In a recent study in patients with familial hypercholesterolemia,20 oxLDL Ab titer was significantly lower in those with a history of myocardial infarction than in those without. The titer of oxLDL Ab was previously believed to mirror the amount of the oxLDL antigens in vivo. However, we recently found that oxLDL Ab titer was in an inverse relationship with circulating oxLDL concentration in a healthy population.21

The discrepancy among these studies indicates the complexity of this system, and raises a possibility that the pathophysiological roles of oxLDL Ab may vary depending on stages of atherosclerosis. Also, although oxLDL Ab shows a wide distribution within a group and there is a considerable overlapping in oxLDL Ab titer between groups, no study has examined the relationship between oxLDL Ab titer and arterial wall changes within a population. Therefore, we

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conducted a cross-sectional study to examine the relationship between oxLDL Ab titer and carotid artery intima-media thickness (CA-IMT) in 446 healthy subjects without advanced atherosclerosis. The result of this study indicated that a raised titer of oxLDL Ab was a significant and independent factor associated with lower CA-IMT values in this population without clinical signs of atherosclerosis.

Methods

Subjects
We screened 514 Japanese subjects who participated in a local health-check program in Osaka City for the study subjects. We excluded those who had a history of ischemic heart disease, cerebrovascular disease, or peripheral vascular disease. We also excluded those who had either diabetes mellitus as defined by fasting plasma glucose >7.0 mmol/L,24 proteinuria, or liver dysfunction as defined by serum alanine aminotransferase (ALT) >50 IU. The remaining 446 subjects were selected to be the study subjects. No one received medication for hypertension, hyperlipidemia, or diabetes mellitus. No sign of myocardial ischemia was found by ECG during an exercise loading test using the Bruce protocol.25 Some of the remaining 446 subjects were selected to be the study subjects. No one received medication for hypertension, hyperlipidemia, or diabetes mellitus. No sign of myocardial ischemia was found by ECG during an exercise loading test using the Bruce protocol.25 Some of the subjects were hyperlipidemic and/or hypertensive at the time of the study. This study was approved by our institutional ethics committee, and the study subjects gave informed consent to participate in the study. Table 1 gives characteristics of the subjects.

Blood Sampling
Venous blood was taken in the morning after an overnight fast for ≥12 hours and transferred to tubes with and without EDTA for serum and EDTA plasma, respectively. Tubes were centrifuged at 2000 rpm for 20 minutes at 4°C to separate serum or EDTA plasma. Serum was kept frozen at −40°C for 1 to 6 months until it could be assayed for oxLDL Ab titer. EDTA plasma was used immediately for lipids and other measurements.

Ultrasonography
Ultrasonographic scanning of the carotid artery was performed by high-resolution real-time ultrasonography with a 10-MHz in-line Sectorscaner (SSD 650 CL, Aloka Co Ltd) as described previously.26–28 Each subject was examined in the supine position. The examination included the carotid bulb and ~4 cm of the right common carotid artery. The site of the most advanced atherosclerotic lesion was examined in the longitudinal and transverse projections to record the maximum IMT.29 IMT was defined as the distance between the leading edges of the lumen-intima interface and the media-adventitia interface of the far wall. The scan converter (Nexus

![Distribution of Serum oxLDL Ab Titer](image)

Figure 1. Distribution of serum anti-oxLDL Ab titer in 446 healthy subjects. oxLDL Ab titer was measured by ELISA as described in the Methods section. Bar graph indicates the number of subjects with oxLDL Ab titer in the indicated range. N indicates number of subjects.

Co Ltd) provided a wide dynamic range and a pixel size of 0.047 mm. The coefficient of variation for CA-IMT was 3.6%.26

Serum oxLDL Ab Titer
Titer of oxLDL Ab was measured by ELISA30 with a commercially available kit (OLAB, Biomedica). Prediluted test sera were incubated at 37°C for 90 minutes in 96-well microtiter wells precoated with copper-oxidized LDL. After a washing, the wells were incubated with anti-human IgG antibody conjugated with a specific peroxidase at room temperature for 30 minutes. The wells were washed, tetramethylbenzidine was added, and the wells were incubated at room temperature for 15 minutes in the dark. Color development was stopped by addition of sulfuric acid. The absorbance at 450 nm was read by a microplate reader. Antibody titer was calculated by construction of a standard curve using the standards included in the kit. The unit for oxLDL Ab is defined by the manufacturer. Intra-assay and interassay reproducibilities (coefficients of variation) of the assay were <5% and <10%, respectively, as described elsewhere.21

Other Measurements
Total cholesterol and triglycerides were measured by enzymatic methods as previously described.31 HDL cholesterol was measured by a dextran sulfate precipitation method.32 Non-HDL cholesterol was calculated by subtracting HDL cholesterol from total cholesterol. LDL cholesterol was calculated according to Friedewald et al.33 Other measurements were done by routine laboratory methods.

Statistical Analysis
Data were summarized as median and range. Comparison between 2 groups was done by Mann-Whitney’s U test. Correlation between 2 variables was evaluated by Spearman’s rank correlation test. Multiple regression was used to evaluate independent associations among variables after appropriate transformation of data to fit the linear model. Values of P<0.05 were taken to be significant.

Results

Distribution of Serum oxLDL Ab Titer
Figure 1 shows serum oxLDL Ab titers in the 446 healthy subjects. The titer distributed in a wide range, up to 2400 mU/mL, with a median of 254 mU/mL. Because the distribution was highly skewed, subsequent analyses were performed with either nonparametric methods or logarithmic transformation of the data.

Factors Affecting Serum oxLDL Ab Titer
OxLDL Ab titer did not differ between men and women or between smokers and nonsmokers (P=0.907 and P=0.156 by

### Table 1. Characteristics of the Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, % male</td>
<td>35</td>
</tr>
<tr>
<td>Smoking status, % smokers</td>
<td>29</td>
</tr>
<tr>
<td>Age, y</td>
<td>54 (18–77)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>124 (88–205)</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>76 (47–113)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.30 (2.89–8.68)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.05 (0.35–4.38)</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.60 (0.83–3.46)</td>
</tr>
<tr>
<td>Non-HDL cholesterol, mmol/L</td>
<td>3.70 (1.65–6.82)</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.10 (1.27–6.02)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.7 (14.5–34.5)</td>
</tr>
<tr>
<td>WHR</td>
<td>0.84 (0.65–1.03)</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; BMI, body mass index; and WHR, waist-to-hip ratio. Median (range) is given for continuous variables, and percentage is given for sex and smoking status.
Anti-oxLDL Antibody and CA-IMT in Healthy Group

Mann-Whitney’s U test, respectively). OxLDL Ab titer did not correlate with age ($r_s = -0.066, P = 0.147$), systolic blood pressure ($r_s = 0.033, P = 0.471$), diastolic blood pressure ($r_s = 0.042, P = 0.363$), total cholesterol ($r_s = -0.064, P = 0.167$), or HDL cholesterol ($r_s = 0.074, P = 0.109$) by Spearman’s rank correlation test. OxLDL Ab titer showed significant inverse correlations with triglycerides ($r_s = -0.109, P = 0.064$) and non-HDL cholesterol ($r_s = -0.107, P = 0.020$). OxLDL Ab titer correlated inversely with LDL cholesterol at a borderline significance ($r_s = -0.084, P = 0.069$).

**Univariate Analyses of Factors Affecting CA-IMT**

In this population, men had significantly greater CA-IMT than women ($P = 0.029$). The difference in CA-IMT between smokers and nonsmokers was not significant ($P = 0.196$). CA-IMT correlated positively with age, systolic blood pressure, body mass index, waist-to-hip ratio, plasma total cholesterol, non-HDL cholesterol, LDL cholesterol, and triglycerides and inversely with HDL cholesterol (Table 2). CA-IMT correlated inversely with serum oxLDL Ab titer (Figure 2).

**Multiple Regression Analysis of Factors Affecting Carotid IMT**

Multiple regression analysis was performed to examine factors associated independently with CA-IMT in the 446 healthy subjects. In this analysis, CA-IMT showed significant positive associations with age, blood pressure, and LDL cholesterol, whereas it showed significant inverse association with oxLDL Ab titer (Table 3).

**Discussion**

The immune response to oxLDL may modulate the process of atherosclerosis, because oxLDL is regarded as an important causative factor for atherosclerosis. In the present study, we demonstrated a significant inverse relationship between serum oxLDL Ab titer and CA-IMT in 446 healthy subjects. This relationship was significant even in multivariate analysis and independent of other confounding variables such as age, sex, blood pressure, smoking status, plasma lipids, and adiposity. The result raises a possibility that oxLDL Ab plays an antiatherogenic role at an early stage of atherosclerosis.

Previous studies indicated either proatherogenic or antiatherogenic roles of immunity to oxLDL in various settings. Palinski et al. first demonstrated that immunization of Watanabe heritable hyperlipidemic rabbits with malondialdehyde-modified homologous LDL remarkably suppressed atherosclerosis. A similar observation was made by Ameli et al. when they immunized hypercholesterolemic rabbits with copper-oxidized LDL. In human studies, serum titer of oxLDL Ab has been measured as an index of LDL oxidation in vivo. Some previous cross-sectional studies showed that the titer of oxLDL Ab was elevated in patients with advanced atherosclerosis. Some reports, however, failed to confirm such a raised titer of oxLDL Ab in patients with atherosclerotic diseases. Hultie et al. recently showed that in patients with familial hypercholesterolemia, oxLDL Ab titer was not higher but rather significantly lower in those with a history of myocardial infarction than in those without. In the present study, we demonstrated that oxLDL Ab titer correlated significantly and inversely with CA-IMT in a healthy population without advanced atherosclerosis. The apparent discrepancy among these studies may result from different settings and also from a small number of subjects in some studies. It is important to note that our study, unlike most of the other human studies, examined only healthy subjects showing no

| TABLE 2. Univariate Correlation Between CA-IMT and Other Variables in 446 Healthy Subjects |
|-----------------------------------------------|------------------|------------------|
| Independent Variable | $r_s$ | $P$ |
| Age | 0.317 | $<$0.0001 |
| Systolic BP | 0.200 | $<$0.0001 |
| Total cholesterol | 0.167 | 0.0003 |
| HDL cholesterol | -0.159 | 0.0005 |
| LDL cholesterol | 0.192 | $<$0.0001 |
| Non-HDL cholesterol | 0.234 | $<$0.0001 |
| Triglycerides | 0.161 | 0.0005 |
| oxLDL Ab titer | -0.098 | 0.0328 |
| BMI | 0.093 | 0.0435 |
| WHR | 0.208 | $<$0.0001 |

Abbreviations as in Table 1. Correlation was analyzed by Spearman’s rank correlation method.

| TABLE 3. Multiple Regression Analysis of Factors Affecting CA-IMT in 446 Healthy Subjects |
|-----------------------------------------------|------------------|------------------|
| Independent Variables | $\beta$ | $P$ |
| Age | 0.197 | $<$0.0001 |
| Sex (female=1, male=2) | 0.006 | 0.923 |
| Systolic blood pressure | 0.185 | $<$0.0001 |
| Smoking status (nonsmoker=1, smoker=2) | 0.076 | 0.168 |
| HDL cholesterol | -0.075 | 0.157 |
| LDL cholesterol | 0.137 | 0.006 |
| Triglycerides | 0.042 | 0.418 |
| BMI | 0.022 | 0.664 |
| WHR | 0.075 | 0.205 |
| oxLDL-Ab titer | -0.098 | 0.032 |

$R^2 = 0.179 (P < 0.0001)$

Abbreviations as in Table 1. Factors independently associated with carotid artery IMT were analyzed by multiple regression. Dummy variables were entered for sex (1 for female, 2 for male) and smoking status (1 for nonsmoker, 2 for smoker). Because of the skewed distribution of CA-IMT and oxLDL Ab titer, these data were logarithmically transformed to fit the linear model.
signs of advanced atherosclerosis. The animals that were immunized with modified LDLs were free of atherosclerosis at the time of immunization. Therefore, the discrepancy among studies suggests that the role of immunity against oxLDL may vary at different stages of atherosclerosis.

The mechanism by which oxLDL Ab titer correlated inversely with CA-IMT is unknown, but several explanations are possible. First, oxLDL Ab may eliminate oxLDL particles from the circulation and prevent them from reentering the arterial wall. We and others have shown that oxLDL is detectable in human plasma at a very low concentration. We recently found that oxLDL Ab titer correlated inversely with plasma oxLDL concentration in a healthy population. In the case of glycated LDL, immunization of rabbits with homologous glycated LDL enhanced the elimination of intravenously injected glycated LDL from the blood stream. These studies support the notion that humoral immunity to modified lipoproteins could promote their clearance from the circulation.

Second, oxLDL Ab may also enhance removal of oxLDL from the arterial wall. Antibodies against LDL were shown to promote the macrophage uptake of LDL via the Fc receptor pathway. This could result in intracellular cholesteryl ester accumulation and thereby promote atherosclerosis. It is important to note that these studies used native LDL and antibodies to it instead of oxLDL and oxLDL Ab. Recently, Horrko et al reported that uptake of oxidized LDL by macrophages via the scavenger receptor was almost completely inhibited by monoclonal antibodies that recognize oxidized phospholipid epitopes of oxidized LDL. This predicts that, in the presence of oxLDL Ab, some of the oxLDL generated in the arterial subendothelium could back-diffuse into the circulation, instead of being taken up by macrophages. In other words, oxLDL Ab may switch the sites of oxLDL metabolism from arterial macrophages to extra-arterial and scavenger receptor–independent pathways. The presence of such novel pathways was recently described by Ling et al. They showed that intravenously injected 125I-labeled oxLDL was rapidly cleared from the circulation by hepatic Kupffer cells in mice and that this clearance was not affected in the knockout mice lacking the scavenger receptor class A type II gene.

Third, although we measured only oxLDL Ab titer, cell-mediated immunity to oxLDL may have beneficial effects on atherosclerosis. Atherosogenesis was promoted in several animal models for deficient cell-mediated immunity, such as rats whose T cells were eliminated with monoclonal antibodies; mice treated with an immunosuppressant, cyclosporin A; and C57BL/6 mice, which are genetically deficient in class I MHC antigen. In humans, development of atherosclerosis has emerged as a new clinical problem in organ transplant recipients, although the role of cyclosporin A appears to be protective in this condition. In any case, cell-mediated immunity specific to oxLDL in humans could be a potential factor modulating the process of atherosclerosis.

Fourth, oxLDL Ab may have affected CA-IMT by modulating plasma lipoprotein metabolism. In univariate correlation analyses, serum oxLDL Ab titer correlated significantly with triglycerides and non-HDL cholesterol and at borderline significance with LDL cholesterol. These results may indicate a possible effect of oxLDL Ab titer on plasma lipids. However, multiple regression analysis indicated that the association between oxLDL Ab titer and CA-IMT was independent of other factors, including the lipid variables. Therefore, the fourth explanation was not supported by our data. We interpret the univariate correlations to indicate that plasma lipids would have affected oxLDL Ab titer.

Although the antibody titer showed a significant relationship with CA-IMT, the relative importance of oxLDL Ab in carotid atherosclerosis does not seem very large compared with other established risk factors. In univariate correlation analyses, CA-IMT showed stronger correlations with age, blood pressure, plasma lipids, and waist-to-hip ratio than with oxLDL Ab titer. It is important to note that the association between CA-IMT and oxLDL Ab titer remained significant in multiple regression analysis in which the effects of other variables were considered. Therefore, the relative importance of oxLDL Ab was not very large but not negligible in this study.

In summary, the present study has demonstrated an inverse relationship between serum oxLDL Ab titer and CA-IMT in a population having no sign of advanced atherosclerosis, supporting the concept that immune response to oxLDL may be antiatherogenic at an early stage of atherosclerosis. Further studies are needed to clarify the relationship between the immunity to oxLDL, either humoral or cell-mediated, and atherosclerosis at various stages of the disease.

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