Temporal Increases in Plasma Markers of Oxidized Low-Density Lipoprotein Strongly Reflect the Presence of Acute Coronary Syndromes

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OBJECTIVES

This study was conducted to test the hypothesis that plasma markers of oxidized low-density lipoprotein (OxLDL) reflect acute coronary syndromes (ACS).

BACKGROUND

Oxidized LDL contributes to the pathogenesis of atherosclerosis, but its role in ACS is not established.

METHODS

Serial plasma samples were prospectively obtained from patients with an acute myocardial infarction (MI) (n = 8), unstable angina (UA) (n = 15), stable coronary artery disease (CAD) (n = 17), angiographically normal coronary arteries (n = 8), and from healthy subjects (n = 18), at entry into the study, hospital discharge (MI group only), and at 30, 120, and 210 days. Chemiluminescent enzyme-linked immunosorbent assay was used to quantitate plasma levels of: 1) immunoglobulin (Ig)M and IgG OxLDL autoantibody titers (presented as a mean OxLDL autoantibody titer by averaging the results of four distinct epitopes); 2) LDL-autoantibody immune complexes (LDL-IC); and 3) minimally OxLDL measured by antibody E06 (OxLDL-E06), as determined by the content of oxidized phospholipids (OxPL) per apolipoprotein B-100.

RESULTS

Baseline OxLDL IgG autoantibody levels were higher in the MI group (p < 0.0001). At 30-day follow-up, the mean IgM OxLDL titers increased by 48% (p < 0.0001) and 20% (p < 0.001), and IgM LDL-IC increased by 60% (p < 0.01) and 26% (p < 0.01) in the MI and UA groups, respectively. The OxLDL-E06 levels increased by 54% (p < 0.01) in the MI group at hospital discharge and by 36% at 30 days. No significant changes in any OxLDL markers were noted in the other groups. The OxLDL-E06 levels strongly paralleled the acute rise in lipoprotein(a), or Lp(a), in the MI group, suggesting that toxic OxPL are preferentially bound to Lp(a). Oxidized LDL-E06 also correlated extremely well with Lp(a) in the entire cohort of patients (r = 0.91, p < 0.0001).

CONCLUSIONS

Circulating OxLDL-specific markers strongly reflect the presence of ACS, implying immune awareness to newly exposed oxidation-specific epitopes and possible release of OxLDL in the circulation. The OxLDL-E06 measurements provide novel insights into plaque rupture and the potential atherogenicity of Lp(a).

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Oxidized low-density lipoprotein (OxLDL) is a critical factor in the initiation and progression of atherosclerosis and contributes to endothelial dysfunction and plaque destabilization through multiple mechanisms (1–3). Ruptured plaques are rich in lipids, which usually occupy more than 40% of plaque volume (4). Human studies have confirmed that OxLDL and oxidized lipid byproducts are present within atherosclerotic plaques (reviewed in Witztum and Steinberg [5]). Presumably, these oxidized lipids are derived from OxLDL and, in part, from degraded foam cells that have released their contents into the atheromatous core. Oxidized low-density lipoprotein (LDL) within atherosclerotic lesions can be quantified and imaged by uptake of intravenously injected, radiolabeled, oxidation-specific antibodies (6) and is preferentially depleted in atherosclerotic mouse and rabbit aortas following a dietary regression/antioxidant intervention (7,8) and in carotid plaques of patients treated with pravastatin (9).

The immune system plays an important role in atherosclerosis by both humoral and cell-mediated mechanisms. T-lymphocytes isolated from whole blood in patients with acute coronary syndromes (ACS) or harvested from human carotid plaques have been shown to specifically recognize OxLDL and proliferate when exposed to OxLDL (10). Oxidized LDL is highly immunogenic and induces autoantibody formation to a variety of oxidation-specific neoepitopes generated when LDL undergoes oxidation. Animal studies have shown that OxLDL autoantibody titers reflect isoprostane levels and the extent of atherosclerosis in apo-
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determination of the presence or extent of atherosclerosis (13).

Considerable data on specific human populations with stable disease suggest that elevated titers of antioxidants (12). The role of OxLDL in ACS, however, has not been fully established in humans. This study was designed to determine whether indirect (autoantibodies and LDL-immune complex [IC]) or direct measures (OxLDL measured by antibody E06 [OxLDL-E06]) of OxLDL would reflect ACS, a setting in which plaque rupture/disruption is known to occur.

**METHODS**

**Study subjects.** This study was performed at UCSD Medical Center/Thornton Hospital and the UCSD Clinical Research Center and was approved by the UCSD Institutional Review Board. Patients were enrolled prospectively with acute myocardial infarction (MI) (n = 8), unstable angina (UA) (n = 15) with Braunwald classification II or III, stable coronary artery disease (CAD) (n = 17) without cardiac events/procedures for more than one year, and angiographically normal coronary arteries (n = 8) (i.e., a completely smooth coronary lumen with normal caliber), as well as healthy subjects (n = 18). All patients with MI experienced an acute MI as the first manifestation of CAD. Six patients in the MI group presented with ST-segment elevation on the electrocardiogram and were treated with primary angioplasty and stenting (mean peak creatine phosphokinase [CPK] 2,425 ± 3,124 IU/l). The UA group was treated with percutaneous coronary intervention (PCI) (88%), all with coronary stents except two patients who underwent rotational atherectomy only, or medical therapy (12%). No patient developed CPK-MB elevation following PCI. Stable CAD patients were diagnosed by a history of classic angina pectoris, coronary angiography, coronary revascularization, or MI (Table 1). The normal coronary artery group underwent coronary angiography because of chest pain and an abnormal stress test (n = 6) or unexplained congestive heart failure (n = 2). The normal subject group was composed of young to middle-aged healthy volunteers.

Patients were entered into the study as outpatients in the nonhospitalized groups and at hospital admission or arrival to the cardiac catheterization laboratory (emergently for MI patients and within 12 h of admission for UA patients). Fasting venous blood samples were collected in tubes containing ethylenediamine-tetraacetic acid on entry into the study and at 30, 120, and 210 days. Blood was also collected at hospital discharge (mean hospital stay of four days) in the MI group. The blood was immediately placed on ice, and plasma was separated by centrifugation at 3,000 rpm for 15 min and stored at −70°C until all assays were performed concurrently.

**Determination of OxLDL autoantibody titers, LDL-IC, and OxLDL-E06 levels.** Chemiluminescence enzyme-linked immunosorbent assay (ELISA) was used to measure OxLDL markers at each time point, as previously described (14–16). All samples for a given analyte were obtained in a single assay. Each sample was assayed in triplicate, and data are expressed as relative light units in 100 ms. A high and low standard plasma was included on each plate of a given assay to detect potential variations between microtitration plates. The intra-assay coefficients of variation for all assays were 6% to 10%.

Titers of immunoglobulin (Ig) G and M autoantibodies, determined at 1:500 dilutions in human plasma, were tested for binding to the following antigens representing different epitopes of OxLDL: 1) malondialdehyde (MDA)-LDL; 2) copper-oxidized LDL (Cu-OxLDL); 3) oxidized cholesteryl linoleate-LDL; and 4) 1-palmitoyl-2-(5-oxovaleryoyl)-phosphatidylcholine (POVPC)-albumin, an oxidation product of the normal phospholipid 1-palmitoyl-2-arachidonoyl-phosphatidylcholine. These antigens were prepared as previously described (16–18).

The baseline levels of OxLDL autoantibodies to the different model oxidation epitopes were expressed individually and, to simplify data analysis, as the “mean” OxLDL titer by summing up the readings of the four different epitopes and determining the average result. For the follow-up period, the OxLDL autoantibody data are presented as the mean percent change compared with the mean baseline values of the four epitopes.

The LDL-IC was measured as previously described (15). The extent of circulating, minimally oxidized LDL (termed

**Abbreviations and Acronyms**

ACS = acute coronary syndromes
ANCOVA = analysis of variance
Apo = apolipoprotein
CAD = coronary artery disease
CPK = creatine phosphokinase
Cu-OxLDL = copper-oxidized low-density lipoprotein
HDL = high-density lipoprotein
Ig = immunoglobulin
LDL = low-density lipoprotein
LDL-IC = low-density lipoprotein-immune complexes
Lp(a) = lipoprotein(a)
MDA-LDL = malondialdehyde-low-density lipoprotein
MI = myocardial infarction
OxLDL = oxidized low-density lipoprotein
OxLDL-E06 = oxidized low-density lipoprotein measured by antibody E06
OxPL = oxidized phospholipids
PC = phosphorylcholine
PCI = percutaneous coronary intervention
POVPC = 1-palmitoyl-2-(5-oxovaleryoyl)-phosphatidylcholine
UA = unstable angina
OxLDL-E06) was measured using the murine monoclonal antibody E06, which binds oxidized phospholipids (OxPL), and the data are expressed as E06 epitopes per apo B-100, as previously described (15,16).

**Lipoprotein assays.** Plasma total cholesterol, triglycerides, and high-density lipoprotein (HDL) were measured by enzymatic assays. Apolipoprotein A, apo B, and lipoprotein(a), or Lp(a), levels were measured by quantitative immunoprecipitin analysis with commercially available antisera (DiaSorin, Stillwater, Minnesota).

**Statistical analysis.** Statistical analysis was performed with GraphPad InStat, version 3.01. For baseline categorical clinical variables, differences were evaluated by the chi-squared test for independence, and for continuous variables by one-way analysis of variance (ANOVA). During the follow-up period, differences between groups at each time point were evaluated by one-way ANOVA, and differences within groups by repeated-measures ANOVA with post-hoc analysis using the Bonferroni multiple comparisons test. A p value <0.05 was considered statistically significant. Correlations between various markers of OxLDL were determined by linear regression analysis. Data are presented in the text and tables as the mean value ± SD and in figures as the mean value ± SEM.

**RESULTS**

**Patient characteristics.** The MI and UA groups had a higher prevalence of hypertension, tobacco use, and beta-blocker use and a lower prevalence of vitamin E supplement use (Table 1). At follow-up, one patient in the MI group underwent rotational atherectomy for in-stent restenosis at six weeks. Two patients in the UA group had recurrent angina at 6 and 10 weeks after presentation and underwent uneventful coronary artery bypass graft surgery. None of the lipid parameters changed significantly in the MI group compared with the other groups (p > 0.05), as compared with the normal subject group. The baseline IgG OxLDL titers and IgM LDL-IC levels were significantly different between the MI (p < 0.05) and UA groups (p < 0.05), as compared with the normal subjects (Table 2). At follow-up, 75%, 54%, and 71% of the MI, UA, and CAD patients, respectively, were on lipid-lowering therapy. In the MI group, LDL cholesterol levels decreased (120 ± 224 mg/dl to 79 ± 25 mg/dl; p = 0.037) and triglyceride levels increased (93 ± 65 mg/dl to 224 ± 112 mg/dl; p = 0.014) at 30 days and remained at these levels during follow-up. None of the lipid parameters changed significantly in the UA, CAD, normal coronary artery, or normal subject group. The baseline IgG OxLDL titers (mean of four OxLDL epitopes, as in the Methods section) were elevated in the MI group compared with the other groups (p < 0.0007) (Table 2). In contrast, the baseline IgM OxLDL titers (p = 0.002) and IgM LDL-IC (p < 0.0001) were significantly higher in the normal subjects compared with the other groups. The baseline IgG LDL-IC and OxLDL-E06 were not significantly different between the groups (Table 2).

**Follow-up OxLDL IgM autoantibody titers and IgM LDL-IC.** The individual IgM OxLDL autoantibody titers (Fig. 1) reflected the trends in the mean OxLDL titers, with
the largest contribution coming from Cu-OxLDL and MDA-LDL autoantibodies. To simplify data presentation, the rest of the analyses are presented as the mean OxLDL titer made up of all four OxLDL epitopes, as described in the Methods. The absolute mean IgM OxLDL autoantibody titers in the MI and UA groups, which at baseline were significantly lower than those in the other groups, showed significant temporal increases compared with their baseline values (Fig. 2). The IgM OxLDL titers were significantly different between the groups at 30 days (p < 0.0001) and 210 days (p < 0.0001) (Fig. 2A), with the MI group significantly different from the other groups (p < 0.01). Compared with their own baseline values, intra-group increases in IgM OxLDL titers were noted in the MI group at 30 (45%; p < 0.001), 120 (17%; p < 0.01), and 210 days (26%; p < 0.05) and in the UA group at 30 (20%; p < 0.001) and 210 days (15%; p < 0.01) (Fig. 2A). Significant differences between groups in LDL-IC were also noted at each time point (p < 0.001 for all three time points), with the MI group significantly different from the other groups (p < 0.01) (Fig. 2B). Compared with their own baseline values, intra-group differences in IgM LDL-IC were noted in the MI group at 30 (60%; p < 0.01) and 120 days (29%; p < 0.05) and in the UA group at 30 (26%; p < 0.001) (Fig. 2B). No significant changes over time were noted in the three “control” groups.

**Follow-up OxLDL IgG autoantibody titers and IgG LDL-IC.** The absolute mean IgG OxLDL levels remained significantly elevated in the MI group at all time points (30 days: p < 0.0001; 120 days: p = 0.036; and 210 days: p = 0.045). Significant differences between groups in IgG OxLDL titers (p = 0.026) (Fig. 3A) were noted at 30 days (p = 0.026) and in IgG LDL-IC at 30 (p = 0.042), 120 (p = 0.017), and 210 days (p = 0.003) (Fig. 3B), with the UA group having a higher percent change than the other groups (p < 0.05 for both IgG OxLDL and IgG LDL-IC).

Intra-group differences showed greater increases in the UA group at 30 days compared with the MI group for both IgG OxLDL autoantibody titers (p < 0.001) and IgG LDL-IC (p < 0.05).

Both IgG and IgM OxLDL autoantibodies and LDL-IC in the MI and UA groups tended to return toward baseline values but were still elevated at seven months. In general, all measurements in the three control groups varied by <10% during the follow-up period.

**Follow-up OxLDL-E06 and Lp(a) levels.** Oxidized LDL-E06 levels at baseline were not significantly different between the groups (Table 2). At follow-up, there were significant differences between the groups at 30 (p = 0.015) and 210 days (p = 0.015) (Fig. 4A). A 54% (p < 0.05) increase in OxLDL-E06 was noted in the MI group at hospital discharge, approximately four days after the acute MI. Seven of the eight MI patients had OxLDL-E06 elevations at discharge and at 30 days. In sharp contrast, there were no significant changes in OxLDL-E06 levels during the follow-up period in any of the other groups. In parallel with the rise OxLDL-E06, there was an approximately twofold rise in Lp(a) in the MI group, which was significantly different at each time point, compared with the other groups (Fig. 4B). No significant temporal changes in Lp(a) were noted in the other groups. Because of the large variation in baseline absolute Lp(a) values (range 1 to 71 mg/dl), significant differences in the MI group were noted only at the 120-day time point (p < 0.05). However, six of the eight MI patients had increases in Lp(a). In comparison, there was a reduction of ~30% in plasma LDL cholesterol (p = 0.029 at 30 days compared with other groups) (Fig. 4C), as well as a 27% reduction in plasma apo B (p < 0.05; data not shown).

**Correlation between OxLDL-E06 and Lp(a).** Plasma OxLDL-E06 levels correlated exceedingly well with plasma Lp(a) levels (Fig. 5). In the entire cohort of patients at each
Figure 1. Percent change from baseline in individual immunoglobulin (Ig)M oxidized low-density lipoprotein (OxLDL) autoantibody titers. The p values at the 30-, 120-, and 210-day labels represent differences between groups at each time point. **p < 0.01 for differences within individuals groups. CAD = coronary artery disease; Cu-LDL = copper oxidized low-density lipoprotein; MDA-LDL = malondialdehyde-low-density lipoprotein; MI = myocardial infarction; POVPC = 1-palmitoyl-2-(5-oxovaleryoyl)-phosphatidylethanolamine.
Figure 2. Percent change from baseline in mean immunoglobulin (Ig)M oxidized low-density lipoprotein (OxLDL) autoantibody titers (A) and IgM low-density lipoprotein (LDL)-immune complexes (B). The p values at the 30-, 120-, and 210-day labels represent differences between groups at each time point. *p < 0.05, **p < 0.01, and ***p < 0.001 for differences within individual groups. CAD = coronary artery disease; MI = myocardial infarction; UNSA = unstable angina.
Figure 3. Percent change from baseline in mean immunoglobulin (Ig)G oxidized low-density lipoprotein (OxLDL) autoantibody titers (A) and IgG low-density lipoprotein (LDL)-immune complexes (B). The p values at the 30-, 120-, and 210-day labels represent differences between groups at each time point. *p < 0.05, **p < 0.01, and ***p < 0.001 for differences within individual groups. CAD = coronary artery disease; MI = myocardial infarction; UNSA = unstable angina.
Figure 4. Percent change from baseline in oxidized low-density lipoprotein measured by antibody E06 (OxLDL-E06) (A), lipoprotein(a) (Lp[a]) (B), and low-density lipoprotein (LDL) cholesterol levels (C). The p values at the 30-, 120-, and 210-day labels represent differences between groups at each time point. *p < 0.05 for differences within individual groups. CAD = coronary artery disease; MI = myocardial infarction.
time point, very strong correlations were noted between OxLDL-E06 and Lp(a) (baseline: \( r = 0.90, p < 0.0001 \); 30 days: \( r = 0.91, p < 0.0001 \); 120 days: \( r = 0.90, p < 0.0001 \); 210 days: \( r = 0.97, p < 0.0001 \)), as well as for the entire cohort of patients and samples at all time points combined (\( r = 0.91, p < 0.0001 \)) (Fig. 5). Similar strong correlations existed within individual groups, including the normal subjects (\( r = 0.97, p < 0.0001 \) for normal subjects at baseline sample).

Correlations among OxLDL autoantibodies. To assess the inter-relationships between OxLDL autoantibodies, we performed a regression analysis by pooling the data points for all five patient groups at each of the time points for each individual autoantibody titer (Table 3). Very strong to moderate correlations were seen among all OxLDL autoantibodies, particularly between Cu-OxLDL and both POVPC and MDA-LDL. Interestingly, all OxLDL autoantibodies and LDL-IC correlated with each other to some extent. There were no significant correlations between OxLDL-E06 and any OxLDL autoantibody measurement, nor with total, LDL-, or HDL cholesterol. There was also no significant correlation between peak or total CPK levels and any OxLDL parameter at any time point.

**DISCUSSION**

In this study, we addressed the question of whether circulating markers of OxLDL reflect ACS, a situation in which atherosclerotic plaque disruption is known to occur. We demonstrate prospectively, for the first time, that indirect and direct plasma markers of OxLDL show significant temporal elevations following ACS, particularly in patients with acute MI, but not in patients with stable CAD or in subjects without CAD. In addition, we demonstrate the novel observation of a very strong correlation between plasma Lp(a) levels and OxLDL-E06 levels, which represent OxPL epitopes, suggesting a physiologic (or patho-physiologic) role for Lp(a) in the transport of OxPL.

Baseline IgG OxLDL titers were elevated at baseline and follow-up in the acute MI group, consistent with a previous study of patients with a healed MI (19). Baseline IgM OxLDL titers and LDL-IC were lower, interestingly, in the three groups of patients with CAD, compared with healthy subjects, but rose significantly at follow-up only in the ACS groups. Lower plasma IgM OxLDL autoantibodies have been previously noted in patients with a previous MI (19), stable CAD (19,20), and borderline hypertension (15) and have been inversely associated with increased carotid intima thickness (20). It has been speculated that OxLDL may form immune complexes with preexisting autoantibodies, which act as vehicles for clearance of antigen (10,13,14). Thus, lower IgM titers in CAD patients may actually reflect the consequence of a protective effect.

During the follow-up period, increases in IgM OxLDL autoantibody titers, despite the fact that they were significantly lower in the MI, UA, and CAD groups, were most dramatic in the MI group. These immune responses likely reflect immune activation due to exposure of OxLDL and oxidation-specific epitopes potentially released from both disrupted plaques and, in the case of acute MI, potential additional sources derived from myocyte cell membranes of apoptotic or dying cells, which contain OxPL (18). These data are also remarkable for the consistency of titers noted at each time point over a seven-month period in normal subjects, an observation that has not been previously reported.

Oxidized phospholipids are a prominent component of minimally modified LDL and OxLDL and have many pro-inflammatory and pro-atherogenic properties (21). The natural autoantibody E06, cloned from apo E-/- mice, binds to OxPL containing the phosphorylcholine (PC) head...
group, but not to native unoxidized PC-containing phospholipids (17), and has been used to develop a chemiluminescent ELISA to detect circulating OxPL (16). E06 and similar E0 autoantibodies were found to be structurally and functionally identical to classic "natural" T15 anti-PC antibodies, which provide protection from pneumococcal infection (22). In addition, a proportion of so-called "antiphospholipid antibodies," which are associated with thrombotic disorders, are actually directed to OxPL, such as oxidized cardiolipin, and cross-react with OxLDL (23). The rise in OxLDL-E06 in the first month in the MI group, as opposed to the other groups, suggests that there is continued release and/or generation of these OxPL epitopes, possibly from both disrupted atherosclerotic plaques and the injured myocardium (24,25). Similarly, isoprostanes, stable end-products of arachidonic acid oxidation, are elevated in patients with acute MI treated with angioplasty (26). In addition, it has been recently appreciated that patients with acute MI may have multiple disrupted plaques in arteries other than the infarct-related artery (27), which may release OxPL.

Recent studies measuring circulating OxLDL using different antibodies and assay procedures have shown an association with CAD (reviewed in Tsimikas and Witztum [24]). By using the antibody DLH3, which detects an OxPL epitope immunologically similar to that recognized by E06 (16), Eghara et al. (25) showed that circulating OxLDL-DLH3 levels, as measured on isolated LDL rather than plasma, reflected the presence of immunochemically detected OxLDL in coronary atherectomy specimens and appeared to differentiate, to some extent, the severity of the underlying clinical presentation. Other studies by Holvoet et al. (28) using antibodies to measure "fully oxidized" LDL, such as MDA-LDL and Cu-OxLDL, showed that OxLDL measured in the emergency room setting is a strong predictor of the presence of ACS, in conjunction with troponin measurements. Because it is not precisely known which OxLDL markers are more relevant to specific disease states, the current work significantly expands on these observations by showing a consistent association of ACS with a comprehensive panel of 11 OxLDL markers, with a prospective follow-up study period. In addition, it provides plausible, novel pathophysiologic links between plaque rupture, OxLDL, and atherogenicity of Lp(a).

The observation that OxLDL-E06 and Lp(a) plasma levels correlate exceedingly well is of considerable interest. Although basal Lp(a) levels are primarily genetically determined, Lp(a) appears to act as an acute-phase reactant under some situations (29). Indeed, in our study, Lp(a) levels increased approximately twofold after MI, consistent with a previous report (30). The observation that OxPL and Lp(a) correlate so closely implies that Lp(a) has a very strong affinity for OxPL, which are toxic oxidative byproducts derived from sources of cellular injury such as plaque disruption and myocyte death. These OxPL may be preferentially transferred to and sequestered by Lp(a) after being released into the circulation. Preliminary data from our laboratory have shown that the majority of E06 epitopes in the circulation are carried on Lp(a), as opposed to other apo B-containing lipoproteins (unpublished observations of C. Bergmark, J. L. Witztum, and S. Tsimikas, 2002). It has been previously speculated that Lp(a) acts as a scavenger of OxPL, as it contains an unusually high content and activity of platelet-activating factor acetylhydrolase, an enzyme with the capacity to degrade OxPL (29,31). Thus, according to this hypothesis, the enhanced levels of both OxPL and Lp(a) may be a reflection of enhanced oxidative stress. It is possible that the same set of cytokines that lead to upregulation of other acute-phase reactants might also lead to upregulation of Lp(a). Because a similarly strong OxLDL-E06/Lp(a) correlation exists for normal subjects, this also suggests that OxPL are continually released during normal cellular homeostasis, and their plasma level will, to some extent, depend on Lp(a) levels. Thus, the pro-atherogenic properties of Lp(a), particularly when plasma levels are elevated, may be due to its predilection for the vessel wall while accompanied by these oxidative byproducts, resulting in enhanced inflammation and progression of atherosclerosis. Indeed, Lp(a) has been documented to exist in larger amounts in unstable coronary plaques compared with stable plaques and to co-localize with macrophages (32). Confirmation of these hypotheses awaits further studies.

**Study limitations.** First, a relatively small number of patients were studied in each group. However, we measured 11 parameters of OxLDL in each blood sample, and changes were noted only in the ACS groups. Second, the majority of patients with ACS underwent PCI, which could have potentially induced increases in OxLDL markers, as PCI has been associated with lipid peroxidation, as noted earlier. Although PCI may have contributed to some of the effect, the data showed that MI patients had more dramatic responses, primarily IgM, whereas the UA group had primarily IgG responses, arguing against this as the sole explanation. Plaque disruption is a common phenomenon in both PCI and spontaneous plaque rupture, making it difficult to dissect out the individual contributions of each. Larger studies in patients with stable angina are required to address the question of whether PCI induces short- or long-term changes in OxLDL markers. Third, because we do not have access to pre-presentation OxLDL markers, one may argue that these are epiphenomena of plaque disruption, rather than direct contributors. Although this study cannot address this issue, previous studies (25,28) have clearly documented a direct relationship between OxLDL and the clinical presentation. The rise and fall of OxLDL markers seen in this study may, in fact, represent both the plaque rupture and healing phase of ACS.

**Clinical implications.** The dramatic changes in OxLDL markers in patients presenting with ACS suggest that OxLDL markers may be useful in understanding plaque destabilization. Measurement of plasma markers of OxLDL may provide a noninvasive window to study atherosclerotic
lesions and should stimulate further research to assess whether these markers provide an enhanced diagnosis, risk stratification, and possibly prognostic information.

Conclusions. This study demonstrates that circulating Ox-LDL markers seem to reflect plaque disruption and oxidative stress associated with ACS. In addition, these findings support the hypothesis that in this setting, Lp(a) may act as an acute-phase reactant and scavenge OxPL, resulting in enhanced atherogenicity. Prospective studies in larger groups of patients are required to evaluate whether these measurements provide long-term prognostic information and to assess the effect of therapeutic interventions on OxLDL markers.

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