Oxidized LDL is a unique plaque-specific protein produced in the arterial wall by the oxidative modification of the apoB-100 moiety of native LDL. Oxidized LDL is a powerful atherogenic protein, which is directly involved in the initiation and progression of atherosclerosis, the main cause of coronary artery disease (CAD). It is now widely believed that for native LDL to be atherogenic, it must be converted to oxidized LDL.

Oxidized LDL is found in atherosclerotic lesions and in the circulation, but not in normal arteries. Oxidized LDL is both a biomarker of accelerated atherosclerosis and a mediator of the atherosclerotic disease process.

In 1998, Holvoet et al (1) demonstrated for the first time that elevated circulating levels of oxidized LDL were found in most untreated patients with both stable CAD and acute coronary syndromes (unstable angina; acute myocardial infarction). In this landmark study, oxidized LDL levels were measured in plasma with an ELISA procedure using the oxidized LDL-specific, murine monoclonal antibody, 4E6.

Mercodia’s commercially available oxidized LDL ELISA kits use Holvoet’s monoclonal antibody, 4E6, which is specific for oxidatively modified LDL (2). The 4E6 antibody is directed against a conformational epitope in the apoB-100 moiety of LDL that is generated as a consequence of aldehyde substitution of the lysine residues of apoB-100 (3).

Several clinical research papers and abstracts have been published in the past few years on immunoassay methods for measuring circulating levels of oxidized LDL. Researchers who did not use Holvoet’s oxidized LDL-specific monoclonal antibody, 4E6, in their immunoassay procedures, were unable to demonstrate elevated plasma/serum levels of oxidized LDL in patients with both stable and unstable CAD.

The twofold purpose of this paper is to [1] alert the cardiovascular research community that all oxidized LDL tests are not created equal in what they measure and [2] to call attention to the fact that circulating levels of oxidized LDL, which are measured with different antibodies, may produce results that will not be comparable to the results obtained by other clinical investigators. The recently published study of Tsimikas et al (4) is a good example of such a situation. Tsimikas et al (4) showed that there was a very strong correlation (r = 0.91, p<0.0001) between plasma levels of oxidized LDL and plasma lipoprotein (a) [Lp(a)]. The correlation was so strong that one could easily conclude that the oxidized LDL test of Tsimikas et al (4) was, in fact, just another test for Lp(a). In the oxidized LDL assay of Tsimikas et al (4), oxidized LDL was measured with a murine monoclonal antibody, E06, which binds oxidized phospholipids. Most
important, Tsimikas et al (4) were unable to demonstrate elevated plasma oxidized LDL levels with their immunoassay in patients with stable CHD or in subjects without CHD

In the study we present here, we compared the data published by Tsimikas et al (4) on oxidized LDL (E06 antibody) versus Lp(a) [Figure I] with our data on oxidized LDL (as measured with Holvoet’s 4E6 antibody) versus Lp(a) [Figure II]. Our results clearly show that there is no significant correlation ($r = 0.032$) between oxidized LDL (as measured with the Mercodia oxidized LDL ELISA using Holvoet’s 4E6 antibody) and Lp(a).

Some interesting questions could be raised by our results and by the results of Tsimikas et al (4). It has been shown that Lp(a) is an acute-phase reactant, more than doubling in concentration in response to the proinflammatory cytokine IL-6 (5). Could the oxidized LDL, which is measured by the E06 antibody, be an acute-phase reactant, and the oxidized LDL measured by the 4E6 antibody not be an acute phase reactant? Also, Lp(a) concentrations are unaffected by most available lipid-lowering therapies, including statin drugs. We know that elevated oxidized LDL levels, as measured by the Mercodia oxidized LDL ELISA method with the 4E6 antibody, are reduced significantly by statin therapy. What is the effect of statin therapy on oxidized LDL levels which are measured with the method of Tsimikas et al (4)?

In conclusion, the Mercodia oxidized LDL ELISA test (4E6 antibody) is substantially different than the oxidized LDL (E06 antibody) test of Tsimikas et al (4). It is especially noteworthy that the 4E6 antibody of Holvoet et al (1) is the only monoclonal antibody, to date, that is capable of detecting elevated levels of oxidized LDL in patients with chronic, stable CAD and in patients with acute coronary syndromes.

REFERENCES


