Oxidized LDL, a Predictive Marker for Development of Atherosclerosis

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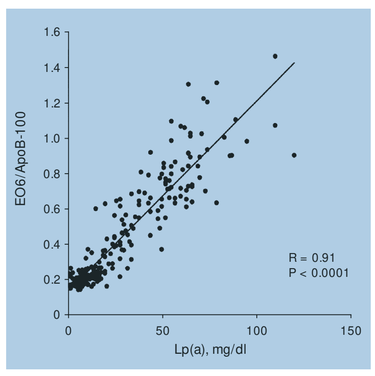
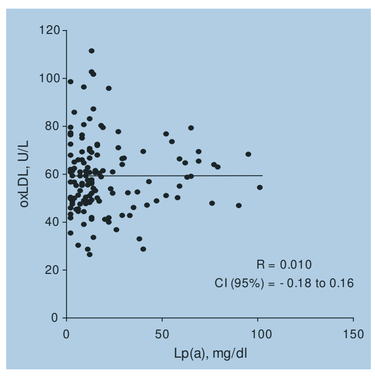
- Oxidized LDL is the atherogenic form of LDL, directly involved in the initiation and progression of the atherosclerotic disease process.
- Oxidized LDL, measured by the Mercodia oxidized LDL ELISAs, has been found to be a predictive biomarker for the subclinical development of atherosclerosis and subsequent events.
- Monitoring circulating oxidized LDL levels may be important in patients with stable plaques since remaining high levels of oxidized LDL, by a continuous stimulation of the immune system, may contribute to the destabilization of growing plaques.

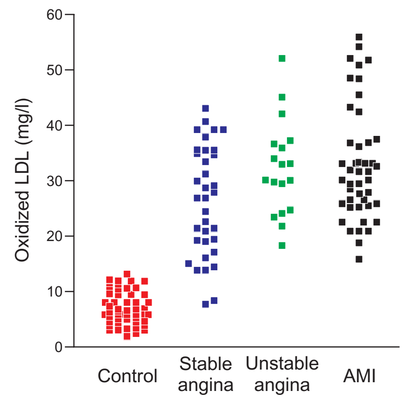
It is today widely believed that the development and progression of atherosclerosis is caused by a chronic inflammation in the vessel wall. Due to the high blood pressure, plasma constituents seep continuously into the intima and at reasonable blood levels low density lipoprotein (LDL) particles can pass in and out of the intima. However, in excess LDL tends to get trapped in the matrix and subjected to modifications. The oxidatively modified LDL particles are considered by the cells as foreign and the immune system is activated. In several studies oxidized LDL has been found to be a predictive biomarker for the subclinical development of atherosclerosis and subsequent events.

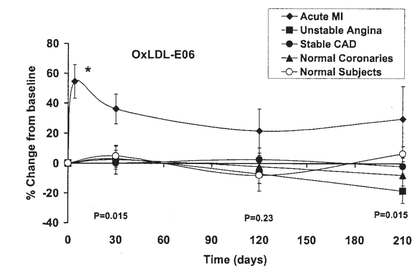
Mercodia has developed oxidized LDL ELISAs, based on the mouse monoclonal antibody 4E6, developed by the professors Holvoet and Collen at the University of Leuven, Leuven, Belgium. The monoclonal antibody 4E6 is directed against a conformational epitope in the Apo B100 moiety of LDL that is generated as a consequence of substitution of at least 60 lysine residues of Apo B100 with aldehydes (Holvoet 2004). This number of substituted lysines corresponds to the minimal number required for scavenger-mediated uptake of oxidized LDL. Substituting aldehydes can be produced by peroxidation of lipids of LDL, resulting in the generation of oxidized LDL. However, lipid peroxidation is not required. Indeed, aldehydes that are released by endothelial cells under oxidative stress or by activated platelets may also induce the oxidative modification of Apo B100 in the absence of lipid peroxidation of LDL. Thus, the antibody 4E6 is different from the antibody FOH1a/DLH3 or the antibody E06 that are both directed to epitopes in oxidized phospholipids.





In several studies, in which the Mercodia Oxidized LDL ELISAs were used, oxidized LDL was shown to be a sensitive and predictive biomarker for the subclinical development of atherosclerosis and subsequent event. By using the 4E6 antibody in a competitive ELISA Professor Holvoet *et al.* (1998) found elevated levels of circulating oxidized LDL in untreated patients with stable coronary artery disease (CAD) as well as in patients with acute coronary syndromes (fig. 3). These findings are important and suggest that this increase is independent of plaque instability. By using the E06 antibody in a similar assay (fig. 4) Tsimikas *et al.* found elevated levels of oxidized LDL only in patients with an acute myocardial infarction and were unable to demonstrate any elevated circulating levels of oxidized LDL in patients with stable coronary heart disease (CHD).





Not only may oxidized LDL measurements be a powerful tool in distinguishing patients with a developing cardiovascular disease from non-risk patients in a seemingly healthy population. Monitoring circulating oxidized LDL levels may also be important in patients with stable plaques since remaining high levels of oxidized LDL, by a continuous stimulation of the immune system, may contribute to the destabilization of growing plaques. The plaque stabilizing fibrin cap may subsequently be degraded by induced secretion of matrix metalloproteinases. If the weakened plaque ruptures, tissue factor, also induced during inflammation, will interact with clot-promoting elements in the blood, causing a thrombus to form.

Holvoet *et al.* (1998) Oxidized LDL and Malondialdehyde-Modified LDL in Patients With Acute Coronary Syndromes and Stable Coronary Artery Disease. Circulation 98: 1487-1494

Holvoet (2004) Oxidized LDL and coronary heart disease. *Acta Cardiol* 59(5): 479-84

Johnston *et al.* (2005) Oxidized low-density lipoprotein as a predictor of outcome in patients with unstable coronary artery disease. *Int J Cardiol* 2005 Dec 7 (in press)

Meisinger *et al.* (2005) Plasma Oxidized Low-Density Lipoprotein, a Strong Predictor for Acute Coronary Heart Disease Events in Apparently Healthy, Middle-Aged Men From the General Population. *Circulation* 112: 651-657

Sigurdardottir *et al.* (2002) Circulating oxidized low-density lipoprotein (LDL) is associated with risk factors of the metabolic syndrome and LDL size in clinically healthy 58-year-old men (AIR study). *J Intern Med* 252: 440-447

Tsimikas *et al.* (2003) Temporal increases in plasma markers of oxidized low-density lipoprotein strongly reflect the presence of acute coronary syndromes. *J Am Coll Cardiol* 5;41(3):360-70

Wallenfeldt *et al.* (2004) Oxidized low-density lipoprotein in plasma is a prognostic marker of subclinical atherosclerosis development in clinically healthy men. *J Intern Med* 256: 413-420

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