Oxidized LDL in risk assessment of coronary heart disease

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Background

Lipoproteins are particles that contain both lipids and proteins. Low-density lipoprotein (LDL) refers to a class of lipoproteins whose main function is to transport cholesterol and triglycerides in the blood for use by various cells. Plasma constituents continuously seep into the intima due to blood pressure, and at reasonable blood levels the LDL particles can pass in and out of the vessel walls. In the blood, LDL particles may be protected from oxidation by blood antioxidants. At elevated blood levels, LDL particles tend to get trapped in the matrix, by proteoglycans and other extracellular matrix constituents, where it is subjected to modifications. Native (unmodified) LDL lacks inflammatory properties whereas the oxidatively modified LDL particles are interpreted by the cells as foreign and the immune system is activated.

Oxidation of LDL is believed to be dependent on the LDL particle size. Small, dense LDL particles tend to be oxidized at a greater extent than larger particles since they pass more easily into the vessel walls and have a greater capacity to bind to proteoglycans in the intima, where the oxidative modifications take place. Scheffer *et al.* (2003) studied the relationship of LDL size with circulating levels of oxidized LDL in type 2 diabetic patients. They found that the prevalence of small, dense LDL particles in diabetic patients is associated with high circulating levels of oxidized LDL (oxLDL). Also Sigurdardottir *et al.* (2002) found an inverse correlation of oxLDL to LDL size.

Risk assessment of coronary heart disease events

Serum levels of LDL-cholesterol is an important factor in the development of atherosclerosis. However, elevated serum levels of LDL-cholesterol, even together with other risk factors, is a poor predictor of a future coronary heart disease (CHD) event. CHD risk functions like Framingham (score includes gender, age, total cholesterol, HDL-cholesterol, cigarette smoking, blood pressure and diabetes) and PROCAM (score includes gender, age, cigarette smoking, blood pressure, history of diabetes, blood levels of LDL-cholesterol, HDL-cholesterol, sugar and triglycerides and heart attack history) seem to over- or underestimate the risk of future CHD events in several populations. This imprecise estimation results in both over- and under-treatment.

Sharper tools are indeed needed for risk assessment of CHD. A novel biomarker like oxLDL could prove to be a good complement to currently used risk scores. Meisinger *et al.* (2005) showed that elevated blood levels of oxLDL were the strongest predictor of future CHD events compared to a conventional lipoprotein profile and other traditional risk factors for CHD. In a study by Johnston *et al.* (2006) oxLDL proved to be an important independent predictor of myocardial infarction but not mortality, and the findings also suggested that oxidized LDL might identify unstable CAD patients at risk for future myocardial infarction, particularly in the absence of myocardial necrosis.

Correlation of oxLDL to LDL-cholesterol

Does oxLDL, as measured with the Mercodia Oxidized LDL ELISA, provide additional information over LDL-cholesterol? In a study of 148 subjects blood levels of oxLDL and LDL-cholesterol were measured. The overall correlation of oxLDL to LDL-cholesterol was found to be 0.70 (R^2=0.4886) (Figure 1). However, when the LDL-cholesterol levels were divided into quartiles the correlation of oxLDL to LDL-cholesterol, within each quartile, decreased with increasing blood levels of LDL-cholesterol with a slight increase in correlation in the highest quartile.

The LDL-cholesterol range within each quartile was determined to be I (0.8-2.6 mM), II (2.6-3.2 mM), III (3.3-3.8 mM) and IV (3.8-5.8 mM). The correlation of oxLDL to LDL-cholesterol was r=0.65 (R^2=0.42) in quartile I, r=0.17 (R^2=0.0285) in quartile II, r=0.13 (R2=0.0168) in quartile III and r=0.29 (R^2=0.0814) in quartile IV (Table 1). In this study, the correlation of oxLDL to LDL-cholesterol was lost at elevated LDL-cholesterol levels.

When blood levels of oxLDL and LDL-cholesterol were compared for their ability to identify patients with CAD in the study by Johnston and colleagues, a strong positive correlation between blood levels of oxLDL and patients with CAD was found, far beyond that of LDL-Cholesterol (Figure 2).

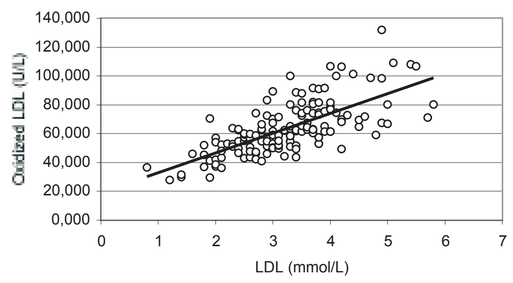

Figure 1. The overall correlation of oxLDL to LDL-cholesterol measured in 148 seemingly healthy subjects (R=0.70).

Quartile	LDL-chol	Subjects	Corr. to oxLDL (R-value)
I	0.8-2.6 mM	1-37 of 148	0.65
II	2.6-3.2 mM	38-74 of 148	0.17
III	3.3-3.8 mM	75-111 of 148	0.13
IV	3.8-5.8 mM	112-148 of 148	0.29
Overall	0.8-5.8 mM	All values (148)	0.70

Table 1. The correlation of oxLDL to LDL-cholesterol measured in 148 seemingly healthy subjects and divided into quartile I, II, III and IV based on blood LDL-cholesterol levels. The overall correlation is 0.70.

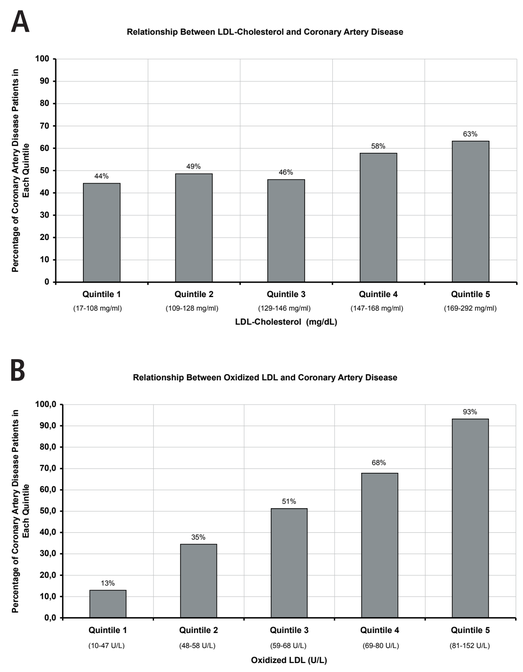

Figure 2. When dividing blood levels of LDL-cholesterol (A) and oxLDL (B) into quintiles, oxLDL correlates much stronger than LDL-cholesterol to the percentage of patients with CAD in each quintile.

Summary

- Native LDL lacks inflammatory properties and does not activate the immune system.
- OxLDL is interpreted by the cells as foreign and the immune system is activated.
- OxLDL is involved in the atherosclerotic early-stage lipid-laden foam cell formation to the development of plaque instability and rupture.
- Blood levels of oxLDL inversely correlate to LDL particle size.
- Elevated oxLDL levels correlate stronger with cardiovascular diseases than LDL-cholesterol.
- OxLDL was shown to be the strongest predictor of future CHD events compared to conventional lipoprotein profiles and other traditional risk factors.

References

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