Impact of phenolic compounds on circulating levels of oxidized LDL

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Summary

- Native LDL lacks inflammatory properties and does not activate the immune system.
- Oxidized LDL is interpreted by the cells as foreign and the immune system is activated.
- Oxidized LDL is directly involved in the initiation and progression of the atherosclerotic disease process.
- Dietary phenolic compounds have been shown to lower circulating levels of oxidized LDL.
- Dietary phenolic compounds may prevent against cardiovascular disease through their antioxidant properties.

Background

In several studies oxidized low-density lipoprotein (oxLDL) was shown to be an atherogenic marker for a developing atherosclerosis and predictive for upcoming cardiovascular events. OxLDL itself has been found to play a significant role in the initiation and progression of atherosclerosis. As a consequence, much effort is put in the search for compounds able to lower circulating levels of oxLDL. Plant phenolic compounds, such as flavonoids, have shown to have a beneficial effect on health. Consumption of foods and diets rich in phenolic compounds has also been found to decrease circulating levels of oxLDL.

Oxidation of LDL

During inflammation a variety of cells (vascular endothelial cells, smooth muscle cells, fibroblasts, neutrophils, monocytes, macrophages) produce inflammatory mediators like oxidants as defense against disease-causing substances (virus, bacteria, parasites, tumors, harmful agents). Enzymes like lipoxigenase, cyclooxygenase, phospholipase A2 and myeloperoxidase are involved in LDL peroxidation by contributing to an increased production of oxidants that may react with various lipids. The formed lipid peroxides, fragment into reactive aldehydes that in turn may substitute lysine residues of proteins such as the ApoB-100 of the LDL particle. Unlike native (unmodified) LDL that lacks inflammatory properties, the oxidatively modified LDL particles are interpreted by the cells as foreign and the immune system is activated.

Macrophage scavenger receptors are involved in the removal of oxLDL deposited in blood vessel walls. Uptake of LDL-cholesterol via the native LDL receptor is subjected to negative feedback regulation. In contrast, the uptake of oxLDL via scavenger receptors is not down-regulated with increasing intracellular cholesterol content and hence results in a massive cholesterol uptake by macrophages, which become foam cells. Foam cells, constituents of the fatty streaks in early steps of atherosclerosis, induce activation of the immune system by the release of inflammatory cytokines. In the progression of atherosclerosis an increasing thickening of the intima is, among other things, due to the intra- and extracellular lipid accumulation and the recruitment of monocytes and T-lymphocytes to the arterial wall. Smooth muscle cell proliferation and migration to the top of the inflamed intima is stimulated by factors secreted from macrophages, endothelial cells and smooth muscle cells. There they synthesize matrix molecules like collagen, which together with the smooth muscle cells, form a plaque stabilizing fibrous cap. The fibrin cap may subsequently be degraded by oxLDL-induced secretion of matrix metalloproteinases. If the weakened plaque ruptures tissue factor, induced during inflammation, will interact with clot-promoting elements in the blood causing a thrombus to form. Thus, oxLDL is involved in the formation of lipid-laden foam cells in early-stage atherosclerotic plaque development to the development of plaque instability and rupture (figure 1).

Mercodia Oxidized LDL ELISA assays are based on the oxLDL specific mouse monoclonal antibody 4E6, developed by professor Holvoet and professor Collen at the University of Leuven, Leuven, Belgium. Holvoet et al. (1998) were the first to demonstrate elevated levels of circulating oxLDL in untreated patients with stable coronary artery disease (CAD) as well as in patients with acute coronary syndromes (ACS) (fig. 2). Since then, circulating levels of oxLDL, as measured by Mercodia Oxidized LDL ELISA assays, have in several studies shown to be a predictive marker for developing atherosclerosis and subsequent events. Thus, there is a gained interest in oxLDL lowering compounds.

Antioxidant-rich foods have been shown to have a beneficial effect on diseases associated with oxidative stress such as cardiovascular disease and aging. Fruits and vegetables have been found to protect against heart disease through their content of micronutrients and antioxidants. Antioxidants such as flavonoids and other phenolic compounds found in fruits and vegetables have been attributed more potent antioxidant properties than, for example, vitamin E or β-carotene.

Phenolic compounds have also been suggested to decrease blood levels of oxLDL. Lapointe et al. (2004) found Mediterranean diet to lower blood levels of oxLDL, and suggested this to be due to the high flavonoid-intake with this diet. Pitsavos et al. (2006) found that a greater adherence to the Mediterranean diet was associated with decreased oxLDL levels in subjects of the ATTICA study population homo/heterozygous for the C677T mutation in the methylene-tyraminehydrofolate reductase gene. Fito et al. (2005) found virgin olive oil to possess oxLDL lowering properties and Weinbrenner et al. (2004) found this to be correlated with the content of phenolic compounds of different olive oils. The phenolic compound contents of red wine (Covas et al., 2003), cranberry juice (Ruel et al., 2005), walnuts (Cor- tés et al., 2006) and Ginkgo biloba (Rodríguez et al. 2007) have also been suggested to be the cause of the oxLDL lowering effect observed by the consumptions of these foods.

Phenolic compounds such as the plant flavonoids have been reported to only reach very low concentrations in human blood after consumption and that they are extensively metabolized in vivo, which may effect their antioxidant capacity. Fito et al. (2005) suggest that the beneficial effect on health observed after consumption of flavonoid-rich foods instead might be caused by indirect flavonoid-induced secondary effects, such as alternation of cell signaling or protein expression, or even by plant macro- and micro-nutrients, rather than the antioxidant capacity of the flavonoids themselves.

In all the above-mentioned studies Mercodia Oxidized LDL ELISA was used to determine circulating levels of oxLDL. If this oxLDL lowering effects of different foods and diets are caused directly by the antioxidant properties of the circulating or tissue accumulated phenolic compounds or their breakdown products or if this is indirectly caused by a phenolics-influenced secondary effect need to be further investigated.

References

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Figure 1. Comparison of circulating oxLDL levels in patients with stable angina, unstable angina and acute myocardial infarction (AMI). Published data by Holvoet et al. (1998).