

Oxidized Low-Density Lipoprotein and its Atherogenic Potential

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Abstract

The emergence of oxidized low-density lipoprotein (OxLDL) is crucial for the progression of cardiovascular diseases (CVD) linked to atherosclerosis. OxLDL stimulates endothelial activation and smooth muscle proliferation and has an atherosclerotic-promoting effect. The measurement of OxLDL correlates with the presence of CVD and may be a prognostic marker for future health outcomes. Circulating OxLDLs can be used as biomarkers since their levels rise in patients with advanced atherosclerosis. Immunological methods have proven to be very useful methodologies. Anti-OxLDL monoclonal antibodies have been developed that bind strongly to OxLDL and are used in ELISA for OxLDL measurements. Routine inclusion of OxLDL estimation in an at-risk population can help the clinicians understand the disease initiation and progression and improve early intervention and management. (**International Journal of Biomedicine. 2022;12(3):339-343.**)

Keywords: oxidized LDL • oxidative stress • atherosclerosis • ELISA

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Abbreviations

ABCA-1, ATP-binding cassette transporter A1; **APH**, 2,2'-Azobis(2-amidinopropane) dihydrochloride; **ApoB**, apolipoprotein B-100; **CVD**, cardiovascular diseases; **ELISA**, enzyme-linked immunosorbent assay; **HDL-C**, high-density lipoprotein cholesterol; **LDL**, low-density lipoprotein; **LDL-C**, low-density lipoprotein cholesterol; **LXR**, liver X receptor; **MAB**, monoclonal antibody; **MDA**, malondialdehyde; **MPO**, myeloperoxidase; **OxLDL**, oxidized LDL; **OxPC**, oxidized phosphatidylcholines; **PUFAs**, polyunsaturated fatty acids; **SRs**, scavenger receptors; **SMCs**, smooth muscle cells; **sdLDL**, small dense LDL.

Introduction

Oxidized low-density lipoprotein (OxLDL) is formed by the modification of LDL, a major group of lipoproteins that enable the transport of multiple, different lipid molecules. OxLDL is labeled as “bad cholesterol” for its key role in the pathogenesis of atherosclerosis leading to cardiovascular diseases (CVD).⁽¹⁾ The formation of atheromatous plaques, a major cause of morbidity and mortality, in the tunica intima of coronary arteries supplying the myocardium manifests as CVD.

Globally, CVD is the major cause of death. Statistics show that in 2019, 17.9 million people died from cardiovascular diseases, which is 32% of the total number of deaths in the world. Atherosclerosis is a long-term inflammatory condition of the arterial wall that is mainly caused by environmental and genetic risk factors, which result in a variety of complications – myocardial infarction, stroke, and other CVDs.⁽²⁾

OxLDL is a potent atherogenic lipoprotein that is known to alter endothelial functions. OxLDL is a form of LDL or “bad” cholesterol, which is formed during oxidative stress.⁽³⁾ LDL particles are the main carriers of cholesterol in the circulation. The LDL particle is made of a hydrophobic core of polyunsaturated fatty acids (PUFAs) and esterified cholesterol surrounded by phospholipids, unesterified cholesterol, and one molecule of apolipoprotein B-100 (ApoB-100). LDL PUFAs (mainly linoleic acids⁽⁴⁾ with minor amounts of arachidonic acid and

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docosahexaenoic acid) are protected against oxidation by antioxidants, primarily α -tocopherol. There are different sizes of LDL.⁽⁵⁾

Brown and Goldstein were the first to postulate that LDL has to undergo some structural changes to achieve atherogenic properties.⁽⁶⁾ Oxidative stress is an important trigger of lipid oxidation.⁽⁷⁾ LDL oxidation leads to the alteration of ApoB recognition sites and the unregulated uptake of LDL by macrophages via scavenger receptors (SRs). The uptake of OxLDL by SRs leads to the accumulation of cholesterol within the foam cells. The emergence of such cells is a specific feature of early atherosclerotic lesions. Oxidation of LDL particles in the vascular endothelium has been reported to be an initial event in atherosclerotic plaque formation. OxLDL stimulates endothelial activation and smooth muscle proliferation evincing pro-atherosclerotic effects. Moreover, the studies demonstrate that all of the changes associated with endothelial cell modification of LDL can be attributed to oxidation.⁽⁸⁾

Inflammation and lipid metabolism alterations play a critical role in atherogenesis. However, the details of the relationships and causality among these fundamental processes still remain a puzzle. According to the classical hypothesis, atherosclerotic plaques are formed over a long duration with an accumulation of OxLDL, thus increasing the risk of myocardial infarction and stroke. A large number of studies indicate that OxLDL is a useful marker of CVD.⁽⁹⁻¹¹⁾

Chemical nature of OxLDL

There are several oxidizable components in LDL, but PUFAs are the major targets of free radicals. Saturated fats are less involved in peroxidation due to their chemical nature and are resistant to oxidative damage. The majority of PUFAs in LDL are present as cholesteryl esters, and therefore, quantitatively, most of the oxidized fatty acids in the fully oxidized LDL are esterified to cholesterol. LDL-PUFAs are oxidized by enzymatic and nonenzymatic pathways in the arterial tissue, specifically by the endothelial cells and macrophages.

It should be noted that LDL particles are rich in antioxidants such as α -tocopherol, β -carotene, and ubiquinol-10, which protect LDL from free radical attack and oxidation.^(12,13) However, at the end of the lag phase of LDL oxidation, the antioxidant property of LDL is diminished, and PUFAs in LDL particles are rapidly oxidized to hydroperoxide, further breaking down to generate more reactive aldehyde products and metabolites, such as MDA and 4-hydroxynonenal.

OxLDL exists in multiple forms, characterized by different degrees of oxidation, including minimally modified LDL, which is still recognized by the LDL receptor, and fully or extensively OxLDL, which is recognized by SRs. Whereas native LDL has no effect on the immune system, OxLDL is immunogenic, and immune complexes formed by oxidized LDL and corresponding antibodies are pro-atherogenic and proinflammatory.^(14,15)

It has been well documented that small dense LDL (sdLDL) has a greater atherogenic potential than that of other LDL subfractions. sdLDL particles have a decreased affinity for the LDL receptor resulting in a prolonged retention time in the circulation. Additionally, they more easily enter the

arterial wall. sdLDL particles contain less antioxidative agents and are therefore more susceptible to oxidation than larger forms of lipoproteins.⁽¹⁶⁾ Circulating sdLDL readily undergoes multiple atherogenic modifications in blood plasma, such as desialylation, glycation, and oxidation, that further increase its atherogenicity.⁽¹⁷⁾

OxLDL contains unoxidized and oxidized fatty acid derivatives both in the ester and free forms, their decomposition products, cholesterol and its oxidized products, proteins with oxidized amino acids and cross-links, and polypeptides with varying extents of covalent modification with lipid oxidation products, and many others.⁽¹¹⁾

Formation of OxLDL in vivo and in vitro

There are a number of mechanisms for the oxidation of LDL: lipoxygenase reaction, copper and ceruloplasmin-mediated oxidation, iron-mediated oxidation, peroxidase-mediated oxidation, peroxynitrite-mediated oxidation, thiol-dependent oxidation, xanthine oxidase, NADPH oxidase, and other superoxide generators.

The most common hypothesis for LDL oxidation is that it occurs in microdomains isolated from the antioxidant environment of the arterial tunica intima. LDL particles react with free radicals and their by-products. Reacted LDL aggressively interacts with the surrounding tissues, causing tissue damage. In vivo, LDL oxidation occurs mainly within the subendothelial space of the arterial wall, in any of the cells within the artery, including the endothelial cells, macrophages, SMCs, and T-lymphocytes. Wen et al. found that LDL oxidation can occur intracellularly, most probably within lysosomes. Transition metals such as iron and copper can do this in a cell-free system.⁽¹⁸⁾ Ojo and Leake⁽¹⁹⁾ have postulated that LDL is oxidized by iron at lysosomal pH by the hydroperoxyl radical (HO₂•), which is more reactive and hydrophobic than the superoxide radical (O₂•⁻).

In vivo, LDL oxidation occurs mainly within the subendothelial space of the arterial wall. Studies have suggested that superoxide, myeloperoxidase (MPO), 15-lipoxygenase, peroxynitrite (ONOO⁻), and thiols may contribute to LDL oxidation (Figure 1). 15-lipoxygenase, produced by endothelial cells and monocytes/macrophages, converts PUFAs into lipid hydroperoxides and thereby oxidizes LDL. Activated macrophages secrete MPO, which generates reactive species, thereby oxidizing LDL. Finally, OxLDL interacts with SRs presented on endothelial cells, macrophages, and SMCs.⁽²⁰⁾

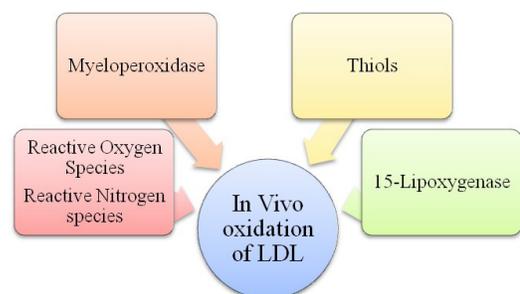


Fig. 1. In vivo mechanisms for oxidation of LDL.

In *in vitro* experiments, fully (80%-100%) oxidized LDLs are usually prepared by exposure to transition metal ions, such as Cu^{2+} ^(21,22) or Fe^{2+} .⁽²³⁾ Incubation with cells producing ROS, or exposure to MPO secreted by activated macrophages, leads to minimally oxidized LDLs, which appear to be better related to the degree of oxidation *in vivo*.⁽²⁴⁻²⁶⁾

Mertens and Holvoet detail the 3 stages of *in vitro* oxidation of LDL by metal ions: an initial lag phase (consumption of endogenous antioxidants), a propagation phase (rapid oxidation of PUFAs to lipid hydroperoxides), and a decomposition phase (formation of reactive aldehydes). Reactive aldehydes such as hydroxynonenal, hexanal and MDA react with lysine residues in ApoB, resulting in OxLDL.

Atherogenic effects of OxLDLs

The most important atherogenic effect of LDL oxidation is that this modification of LDL shifts the recognition and internalization of the lipoprotein from the LDL receptor (LDLR) to SRs.⁽²⁷⁻³⁰⁾ The binding of OxLDL to SRs can trigger a number of intracellular events that depend on the type of cell and SR involved.⁽²⁷⁾ Interaction of OxLDL with SRs (SR-A, SR-B1, CD36, LOX-1) induces rapid and unregulated uptake of OxLDL by special cells. Thus, macrophages uptake OxLDL via SR-A and CD36; endothelial cells uptake OxLDL via CD36 and LOX-1. These receptors internalize OxLDL in a specific manner until foam cells are formed.⁽³¹⁾ Uptake of OxLDL by macrophages leads to marked accumulation of cholesterol, converting the macrophages to foam cells^(18,32) and initiating the development of atherosclerotic lesions (Figure 2).

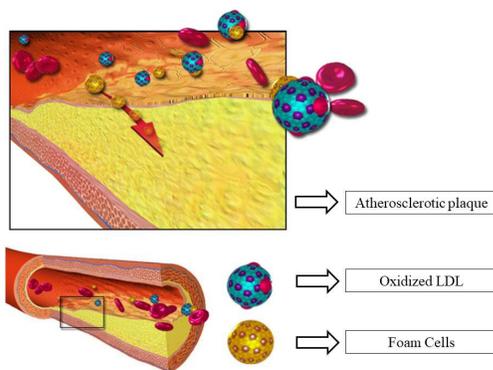


Fig. 2. Uptake of OxLDL by macrophages, formation of foam cells and atherosclerotic plaque.

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OxLDL also activates a number of cellular responses in macrophages, dendritic cells, endothelial cells, T cells, SMCs, and platelets, which in the aggregate promote inflammation, lesion formation, atherogenesis, unstable atherosclerotic plaques, and thrombosis.⁽³³⁻³⁹⁾ OxLDL stimulates the expression of endothelial adhesion molecules, has chemotactic effects, and inhibits the migration of macrophages outside the subendothelial space, thus increasing the number of leukocytes

and proinflammatory elements involved in atherogenesis.⁽²⁴⁾ As a highly atherogenic moiety, OxLDL was reported to upregulate endothelial ABCA1, a cell membrane protein that mediates the transport of cholesterol, phospholipids, and other metabolites from cells to lipid-depleted HDL apolipoproteins, through the activation of the peroxisome proliferator-activated receptor gamma (PPAR γ)–liver X receptor (LXR) pathway in lipid-loaded macrophages.⁽⁴⁰⁾ OxLDL appears to transcriptionally downregulate ABCA1 via the inhibition of LXR. Thus, OxLDL-regulated ABCA1 may contribute to endothelial dysfunction, accumulation of lipid within the vascular wall, and the subsequent development of atherosclerosis.^(41,42) Wang et al.⁽⁴³⁾ showed that OxLDL up-regulates arginase I, which contributes to endothelial dysfunction by reducing L-arginine availability to eNOS for NO production and thus vasodilation. Thus, OxLDL instigates atherosclerotic events throughout the disease progression, starting from endothelium dysfunction, white blood cell activation, foam cell formation, SMC migration, and proliferation to platelet adhesion and aggregation⁽¹⁸⁾ (Figure 3)

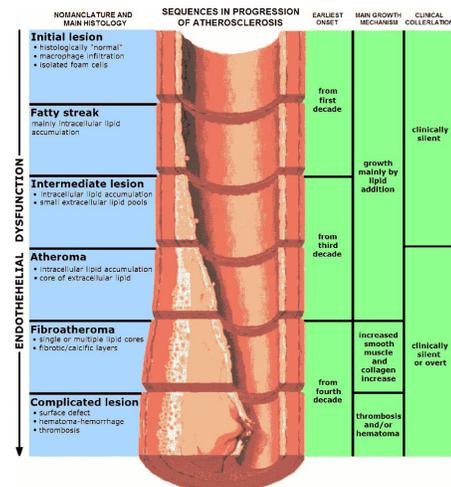


Fig. 3. Endothelial dysfunction and progression of atherosclerosis

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Measurement of OxLDL

OxLDL levels could be a useful marker for predicting future cardiovascular events; however, substantial differences exist among the different methods of OxLDL measurement.⁽⁴⁴⁾ In the past 10 years, it has been possible to generate MABs to OxLDL to measure OxLDL in the plasma directly.⁽²¹⁾

Challenges in estimating OxLDL in humans have been overcome with ELISA. ELISA methods are used to determine OxLDL levels in plasma by either “sandwich assays or competitive assays.” ELISA methods have demonstrated that OxLDL levels increase under certain pathological conditions, including acute

myocardial infarction and carotid artery atherosclerosis.⁽⁴⁵⁾ Human Oxidized LDL ELISA Kit is an enzyme immunoassay developed to detect and quantify human oxidized LDL in plasma, serum, or other biological fluid samples. The kit contains a copper oxidized LDL standard against which unknown samples may be compared. Each oxidized LDL assay is configured to selectively measure either carboxymethyl-lysine-modified LDL, 4-Hydroxynonenal-modified LDL(HNE-LDL), or MDA-LDL.⁽⁴⁴⁾

Accumulation of OxLDL in atherosclerotic lesions has also been demonstrated by immunohistochemical and biochemical studies using the DLH3 antibody. This antibody recognizes oxidized phosphatidylcholines (OxPC) generated during oxidative modification of LDL, and OxPC-apoB adducts formed in OxLDL are the presumed antigens. The presence of OxLDL in the LDL fraction of human plasma was demonstrated by introducing a sandwich ELISA procedure using DLH3 together with an anti-apoB antibody.⁽⁴⁶⁾

Several immunoassays with antibodies against OxLDLs, MDA-modified LDLs, lysine-substituted LDLs, and OxPCs have been developed and widely used to measure OxLDLs in biological samples. Among many antibodies against atherosclerotic lesions, a clone that strongly reacts with copper-induced OxLDL was raised. The antibody, DLH3, recognizes OxPCs, where 1-palmitoyl-2-(9-oxo)nonanoyl-PC (9CHO-PC, also called PONPC) is one of the potent antigenic molecules.⁽⁴⁶⁾

Tan et al.⁽⁴⁷⁾ established a simple, specific and rapid gold nanoparticle-based lateral flow immunoassay (LFIA) on quantifying OxLDL/ β 2GPI complexes from test samples. β 2GPI recognizes the structural part of 7-ketocholesteryl-9-carboxynonanoate(oxLig-1), a specific ligand in OxLDL, to form indissociable OxLDL/ β 2GPI complexes.⁽⁴⁸⁾ Presently, serological levels of OxLDL/ β 2GPI complexes are measurable by ELISA. Tan et al.⁽⁴⁷⁾ fabricated another MAB, 3H3, which shares antigen-specificity similar to WB-CAL-1, yet with improved affinity and specificity towards β 2GPI complexed with OxLDL.⁽⁴⁹⁾ The developed OxLDL/ β 2GPI LFIA offers a simple test procedure to quantitatively assess OxLDL/ β 2GPI in serum or a sample containing the same.

A valid measure of in vivo OxLDL formation is represented by the susceptibility to oxidation of isolated plasma LDLs, as assessed by the lag time for forming conjugated dienes⁽⁵⁰⁾ induced by Cu²⁺ that can be spectrophotometrically detected at 234 nm. Another method is to evaluate the acid hydrolysis products of lipoperoxides such as MDA, which reacts with thiobarbituric acid (TBA) to form MDA-TBA adducts. The TBA-reactive substances can be measured spectrophotometrically, fluorometrically, or by high-pressure liquid chromatography.⁽²⁴⁾

In conclusion, oxidative stress is an important trigger of lipid oxidation. OxLDL was found to modulate different signal transduction cascades leading to gene expression, apoptosis, adhesion, inflammation, differentiation, and migration, all of which contribute to the development of atherosclerosis. Circulating OxLDLs can be used as biomarkers since their levels rise in patients with advanced atherosclerosis. Routine inclusion of OxLDL estimation in an at-risk population can help the clinicians understand the disease initiation and progression and improve early intervention and management.

Competing Interests

The authors declare that they have no competing interests.

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