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Review Article

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Oxidized Low-Density Lipoprotein as an Emerging Biomarker in Atherosclerosis: Synthesis and Clinical Implications in Cardiovascular and Metabolic Diseases

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ABSTRACT

Oxidative modification of low-density lipoprotein is a key process in the onset and development of atherosclerosis and associated cardiometabolic diseases. Unlike LDL cholesterol, oxidized low-density lipoprotein (OxLDL) is a biologically active mediator that induces endothelial dysfunction, foam cell formation, chronic vascular inflammation, plaque progression and plaque destabilization. This review synthesizes the current knowledge on the molecular biology of oxLDL, the molecular pathways controlling formation of oxLDL, and multiple pathogenic effects of oxLDL on the vascular wall. We critically analyse current methods for the measurement of oxLDL, emphasizing their analytical strengths, limitations and problems associated with assay standardization. The clinical significance of oxLDL is reviewed in relation to major disease conditions, such as coronary artery disease, acute coronary syndromes, diabetes mellitus, metabolic syndrome, chronic kidney disease, hypertension, non-alcoholic fatty liver disease, stroke and peripheral arterial disease. Accumulating evidence shows that oxLDL is a source of prognostic information in addition to conventional lipid parameters and improves the cardiovascular risk stratification. Although there are still limits on routine clinical implementation, further improvements in assay technology and increasing mechanistic insight make oxLDL a promising next-generation biomarker for personalised cardiovascular prevention and therapeutic monitoring.

1. INTRODUCTION

Cardiovascular disease (CVD) is the first leading cause of death worldwide, with an estimated 20.5 million deaths per year, which is almost one-third of all deaths worldwide (World Health Organization [WHO], 2023). Atherosclerosis is the cause of most of these cardiovascular events such as coronary artery disease (CAD), stroke, and peripheral arterial disease. Despite major developments in lipid-lowering interventions and preventive measures, the worldwide disease burden of atherosclerosis continues to increase, especially in low and middle-income countries where metabolic disorders and lifestyle changes are driving the increasing prevalence of the disease (Roth et al., 2020).

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Atherosclerosis is now not only considered to be a disease of lipid storage, but a complex inflammatory disease involving dysregulated lipid metabolism, oxidative stress, endothelial dysfunction and immune activation. Epidemiological studies show that subclinical atherosclerosis is present in almost 50% of adults over 45 years of age even in populations without overt cardiovascular symptoms (Benjamin et al., 2019). These are important findings highlighting the urgent need for better biomarkers and mechanistically relevant tools for early detection and risk stratification.

Low-density lipoprotein cholesterol (LDL-C) has been the foundation biomarker in the assessment of cardiovascular risk and decision-making for therapeutic intervention for decades. Although LDL-C in the blood is a very strong predictor of cardiovascular risk, there are many clinical observations showing that cardiovascular events commonly occur in people with normal or moderately elevated LDL-C levels (Ference et al., 2017). Furthermore, intensive LDL-C lowering does not completely eliminate residual cardiovascular risk, suggesting that LDL quantity does not represent the full biological complexity of atherogenesis (Ridker et al., 2018).

The oxidative modification theory of atherosclerosis, as first proposed by Steinberg and co-workers, completely revolutionized our perception of how lipid injury can lead to vascular injury. This hypothesis suggested that oxidized low-density lipoprotein (oxLDL), not the LDL itself, is the major atherogenic agent at the arterial wall (Steinberg et al., 1989). Subsequent experimental and clinical studies have shown that oxLDL possesses strong pro-inflammatory, cytotoxic, immunogenic and pro-thrombotic properties, actively promoting endothelial dysfunction, foam cell formation, plaque progression and plaque destabilization (Witztum & Steinberg, 1991; Berliner et al., 1995).

Unlike the LDL from normal subjects, the presence of oxLDL is recognized by the scavenger receptors on the macrophages and vascular cells, resulting in out-of-control uptake of lipids and the formation of foam cells, which are characteristic features of early atherosclerotic lesions (Brown & Goldstein, 1983; Itabe & Takano, 2000). Moreover, the oxLDL has a direct effect on gene expression, enhances vascular inflammation, and disturbs the vascular endothelium homeostasis thus linking oxidative stress and immune-mediated vascular injury (Cominacini et al., 2001; Tsimikas & Miller, 2011).

Given the growing body of evidence for the central role of the oxLDL in cardiovascular and metabolic diseases, the aim of this review is:

1. Synthesize current knowledge on how oxidized LDL is biologically formed and what its molecular characteristics are;
2. Study the mechanistic role of the oxLDL in atherosclerosis and vascular pathology;
3. Assess methodologies for measurement of oxLDL that are available, as well as their strengths and limitations from a clinical perspective;
4. Discuss clinical implications of oxLDL in the major cardiometabolic disorders; and
5. Discuss the potential of oxLDL as a new-generation biomarker to risk stratify patients with CVD and monitor therapy.

2. BIOLOGY OF OXIDIZED LDL

An understanding of the nature of oxidized low-density lipoprotein (oxLDL) involves an appreciation of the nature of LDL structure, its metabolic processing, and the various types of oxidative modifications that convert it to a potent atherogenic particle.

2.1. LDL Structure and Metabolism

Low-density lipoprotein (LDL) is a spherical particle of plasma lipoprotein, which is responsible for transporting cholesterol from the liver to the peripheral tissues. Each LDL particle is made up of a hydrophobic core of mainly cholesteryl esters and triglycerides, covered by a phospholipid monolayer that is embedded with free cholesterol and one molecule of apolipoprotein B-100 (apoB-100). ApoB-100 is the structural backbone of the LDL particle and the ligand for the LDL receptor and regulates the receptor-dependent cellular uptake (Segrest et al., 2001).

LDL particles are derived from the metabolic processing of the very-low-density lipoproteins (VLDL) secreted by the liver. In circulation VLDL is broken down by progressive hydrolysis of triglyceride through lipoprotein lipase (LPL) to form intermediate density lipoprotein (IDL) which is further remodeled to LDL by hepatic lipase. While part of IDL is cleared by hepatic LDL receptors, the rest of the IDL is converted to LDL and released into the bloodstream where it circulates for about 3-5 days (Goldstein & Brown, 2009).

Under physiological conditions, LDL distributes the cholesterol to cells by controlled receptor-mediated endocytosis. However, disruptions in energy balance of lipids, oxidation, and inflammatory signaling pathways encourage the conversion of native LDL to forms that are structurally and functionally altered and have increased atherogenic potential.

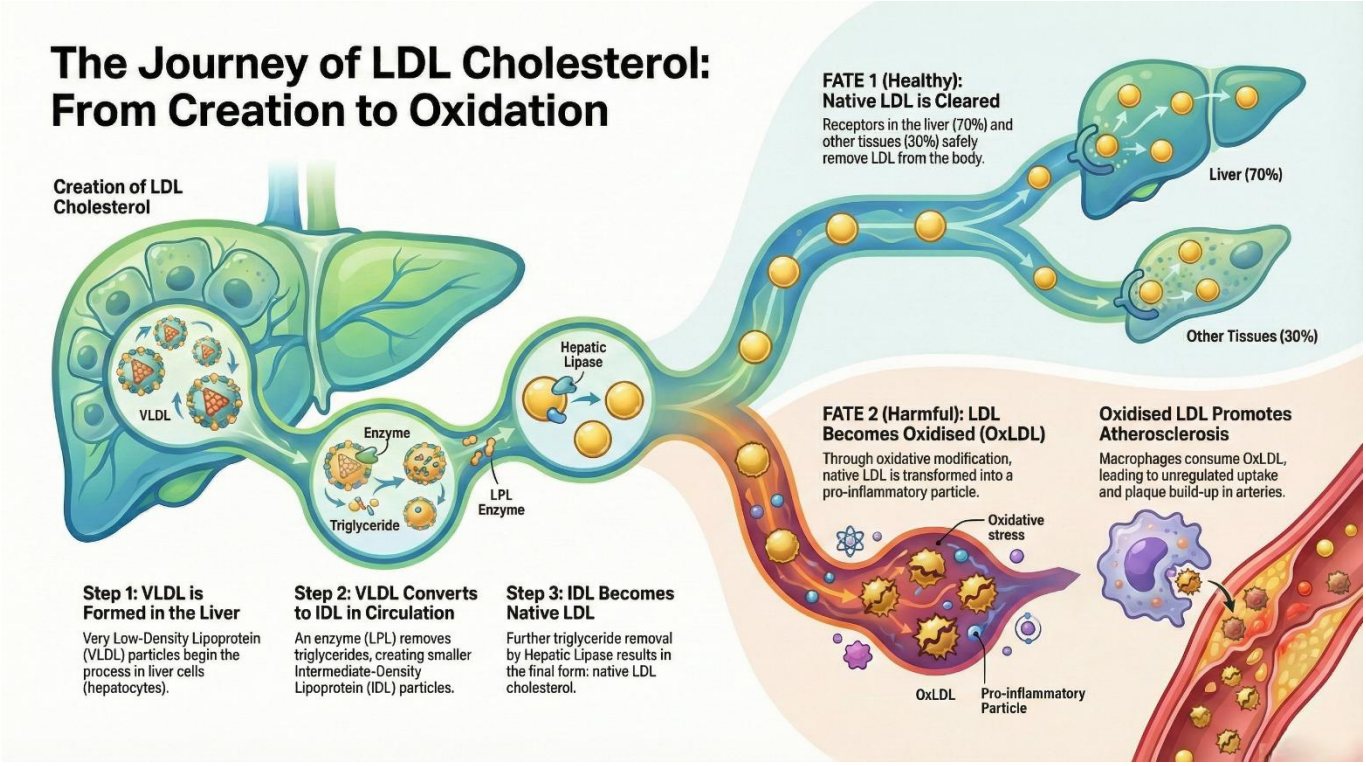

Figure 1. The metabolic journey of low-density lipoprotein from hepatic production to oxidative modification

2.2. What Is Oxidized LDL?

Oxidized LDL is a heterogeneous population of LDL particles which have gone through a process called oxidative modification of both the lipid and protein components. This process includes lipid peroxidation of polyunsaturated fatty acids contained in phospholipids and cholesteryl esters, oxidative modification of cholesterol molecules, and massive structural change of apoB-100 by fragmentation, cross-linking, and covalent binding of reactive aldehydes (Esterbauer et al., 1992; Heinecke, 1997).

The extent of oxidative modification is variable along a continuum from minimally modified LDL (mmLDL), which still retains partial recognition by the LDL receptor, to extensively oxidized LDL which is no longer bound by the classical LDL receptor but is avidly bound by scavenger receptors expressed on macrophages and vascular cells (Itabe & Takano, 2000).

This structural change fundamentally changes the biological behavior of the LDL, and it turns the LDL from a physiologically required cholesterol carrier into a highly pro-inflammatory, cytotoxic and immunogenic particle that actively promotes atherogenesis.

2.3. Pathways of LDL Oxidation

LDL oxidation mainly takes place in the subendothelial space of the arterial wall where LDL particles are trapped by the proteoglycans and are exposed to a highly oxidative microenvironment. Multiple overlapping mechanisms are involved in the formation of LDL oxidation:

Enzymatic Oxidation: Several enzymes catalyze LDL oxidation directly, such as lipoxygenases (5-LOX, 12/15-LOX), myeloperoxidase (MPO) and NOX (NAD+ dependent proteinases). These enzymes produce reactive oxygen species (ROS) and reactive nitrogen species (RNS) which result in the formation of lipid hydroperoxides, oxidized phospholipids, and modified apoB-100 (Griendling et al., 2000; Heinecke, 1997).

Metal-Catalyzed Oxidation: Transition metals such as iron (Fe3+) and copper (Cu2+) are responsible for the catalysis of oxidation reactions by Fenton and Haber-Weiss chemistry resulting in the generation of

highly reactive hydroxyl radicals that trigger lipid peroxidation in LDL particles. These metals are available in high concentrations in atherosclerotic lesions, bound to proteins or released from affected cells and accelerate oxidative injury even further (Lamb & Leake, 1994).

Cell-Mediated Oxidation: Vascular endothelial cells, smooth muscle cells, macrophages, and activated neutrophils contribute to the LDL oxidation by the continuous production of superoxide, hydrogen peroxide, nitric oxide, and peroxynitrite. These species interact to form powerful oxidants that propagate LDL modification in the arterial intima (Heinecke, 1997).

Glycoxidation: In hyperglycemic conditions LDL undergoes a non-enzymatic glycation of apoB-100 that makes it more vulnerable to oxidative modification. This combined process is known as glycooxidation and is especially prominent in diabetes mellitus and plays a large role in the accelerated atherosclerosis seen in diabetic patients (Lyons & Jenkins, 1997).

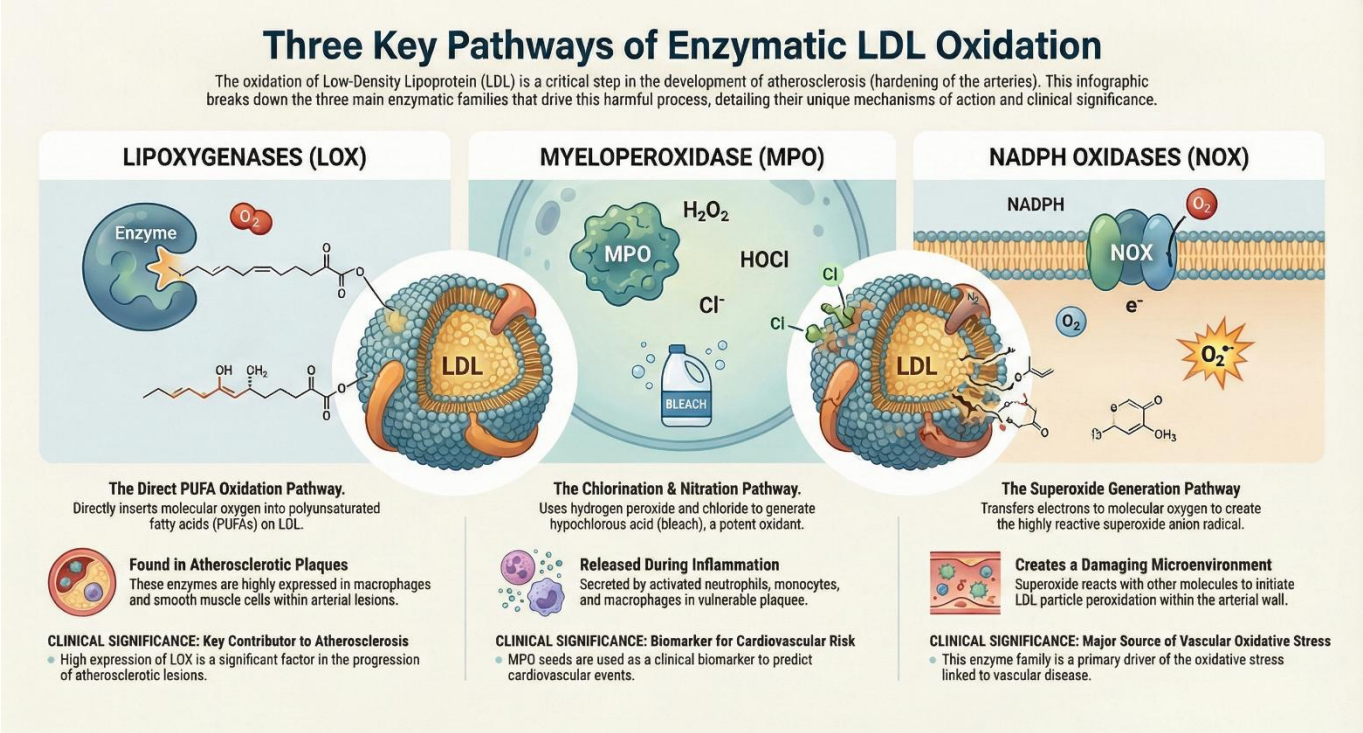

Figure 2. Major enzymatic pathways involved in oxidative modification of low-density lipoprotein

2.4. Molecular Products of Oxidation

Oxidative modification of LDL leads to the production of a complex of biologically active molecules including:

- Lipid hydroperoxides of oxidized phospholipids and cholesteryl esters
- Reactive aldehydes, such as malondialdehyde (MDA), 4-hydroxynonenal (4-HNE) and acrolein
- Oxysterols, such as 7-ketocholesterol, and 7b-hydroxycholesterol
- Structurally modified apoB-100, including fragmentation, cross-linking and aldehyde adduct formation

These products not only disrupt the structural integrity of LDL but are also very powerful signaling molecules that enhance inflammation, endothelial dysfunction and activation of the immune system within the vascular wall (Uchida, 2000; Berliner & Heinecke, 1996).

3. PATHOPHYSIOLOGICAL ROLE OF OXIDIZED LDL IN ATHEROSCLEROSIS

Oxidized low-density lipoprotein (oxLDL) is not only a hallmark of lipid oxidation, but is a key biological mechanism of atherogenesis, directing the activity of endothelial dysfunction, lipid accumulation, vascular inflammation, plaque progression, and plaque destabilization. Its multifaceted actions combine the oxidative stress, activation of the immune system and vascular injury.

3.1. Endothelial Dysfunction

Endothelial dysfunction is one of the first events that can be detected in the development of atherogenesis, and is strongly affected by the presence of oxLDL. Exposure of endothelial cells to oxLDL decreases nitric oxide (NO) availability through increased production of superoxide and activation of the covalently bound oxidases known as the NADPHs, this then affects vasodilation and favors vasoconstriction (Cominacini et al., 2001; Griendling et al., 2000). OxLDL also induces expression of endothelial adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin promoting adhesion and trans-migration of monocytes to the arterial wall (Berliner et al., 1995). In addition, oxLDL affects the integrity of the endothelial barrier, through alterations in tight junction proteins and the increase of vascular permeability, further increasing the retention of lipoproteins in the intima and accelerating plaque formation.

3.2. Foam Cell Formation

Foam cell formation is the histological feature of the early atherosclerotic lesion and is caused mainly by the uptake of oxLDL by macrophages. Unlike native LDL as a result of tightly regulated LDL receptors, in an unregulated manner, oxLDL is internalized in the form of scavenger receptors such as SR-A, CD36 and LOX-1, causing massive intracellular cholesterol accumulation (Brown & Goldstein, 1983; Itabe & Takano, 2000). This uncontrollable lipid uptake converts the macrophages to lipid-laden foam cells, which produce FDA pro-inflammatory cytokines, chemokines and matrix-degrading enzymes that further destabilize the plaque microenvironment.

3.3. Inflammation and Plaque Progression

OxLDL acts as a strong pro-inflammatory stimulus in the wall of the artery. It activates the nuclear factor-kB (NF-kB) signalling pathways stimulating the release of inflammatory mediators such as tumour necrosis factor-a (TNF-a), interleukin-1b (IL-1b) and monocyte chemoattractant protein-1 (MCP-1) that perpetuate leukocyte recruitment and inflammation (Liao et al., 1993). OxLDL also increases smooth muscle cell migration from the media into the intima, and stimulates their proliferation, which is a factor in the formation of the fibrous cap and expansion of the plaque. Over time, chronic inflammation perpetuated by oxLDL leads to progressive lipid core enlargement and plaque vulnerability.

3.4. Plaque Instability and Thrombosis

In advanced atherosclerotic lesions, the oxLDL is directly involved in stabilized plaque instability and thrombotic complications. OxLDL causes the endothelial cells and smooth muscle cells to undergo apoptosis resulting in weakening of the fibrous cap and making it more prone to rupture (Hundal et al., 2001). It also stimulates expression of tissue factor and stimulates platelet activation and inhibits fibrinolytic activity, which together create a pro-thrombotic environment leading to the precipitating factors in acute coronary syndromes and ischemic stroke (Chen et al., 2002). Autopsy and imaging studies have shown widespread deposit of oxLDL in vulnerable plaques in association with macrophages and T-lymphocytes, and thus it has a central role in plaque rupture and sudden cardiovascular death (Naruko et al., 2002).

4. MEASUREMENT OF OXIDIZED LDL

Accurate determination of oxidized low-density lipoprotein (oxLDL) is critical to be able to translate the biological relevance into clinical application. Unlike native lipid parameters, oxLDL is a heterogeneous population of structurally modified particles and hence, its quantification is technically challenging. A variety of analytical approaches have been devised for the identification of various oxidative epitopes and molecular products of LDL oxidation.

4.1. Available Assay Techniques

Immunological Assays: Enzyme-linked immunosorbent assays (ELISA), the most widely used clinical technique for the quantification of oxLDL. These assays make use of monoclonal antibodies against oxidation-specific epitopes of apoB-100 or oxidized phospholipids. Commercial use of the tests (ELI) has acceptable reproducibility, relatively simple operation, and is suitable for large-scale clinical studies. Plasma measurements of levels of oxLDL by enzyme immunoassays (ELAs) in healthy people generally run from 20-50 U/L, and much higher levels are found in patients with cardiovascular diseases and metabolic disorders (Toshima et al., 2000; Holvoet et al., 2008). Chemiluminescence based immunoassays provide greater sensitivity and dynamic range, allowing for subtle changes in the levels of oxLDL in the early stages of disease to be detected.

Biochemical Methods: Traditional biochemical methods include measurements of lipid peroxidation products related to LDL such as thiobarbituric acid-reactive substances (TBARS) and

conjugated dienes. Although these methods give indirect estimates of LDL oxidation, they are not specific for oxLDL and are prone to interference by products of non-lipoprotein lipid peroxidation.

Chromatographic and Mass Spectrometry: High-performance liquid chromatography (HPLC) and liquid chromatography-mass spectrometry (LC-MS) provide the ability to accurately identify and quantify specific oxidized lipid species, oxysterols and oxidized phospholipids. These techniques are useful to obtain detailed molecular information but are expensive, time consuming and are impractical for routine clinical use.

Functional Assays: Functional assays measure the biological activity of oxLDL such as the ability to induce macrophage foam cell formation, endothelial dysfunction or inflammatory cytokines. While very informative in a research setting, these assays are not standardised and scalable for clinical use.

4.2. Strengths and Limitations of Current Methods

Immunoassays provide the best compromise between specificity, feasibility, and clinical usefulness and therefore appear to be the most promising method for routine oxLDL measurement. However, different commercial kits are targeting different oxidation epitopes, resulting in variability in the values reported and a lack of comparability across studies (Tsimikas & Miller, 2011). Advanced analytical methods have better molecular resolution but require special infrastructure and expertise. On the other hand, biochemical assays are low cost, but have poor specificity and limited clinical reliability.

4.3. Pre-analytical Challenges and Standardization

OxLDL is prone to ex vivo oxidation while collecting, handling and storing the samples. Delayed processing, exposure to light, elevated temperature and repeated freeze-thawing can artificially raise oxLDL concentration measured. Therefore, stringent pre-analytical protocols, including quick plasma separation, antioxidant supplementation, storage at [?]80degC and minimizing the number of freeze-thawing steps are necessary for correct measurement (Holvoet, 2004). The lack of any international reference standards and universal calibration materials is still a huge hurdle to large-scale clinical adoption. Establishment of standardized assays, reference range and clinically validated cut-off values is an important priority for future research.

5. CLINICAL IMPLICATIONS OF OXIDIZED LDL

Elevated circulating levels of oxidized low-density lipoprotein (oxLDL) have been consistently linked to a plethora of CVD and metabolic disorders. Unlike conventional lipid parameters, oxLDL is a marker of biological quality of LDL particles, it combines oxidative stress, inflammation and immunological activation into one clinically meaningful parameter.

5.1. Coronary Artery Disease and Acute Coronary Syndromes

Patients with coronary artery disease (CAD) have substantially increased levels of oxLDL compared to normal people. Prospective cohort studies have shown that people in the top quartile of oxLDL having a 2-5 fold higher risk of serious adverse cardiovascular events independent of LDL-C and traditional risk factors (Toshima et al., 2000; Meisinger et al., 2005). In acute coronary syndromes (ACS), such as unstable angina and myocardial infarction, the level of oxLDL is sharply increased as a result of increased oxidative stress and plaque rupture. High levels of oxLDL in the acute phase are predictive of recurrent cardiovascular events and death over long-term follow-up (Johnston et al., 2006; Tsimikas et al., 2003). Imaging studies further show that oxLDL is associated with plaque vulnerability, thin fibrous cap thickness and macrophage infiltration and hence is useful to identify high-risk lesions.

5.2. Diabetes and Metabolic Syndrome

Individuals with type 2 diabetes mellitus exhibit much higher levels of oxLDL even when LDL-C is similar to non-diabetic patients. Each 10 U/L increase in oxLDL is linked to a risk that is about 18% higher of cardiovascular events for diabetic patients (Kondo et al. 2009). Likewise, the level of oxLDL increases progressively as the number of metabolic syndrome components and is an independent predictor of incident diabetes and cardiovascular disease (Holvoet et al., 2008; Shimada et al., 2004). Hyperglycemia, insulin resistance, and visceral adiposity act in a synergistic manner in the process of oxidative modification of LDL, thereby speeding up the vascular damage process.

5.3. Chronic Kidney Disease and Hypertension

Chronic kidney disease (CKD) is associated with severe oxidative stress and impaired antioxidant defense that results in highly raised oxLDL levels that rise with decreasing glomerular filtration rate. OxLDL is found to correlate strongly with carotid intima-

media thickness and cardiovascular mortality in CKD patients, especially in those who are receiving dialysis (Toshima et al., 2000; Pawlak et al., 2004). Hypertensive persons also show significantly higher levels of oxLDL than normotensive controls. OxLDL promotes hypertension by decreasing the bioavailability of endothelial nitric oxide and vascular remodeling while hypertension advances the oxidation of LDL creating a self-perpetuating pathological cycle (Ishigaki et al., 2009).

5.4. NAFLD, Stroke, PAD and Systemic Disorders

In the non-alcoholic fatty liver disease (NAFLD), the increased levels of oxLDL are associated with the severity of the disease and the progression to non-alcoholic steatohepatitis and cirrhosis. OxLDL is also responsible for the high correlation between NAFLD and cardiovascular disease (Yesilova et al., 2005). The levels of oxLDL are predictive of occurrence of ischemic stroke, infarct size, neurologic recovery as well as risk of recurrent stroke (Uno et al., 2005). In the case of peripheral arterial disease (PAD), oxLDL is associated with disease severity, ankle-brachial index, limb ischemia and the risk of amputation (Skora et al., 2006). Beyond the cardiometabolic disorders, however, oxLDL is involved in vascular pathology of autoimmune diseases, obstructive sleep apnea and hypertensive disorders during pregnancy, revealing the wide-ranging systemic nature of this molecule.

6. OxLDL AS A BIOMARKER

The idea of oxidized low-density lipoprotein (oxLDL) as a biomarker of cardiovascular events is a paradigm shift from the traditional approach to assessing lipids to biologically relevant risk assessment. As opposed to classical lipid parameters that define lipoprotein concentration, oxLDL is an indicator of the functional quality and pathogenic potential of LDL particles by combining oxidative stress, inflammation and immune activation.

6.1. Superiority over Conventional Lipids

Multiple large-scale clinical studies demonstrate that oxLDL adds prognostic information over and above standard lipid measures, i.e. LDL-C, total cholesterol, HDL-C, and triglycerides. People with high levels of oxLDL have far greater rates of cardiovascular events even with LDL-C levels at guideline-recommended concentrations (Meisinger et al., 2005; Shimada et al., 2004). OxLDL is a better measure of the atherogenic capacity of circulating LDL since it identifies the proportion of circulating LDL particles which are actively engaged in endothelial injury, foam cell formation, and amplification of inflammation. This mechanistic relevance explains the reason that, in the literature, we often observe that oxLDL is associated more strongly with cardiovascular outcome than LDL-C alone.

6.2. Role in Risk Stratification

OxLDL helps increase cardiovascular risk stratification by identifying high-risk individuals that fall into the low and intermediate risk classes by using traditional scoring system. In prospective cohorts the subjects with the highest levels of oxLDL showed a 2-4 fold higher risk of myocardial infarction and stroke independent of Framingham risk factors (Toshima et al., 2000; Holvoet et al., 2008). Incorporation of oxLDL in existing risk prediction models results in significant improvement of both discrimination, calibration and reclassification of patients at risk for cardiovascular events in the future. This makes it possible to make preventive interventions earlier and more aggressive in susceptible individuals.

6.3. Utility in Treatment Monitoring

OxLDL measurement gives a dynamic tool to monitor therapeutic response. Statin therapy not only lowers LDL-C but also lowers the level of oxLDL through antioxidant and anti-inflammatories. Importantly, the extent of reduction in oxLDL was found to be more closely related to the reduction of cardiovascular events than was the extent of LDL-C reduction (Johnston et al., 2006). Lifestyle interventions, such as dietary modification, physical activity, weight loss and smoking cessation, also result in large reductions in oxLDL, often larger than the proportionate reduction in LDL-C. This makes oxLDL a strong biomarker for measuring compliance and biological response to non-medication based therapies. Emerging therapies focused on oxidative pathways and LDL modification may further increase the clinical relevance of oxLDL as a companion diagnostic for individual cardiovascular management.

7. CONCLUSIONS

Oxidized low-density lipoprotein has become a key mediator in the link between lipid metabolism, oxidative stress, inflammation, and immune activation in pathological processes of atherosclerosis and its cardiometabolic disorders. Unlike native LDL cholesterol, which is primarily a quantitative risk marker, oxLDL is the biologically active and pathogenic form of LDL that is directly involved in promoting endothelial dysfunction, foam cell formation and plaque progression and

destabilization. Accumulating clinical evidence clearly shows that elevated levels of oxLDL predict cardiovascular events, severity of disease, and mortality independently in a wide range of conditions such as coronary artery disease, diabetes mellitus, metabolic syndrome, chronic kidney disease, hypertension and stroke. Advances in analytical methods have made measurement of oxLDL more feasible although there are still challenges associated with assay standardization, pre-analytical variability, and cost which are barriers to routine clinical implementation. Nevertheless, the better mechanistic relevance and prognostic performance of oxLDL than conventional lipid parameters demonstrate the considerable potential of oxLDL for better cardiovascular risk stratification and personalised therapeutic interventions. Future studies should focus on the development of standardized, cost-effective assays, establishment of universally accepted reference ranges, and combination of oxLDL in existing risk prediction models. With the further development of scientific and technologies, the evaluation of oxLDL may form an intrinsic part of next-generation strategies for the prevention and management of cardiovascular disease.

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