Oxidation Of LDL :Role In Atherosclerosis

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Abstract

Atherogenesis is a multifaceted condition which has a complicated pathogenesis that is still being unraveled. Both systemic and local inflammation have been implicated in the development of atherosclerosis. Oxidative stress, or oxidation of LDL, is considered a marker of inflammation. This brief review focuses on the role of oxidation of LDL in development of atherosclerosis.

INTRODUCTION

Atherosclerosis is now thought to be a chronic low grade vascular inflammation. The ongoing search for markers of inflammation [(1)], which can be used as predictors of cardiovascular (CV) risk, has yielded many promising candidates.

These include C- reactive protein (CRP), cytokines such as interleukin -6 (IL-6), interleukin -18 and tumor necrosis factor –□ (TNF – □), markers of hemostasis such as fibrinogen, plaminogen activator inhibitor -1 (PAI-1), D-dimer and von Willebrand factor (vWF), as well as total white blood cell count, especially neutrophil count.

Recently however, lipid –related biomarkers have been used as markers or surrogates for atherosclerosis. These include myeloperoxidase , a leukocyte –derived enzyme, lipoprotein –associated phospholisase A2, which is produced by monocytes, macrophages ,T lymphocytes, liver and mast cells, and adiponectin, an anti –atherogenic marker made in white adipose tissue [(1)].

One lipid –related marker, however, which, perhaps, has not got the attention it deserves, is oxidized LDL. This review focuses on the role of oxidized LDL (ox LDL) in the pathogenesis and risk stratification of atherogenesis.

FUNCTIONS OF OXLDL

LDL is modified by oxidation to produce an oxidized form of LDL (oxLDL) which promotes atherogenesis. This mechanism is known as the oxidative modification hypothesis[(1)] .

Ox LDL acts by various mechanisms mediated through its multiple biological effects. These are summarized in Table 1.

Figure 1

Table 1: Proatherogenic Properties Of Oxidized LDL

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Biological effect	Possible mechanism
Free cell formation	Direct uptake of cholesterol by scavenger receptor as well as inhibition of their export from macrophages
Chemoattraction of monocytes, T lymphocytes	Increased expression of MCP-1 and direct chemotactic effect
Macrophage trapping within the intima impaired vascular function (vasoconstrictor effect)	Inhibition of motility of macrophages
Adhesion of monocytes to endothelium	Increased expression adhesion molecules
Plaque rupture	Enhanced formation of matrix metalloproteinases
Cell proliferation	Induction of growth factors
Thrombogenesis	Promotion of platelet aggregation and increased tissue factor activity
Increased cellular death	Induction of Fas-mediated apoptosis
Induction of proiinflammatory genes	Activation of nuclear factor-kappa B
Increased antigenicity	Induction of autoantibody (IgG) formation

OxLDL promotes foam cell formation, and attracts /traps/adheres monocytes, lymphocytes and macrophages, while causing vasoconstriction, and cell proliferation. These effects, coupled with increased apoptosis and plaque rupture, induction of pro-inflammatory genes, and antigenicity, lead to atherogenesis.

Ox LDL promotes the transition from stable plaques to unstable plaques. This is done by stimulating matrix metalloproteinase (MMP) -1 and MMP -3 in vascular endothelial cells as well as in monocyte –derived macrophages [(2,3)]. OxLDL upregulates the expression of MMP-1 and MMP -3 in human coronary endothelial cells

through the endothelial receptor LOX-1 [4]. It also induces endothelial injury by causing a prolinflammatory reaction through the CD 40/CD 40 L signaling pathway.[5]

CLINICAL STUDIES: PRESENCE OF ATHEROSCLEROSIS

Cross sectional studies have shown that patients of stable patients of stable coronary heart disease and acute coronary syndrome have higher plasma levels of of ox LDL than healthy controls [6,7]. Concentration of oxLDL is higher in patients with severe acute coronary syndrome (myocardial infarction) than in those with angina [8]. ox LDL has also been shown to correlate with the extent of coronary heart disease in heart transplant recipients [9].

Studies have also demonstrated an association of ox LDL levels with subclinical atherosclerosis in asymptomatic general population [10] and in members of familial combined hyperlipidemia families [11].

Thus, ox LDL may be a useful marker, more sensitive than the Global Risk Assessment Score (GRAS) for identifying coronary artery disease.[12]

CLINICAL STUDIES: PROGRESSION OF ATHEROSCLEROSIS

Authors have also performed prospective studies to assess the effect of ox LDL on progression of atherosclerosis.

In a Finnish study, titre of antibodies to ox LDL was found to be an independent predictor for the progression of carotid atherosclerosis, in 30 male cases followed up for 2 years [13].

Another study lasting 2.6 years found that ox LDL /plasma cholesterol ratio was higher in cases of acute myocardial infarction than in controls, and also higher than in other cardiac events [14]. The results suggest that high plasma ox LDL /total cholesterol ratio may be utilized as a method of risk stratification.

A part of two population – based MONICA/KORA Augsburg surveys, a nested case control study investigated the relationship between plasma ox LDL and risk of future CHD over a mean duration of 5.6 years in 88 cases and 258 controls [15] Plasma ox LDL was found to be the strongest predictor of coronary heart disease events as compared to conventional lipid profile. Plasma ox LDL also improved the prediction of cardiac events when added to other risk factors.

DISCUSSION

Oxidative stress and low grade inflammation are well known pathogenesis factors in the development of atherosclerosis. Oxidation of LDL leads to atherosclerosis by multiple mechanisms.

Both cross sectional studies and prospective studies have demonstrated the importance of ox LDL concentrations as a means of diagnosing the presence of coronary heart disease, as well as predicting future cardiac events.

Oxidation of LDL, therefore, becomes not only a pathogenesis factor, but also a potential diagnostic and prognostic tool which can be used for risk stratification.

References

1. Khuseyinova N, Koeng W. C reactive Protein and other inflammatory markers in cardiovascular disease, In :Davidson MH, Toth PP, Maki KC. Contemporary Cardiology :Therapeutic Lipidiology. Humana, Totowa, NJ, 2007; 69-112.
2. Huang Y, Mironova M, Lopes –Virella MF. Oxidized LDL stimulates matrix metalloproteinase -1 expression in human vascular endothelial cells. Arterioscler Thromb Vasc Biol 1999; 19:2640 -2467.
3. Xu XP, Meisel SR, Ong JM, Kaul S, Cerceck B, Shah PK. Oxidized low –density lipoprotein regulates matrix metalloproteinase -9 and its tissue inhibitor in human monocyte –derived macrophages. Circulation 1999;99:993-998.
4. Li D, Liu L, Chen H,Sawamura T, Ranganathan S,Mehta Jl. LOX -1 mediates oxidized low – density lipoprotein induced expression of matrix metalloproteinases in human coronary artery endothelial cells. Circulation 2003;107:612 -617.
5. Li D, Liu L, Chen H, Sawamura T, Ranganathan S,Mehta Jl.LOX -1 mediates oxidized LDL endothelial receptor, induces CD40/CD40L signaling in human coronary artery endothelial cells. Arterioscler Thromb Vasc Biol 2003; 23:816 -821.
6. Holvoer P,Vanhaeck J, Janssens S, Vande Werf ,Collen D. Oxidized LDL and malondialdehyde modified LDL in patients with acute coronary syndromes and stable coronary artery disease. Circulation 1998;98 1487-1494.
7. Toshima S, Hasegawa A, Kurabayashi M,Itabe H, Takano T, Sungano J,Shimamura K,Kimura J,Michishita I, Suzuki T,Nagai R .Circulating oxidized low density lipoprotein levels. A biochemical risk marker for coronary heart disease. Arterioscler Thromb Vasc Biol 2000;20:2243-2247.
8. Ehara S,Ueda M, Naruko T, Haze K, Itoh A, Otsuka M,Koamtsu R,Matsuo T, Itabe H,Takano T,Tsukamoto Y,Yoshiyama M, Takeuchi K. Yoshikawa J, Becker AE. Elevated levels of oxidized low density lipoprotein show a positive relationship with the severity of acute coronary syndromes. Circulation 2001:103:1955-1960.
9. Holvoet P, Mertens A, Vehamme P, Bogaerts K, Beyens G,Verhaege R,Collen D, Muls E, Van De Werf F. Circulating oxidized LDL is useful marker for identifying patients with coronary artery disease. Arterioscler Thromb Vasc Biol 2001;21:844-848.
10. Holvoet P, Stassen JM, Van Cleemput J, Collen D,Vanhaecke J. Oxidized low density lipoproteins in patients with transplant –associated coronary artery disease. Arterioscler Thromb Vasc Biol 1998;18:100-107.
11. Liu ML, Yitalo K,Salonen R, Salonen JT, Taskinen MR. Circulating oxidized low –density lipoprotein and its issue

association with carotid intima –media thickness in asymptomatic members of familial combined hyperlipidemia families.Arterioscler Thromb Vasc Biol 2004;24:1492-1497.
12. Hulthe J,Fagerberg B. Circulating oxidized LDL is associated with subclinical atherosclerosis development and inflammatory cytokines (AIR study). Arterioscler Thromb Vasc Biol 2002; 22:1162-1167.
13. Salonen JT, Yia –Herttula S, Yamamoto R, Butler S,Korpela H, Salonen R, Nyyssonen K, Palinski W, Wiztum JL. Autoantibody against oxidised LDL and progression of carotid atherosclerosis. Lancet 1992;339:883-887.
14. Nordin Fredrikson G, Nilsson J. Plasma oxidized LDL: a predictor for acute myocardial infarction ? J Intern Med 2003;253:425-429.
15. Meisinger C, Baumert J, Khuseyinova N, Loewel H,Koenig W. 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 2005;112:651 -657.

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