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Perspective

Association between circulating oxidized low-density lipoprotein and atherosclerotic cardiovascular disease

Shen Gao, Jing Liu*

Department of Epidemiology, Beijing An Zhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing 100029, China

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Abstract

Atherosclerosis is a chronic, progressive disease which eventually leads to coronary heart disease (CHD), ischemic stroke and other atherosclerotic cardiovascular disease (ASCVD). Numerous studies have demonstrated an atherogenic role of oxidized low-density lipoprotein (ox-LDL) in the progression of ASCVD. This article briefly reviews the atherogenic mechanism of ox-LDL, the methods of measuring ox-LDL in the circulation, effect of medical therapy and life-style modification on ox-LDL level, and the association between circulating ox-LDL and atherosclerosis, including clinical ASCVD events and subclinical atherosclerosis, in observational studies.

Keywords: Oxidized low density lipoprotein; Atherosclerosis; Cardiovascular disease; Subclinical atherosclerosis; Review

Introduction

Atherosclerosis is a chronic, progressive pathological process that involves vascular endothelial injury, lipid infiltration, macrophage activation, vascular smooth muscle cell proliferation, thrombosis, and inflammatory immune response, eventually leading to coronary heart disease (CHD), ischemic stroke, and other atherosclerotic cardiovascular diseases (ASCVDs). Among the pathogenesis of atherosclerosis, lipid deposition has been most extensively studied. It is well known that low-density lipoprotein (LDL), the major carrier of cholesterol, accumulates in the intima and stimulates the expression of adhesion molecules and chemoattractants on the surface of endothelial cells, activating the adhesion of circulating monocytes to the endothelium. After adhesion, the monocytes migrate into the intima, differentiate into macrophages, internalize and accumulate the cholesterol in cells, and eventually become foam cells that are characteristic of atherosclerosis.[1] A study by Goldstein and Brown demonstrated that LDL receptors (LDL-Rs), which identify and internalize native LDL, played a vital role in the cellular metabolism of cholesterol.[2] However,

* Corresponding author. Tel.: +86 010 64456710.
E-mail address: jingliu@ccmu.edu.cn (J. Liu).

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it was found that cholesterol accumulation also occurred in patients with familial hypercholesterolemia whose LDL-Rs were genetically impaired.[2] Moreover, an *in vitro* experiment revealed that when incubated in high concentrations of native low-density lipoprotein cholesterol (LDL-C), macrophages did not convert to foam cells, which suggested that LDL-Rs expressed on macrophages may be down regulated in an environment of high LDL-C concentration.[3] These observations implied that foam cells can be formed through the uptake of cholesterol by receptors other than LDL-Rs.

In 1984, Steinbrecher et al[4] found that incubation of LDL with endothelium cells or smooth muscle cells could convert LDL into a modified form that is recognized by a novel receptor, increasing the rate of cholesterol uptake by macrophages. Oxidized LDL (ox-LDL) is the major modified form of native LDL because LDL particles are extremely sensitive to oxidative damage: each native LDL particle contains approximately 700 molecules of phospholipids, 600 molecules of free cholesterol, 1600 molecules of cholesterol ester, 185 molecules of triglycerides, and an apolipoprotein B-100 (apoB-100) protein with 4536 amino acids.[1] Both the lipids and the proteins can be oxidized. The oxidation of native LDL is a complex process that can be divided into three stages. During the initial stage, known as the lag phase, endogenous antioxidants such as vitamin E are consumed. During the proliferation phase, polyunsaturated fatty acids (PUFAs) in the lipids of the LDL particles can be rapidly oxidized to fatty acid fragments, oxidized phospholipids (ox-PL), and oxygen free radicals. During the decomposition stage, fatty acid fragments are converted to aldehyde, which can interact with the lysine residue of apoB-100 to form new epitopes. Importantly, these new epitopes inhibit the ability of LDL to bind to the LDL-Rs expressed on macrophages.[5]

The most important atherogenic effect of ox-LDL is that this modification of native LDL shifts the recognition and internalization of the lipoprotein from the LDL-Rs to novel receptors termed as scavenger receptors (SRs).[6] SRs are the cell surface receptors expressed on macrophages and other vascular cells that recognize and internalize ox-LDL rather than native LDL; these include SR-A, cluster differentiating 36 (CD36), SR-BI, cluster differentiating 68 (CD68), scavenger receptor for phosphatidylserine and oxidized lipoprotein (SR-PSOX), and lectin-like oxidized LDL receptor-1 (LOX-1), among others.[7] Among these, SR-A binding to oxidized lysine residue of apoB-100 and CD36 binding to ox-PL are responsible for most of the ox-LDL uptake by macrophages *in vitro*.[8,9] The most important point is that contrary to LDL-R, SRs are not down regulated by elevated levels of intracellular cholesterol (Fig. 1).[4] Uptake of ox-LDL by macrophages through SRs leads to remarkable cholesterol accumulation, converting macrophages to foam cells and promoting the development of atherosclerotic lesions.[10]

To date, three monoclonal antibodies have been developed for determination of circulating ox-LDL by enzyme linked immunosorbent assay (ELISA): ox-LDL-4E6,[11] ox-LDL-E06,[12] and ox-LDL-DLH3 antibody.[13] Ox-LDL-4E6 was the first to be established and widely used. It can directly recognize the epitope that is generated after modification of lysine residues in apoB-100 by aldehydes, while DLH3 and E06 antibody recognize oxidized phosphatidylcholine (ox-PC) generated after modification of phospholipids containing PUFAs.[14] However, ox-LDL with fewer than 60 lysine modifications cannot be detected using the ox-LDL-4E6 antibody.[14]

Association between circulating ox-LDL and atherosclerosis

We searched PubMed and the Cochrane Library for observational epidemiological studies on associations between circulating ox-LDL and atherosclerosis. The key words “oxidized low density lipoprotein”, “cardiovascular disease,” and “atherosclerosis” were used to build our search strategy. Thus far, 21 case–control or prospective cohort studies[15–35] have reported the association between circulating ox-LDL and atherosclerosis in PubMed and Cochrane Library, including 19 studies[15–19,21–26,28–35] on clinical ASCVD events and three studies[16,20,27] on subclinical atherosclerosis (one study reported the data for both clinical and subclinical atherosclerosis[16]).

Association between circulating ox-LDL and clinical ASCVD events

Among six hospital-based cohort studies,[15,18,23,28,32,33] two studies found that after adjusting for LDL-C, increased level of circulating ox-LDL was significantly associated with the risk of clinical ASCVD events; one study reported that among 1371 patients with acute myocardial infarction (AMI), the hazard ratio (*HR*) of death due to cardiovascular diseases (CVD), or the occurrence of unstable angina pectoris (UAP) or myocardial infarction (MI) at the 6-month follow-up was 1.66 (95% confidence interval (*CI*): 1.07–2.57) in patients with the highest tertile of circulating ox-LDL, compared with those with the lowest tertile.[23] Another study showed that in 246 patients with more than 50%