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Editorial

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An Intriguing and Important Concept Relevant to Oxidized Low-Density Lipoprotein and Atherogenesis is Still Problematic for its Contribution to the Better Understanding of Clinical Atherosclerosis

Hiroshi Yoshida

Department of Laboratory Medicine, Jikei University Kashiwa Hospital, Chiba, Japan

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Oxidization of low-density lipoprotein (LDL) is thought to be a risk factor of atherosclerosis. Oxidized LDLs are taken up by macrophages and accelerate the formation of foam cells, indicative of an underlying finding of initial atherosclerotic lesions[1, 2]. Unlike LDLs, oxidized LDLs can be internalized by scavenger receptors, which are not downregulated by elevated cellular cholesterol levels in macrophages[3, 4]. In addition to contributing to foam cell formation in vessel walls, oxidized LDL has been found to play roles in pro-atherogenic effects, including endothelial dysfunction, vascular cell proliferation, inflammation, immune response, and thrombogenesis, through some scavenger receptors (Lox-1 and CD36)[5-7].

Gao *et al.* have demonstrated that serum oxidized LDL levels are associated with a 10-year progression risk of subclinical atherosclerosis defined as carotid atherosclerotic plaque, which is independent of LDL cholesterol level, total particle number and particle size of LDL in a population-based cohort study (n=804)[8]. Previously, Bruneck study also showed that oxidized phospholipid (PL)/apolipoprotein B (apo B) was associated with the presence and progression of carotid and femoral atherosclerosis independent of LDL cholesterol levels. However, oxidized LDL in the present study is different from oxidized PL/apo B, although they are indicative of oxidatively modified LDL as follows. First, the used antibody and its binding site are different between these oxidized LDL-related biomarkers and malondialdehyde LDL (MDA–LDL), approved for clinical use in Japan, is also different from these biomarkers[10-12]. Second, the levels of MDA–LDL and the present study's oxidized LDLs decrease in varying degrees with statin therapy, but oxidized PL/ apo B level is conversely increased[11-13]. Third, oxidized LDLs in the present study are insignificantly correlated with lipoprotein(a) [Lp(a)], but oxidized PL/apo B is markedly correlated with Lp(a), which is a carrier of oxidized PL[9, 14]. For comparison, MDA–LDL is not correlated with Lp(a). Nevertheless, both markers of oxidatively modified LDL (the present study's oxidized LDL and oxidized PL/ apo B) were similarly associated with carotid atherosclerosis progression.

Despite intensive research on LDL oxidative modification relevant to atherogenesis, many questions remain to be delineated even now. As mentioned as a study limitation by Gao *et al.*, whether circulating oxidized LDLs reflect the atherogenic actions of oxidized LDLs present in the atherosclerotic lesions has not been fully understood yet. Oxidized LDLs in the present study are different from oxidized PL/apo B reported by Tsimikas *et al.*[9, 10], and thus, standardization of evaluating methods for oxidized LDL may be required. Otherwise, these issues and differences may still leave difficulty in the comparison of oxidized LDL-related clinical studies. In addition, clinical trials on antioxidants including vitamin E and beta-carotene failed to show that they prevent cardiovascular diseases[2]. To answer all questions, further studies at a basic level and in clinical settings will provide a hopeful framework for revisiting the lipoprotein oxidation hypothesis related to atherosclerotic cardiovascular diseases.

Conflicts of Interests

None.

Address for correspondence: Hiroshi Yoshida, Department of Laboratory Medicine, Jikei University Kashiwa Hospital, 163-1 Kashiwashita, Kashiwa, Chiba 277-8567, Japan E-mail: hyoshida@jikei.ac.jp; hyoshida3785@gmail.com

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