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Editorial

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To be Functional, or not to be Low in Cholesterol, that is the Clinical Concern when Evaluating Anti-Atherosclerotic Actions of High-Density Lipoproteins

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Many epidemiologic studies have reported an inverse relationship between coronary heart disease (CHD) events and high-density lipoprotein (HDL)-cholesterol (HDL-C) levels[1]. However, the Copenhagen studies (City Heart Study and General Population Study) demonstrated U-shaped associations between HDL-C levels and cardiovascular mortality, and the Canadian CANHEART study also showed similar U-shaped associations between them[2, 3]. Namely, not only low HDL-C but also extremely high HDL-C may be associated with high CHD mortality.

The HDL mediates reverse cholesterol transport (RCT), acts as an antioxidant, suppresses inflammation, and improves endothelial function[4]. In RCT, accumulated cholesterol is transported from peripheral tissues back to the liver, and the RCT process requires HDL or apolipoprotein A-1 [4-6]. The first step of RCT is cholesterol efflux from macrophages; this is thought to be the most important function of HDL or apolipoprotein A-1 [4-6]. Indeed, studies have reported that CHD events show a stronger inverse correlation with cholesterol efflux capacity (CEC) than with HDL-C levels[7-9]. A retrospective study suggested that CEC is a useful prognostic surrogate for the secondary prevention of CHD[10].

The HDL has been reported to have a chameleon-like nature[11]. In the absence of an acute phase response or systemic inflammation, the HDL proteome constitutes anti-inflammatory particles, but in the presence of these pathological conditions, the HDL proteome is re-modeled to constitute particles that enhance the inflammatory response. Namely, under pathological conditions, including inflammation, HDL loses its protective properties against atherosclerosis, resulting in the re-modeling from functional to dysfunctional HDL[11, 12]. In addition to these proteomic changes in HDL, another possible mechanism for dysfunctional HDL re-modeling is the oxidative modification of HDL.

Therefore, evaluating HDL dysfunctionality could lead to better understanding and a new diagnostic approach to atherosclerotic disease risk in clinical practice. Recently, Okada *et al.* have demonstrated a novel sandwich enzyme-linked immunosorbent assay for oxidized HDL with antibodies against apolipoprotein A-1 and the epitope composed of oxidized products of phosphatidylcholine[13]. They also showed that serum oxidized HDL levels were substantially high in patients with cholesterol ester transfer protein deficiency and that patients with familial hypercholesterolemia, when treated with probucol, showed low levels of serum oxidized HDL.

The present new method might contribute to a useful and convenient strategy to assess HDL functionality. In the component of HDL, apolipoprotein A1 is prone to be oxidized, but phospholipids, a main lipid of HDL, are also oxidized. HDL phospholipids can be oxidized *in vivo*, leading to the formation of biologically active oxidized compounds[14, 15].

Conflicts of Interest

H. Yoshida received honoraria for speaking activities from Bayer, Denka, Kowa, and Takeda.

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