Editorial

Very High Levels of High-Density Lipoprotein Cholesterol and Cardiovascular Events in Japanese Population

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See article vol. 23: 800-809

A reduction in plasma high-density lipoprotein cholesterol (HDL-C) level accelerated the frequency of cardiovascular (CV) event, which was strongly enhanced in combination with an increased low-density lipoprotein cholesterol (LDL-C) level in the Framingham study populations[1]. The Japan Atherosclerosis Society Guidelines for the Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases 2012 (JAS Guidelines 2012) defined an HDL-C level of <40 mg/dL as hypo-HDL-cholesterolemia, which is correlated with an increased CV event rate based on the results of many clinical investigations[2]. Because the morbidity of CV event negatively correlated with HDL-C level, it is believed that subjects with very high HDL-C level (>80 mg/dL) had a lower incidence of CV event or CV death. Although subjects with very high HDL-C level are frequently observed in Japan, little is known about the atherogenicity in patients with very high HDL-C level in Japanese dwellers. In the current study, Hirata *et al*. investigated the relationship between serum HDL categories including the very high HDL-C level (>80 mg/dL) and all-cause/CV mortality for a long observational period from 10 to 20 years using the national cohort, surveillance study of "NIPPON DATA90"[3]. HDL-C level was not associated with all-cause mortality or stroke. As we suspected, the risk for coronary heart disease (CHD) in the high HDL-C group (1.56−2.06 mmol/L; 60−79 mg/dL) was lower than that in the reference group (1.04−1.55 mmol/L; 40−59 mg/dL) and hazard ratio was 0.51 in men, 0.33 in women, and 0.41 in the combination of men and women. However, the very high HDL-C group (>2.07 mmol/L; >80 mg/dL) did not show significant association the CHD, which significantly revealed that the very high HDL-C levels were not always anti-atherogenic status in Japanese populations.

HDL is a main lipoprotein particle working for an anti-atherogenic, reverse cholesterol transport (RCT) system. HDL and its major protein, apolipoprotein (apo) AI, take up free cholesterol from foam cells via ABCG1 and ABCA1 in the atherosclerotic plaque. Cholesteryl ester is transferred to VLDL, IDL, and LDL by plasma cholesterol esterified transfer protein (CETP) in exchange for triglyceride. As a result, excessive cholesterol in foam cells is delivered to the liver by the hepatic uptake of IDL and LDL. If the CETP activity was reduced, it may lead to a decreased function of RCT system and the progression of atherosclerotic plaque. Formerly, we reported that the morbidity of CHD increased in patients with genetic mutation of CETP despite increased HDL levels epidemiologically[4, 5]. Recent trials of CETP inhibitors demonstrated a negative effect on the prevention of CV events and carotid atherosclerosis[6, 7]. As shown in Framingham Heart Study[8] and Ludwigshafen Risk and Cardiovascular Health Study[9], the plasma CETP activity/mass was negatively correlated with the incidence of CHD. Furthermore, the cholesterol efflux capacity from macrophage has a strong inverse association with CHD independent of serum HDL-C levels[10] and is improved by the physical exercise in patients with acute coronary syndrome[11]. Besides the cholesterol efflux or RCT, HDL has various capabilities such as anti-inflammatory, anti-oxidation, and anti-thrombotic functions[12], the impaired functions of HDL may lead to the development of CV events. Recent findings showed that the oxidized HDL particle was increased in patients with chronic kidney disease who had a high frequency of CV events[13].

In conclusion, the current study conducted by

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Received: April 14, 2016
Accepted for publication: April 15, 2016

Hirata *et al*. is valuable as it explicitly demonstrates that the status of very high HDL-C level (>80 mg/dL) is not always anti-atherogenic. The importance of evaluating HDL function may be enhanced for preventing CHD event, and we must establish easy and suitable method for evaluating HDL function besides the conventional measurement of HDL-C level for the future.

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