Is Low-Density Lipoprotein/High-Density Lipoprotein (LDL/HDL)-Cholesterol Ratio a More Important Predictor of Vulnerable Plaque in Coronary Artery Disease Than LDL- or HDL-Cholesterol?

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The plasma lipid profile of both low-density lipoprotein (LDL)- and high-density lipoprotein (HDL)-cholesterol is strongly related to atherosclerotic diseases including coronary heart disease. Both high LDL- and low HDL-cholesterol are major risk factors of coronary heart disease, which has been demonstrated by many epidemiological investigations. Thus high LDL/HDL-cholesterol ratio must be strongly related to atherosclerotic diseases, but as yet there have been no direct studies on the relationship between plasma lipid profile such as LDL/HDL-cholesterol ratio and lipid-rich plaques in atherosclerotic coronary arteries.

In this issue of the Journal, Kimura et al found that the LDL-cholesterol/HDL-cholesterol ratio might be a positive predictor of lipid-rich coronary plaque in ischemic heart disease patients. They studied not only plaque volume but also the lipid pool area of atherosclerotic coronary arteries in chronic coronary artery disease (CCAD) and acute coronary syndrome (ACS) using integrated backscatter (IB) intravascular ultrasound (IVUS).

Recently new imaging modalities, such as IVUS, angiography, and optical coherence tomography (OCT), have undergone remarkable developments. These imaging modalities could enable the identification of not only plaque volume but also plaque characteristics in coronary arteries of ischemic heart disease patients including those with CCAD and ACS. IB-IVUS enables identification of each tissue component, such as calcification, lipids, and fibrosis, based on IB values. Another identification method for tissue characterization of plaque images is virtual histology (VH)-IVUS. VH-IVUS allows for a more detailed plaque characterization according to the amount and location of fibrous, fibrofatty, dense calcium, and necrotic core compared to IB-IVUS. Okubo et al directly compared those technologies based on histology acquired from 46 coronary arteries from 25 cadavers. They reported that in the quantitative comparison the overall agreement between histology and IB-IVUS diagnoses was higher than that of IVUS-VH diagnoses, so IB-IVUS provided a higher diagnostic accuracy than VH-IVUS.

Ko et al assessed the relationship between vessel size and lipid content of coronary plaques using IB-IVUS. They evaluated the plaque burden and lipid content of target lesions of coronary arteries in CCAD and ACS patients with IVUS and IB-IVUS, and found that ACS, positive remodeling, and larger plaque burden were associated with higher lipid content of coronary plaque. They reported that the lipid content of plaque was not significantly related with plasma lipid profile such as LDL-cholesterol but they did not mention the LDL/HDL-cholesterol ratio. The findings that plaque in larger-sized vessels had a larger lipid pool area and that the percentage of lipid pool area in the ACS patients was significantly higher than in CCAD patients on IB-IVUS were identical with that of the Kimura et al study.

Cardiovascular mortality and morbidity in patients with hypercholesterolemia without CAD can be significantly decreased by lipid-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins). Aggressive lipid lowering with high-dose statin significantly reduced progression of coronary atherosclerosis compared with moderate lipid-lowering therapy. Furthermore, the ASTEROID trial demonstrated a significant reduction in coronary plaque volume using 40 mg rosuvastatin for 24 months, with a final average LDL-cholesterol of 60.8 mg/dl. In the Japanese Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome (JAPAN-ACS) Study, intensive statin therapy induced significant regression of coronary plaque volume in the Japanese patients with ACS. Furthermore, Takayama et al reported that intensive lipid lowering using rosuvastatin produced significant regression of plaque volume in Japanese patients with stable CAD in a COSMOS trial. These trials suggested that LDL-cholesterol was strongly related to plaque volume and lipid content of plaque burden in CCAD and ACS patients, while those trials did not assess the relationship between coronary plaque and HDL-cholesterol or LDL/HDL-cholesterol ratio. The ASTEROID trial found that 40 mg rosuvastatin increased HDL-cholesterol by 14.7%.

Kimura et al demonstrated that LDL/HDL ratio was an independent predictor for lipid pool/non-lipid pool area ratio in both ACS and stable CAD. This finding indicates that LDL/HDL-cholesterol ratio might be a more important risk factor than LDL-cholesterol itself in CAD patients, and should be investigated further.
The Japan Atherosclerosis Society published guidelines for diagnosis and prevention of atherosclerotic cardiovascular diseases in Japanese patients in 2007. In this guideline lipid management goals were defined on different risk categories for patients diagnosed as having dyslipidemia. For secondary prevention, an intensive LDL-cholesterol goal (<100 mg/dl) is proposed, and immediate initiation of drug therapy should be considered. For primary prevention, to prevent CAD in the future, patients are categorized into low-risk, intermediate-risk, or high-risk groups depending on the number of risk factors other than LDL-cholesterol. In the case of low risk the management goal for LDL-cholesterol is <160 mg/dl. For intermediate risk this is <140 mg/dl, and in the high-risk group it is <120 mg/dl. Although low HDL-cholesterol (<40 mg/dl) is described as one risk factor of atherosclerotic cardiovascular diseases, there was no information on LDL/HDL-cholesterol ratio.

What, then, is the therapeutic target value of LDL/HDL-cholesterol ratio? Nicholls et al have demonstrated that LDL/HDL-cholesterol ratio >2.0 in spite of statin usage was related to plaque progression (percent plaque volume increased by 1.2%), while that <1.5 was significantly related to plaque regression (percent plaque volume decreased by 0.3%). Studies of large numbers of patients or meta-analysis of lipid-lowering trial for atherosclerotic heart disease are needed to determine the clinical significance of LDL/HDL-cholesterol ratio in atherosclerotic cardiovascular diseases in order to provide information for the clinical guidelines.

References