The New Strategy for Modulating Dyslipidemia: Consideration from Updated Understanding on High-Density Lipoprotein

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ABSTRACT With further researches on blood lipids and atherosclerosis, especially after the conception of "residual cardiovascular risk", high-density lipoprotein cholesterol (HDL-C) becomes a new therapeutic target against atherosclerosis. However, the failure of ILLUMINATE study that was targeted at raising HDL-C level disappointed cardiologists all over the world, which indicates the limitation of HDL-C concentration in representing HDL function. The updated understanding of HDL from "quantity" to "quality" brings a new cut-in point for Integrative Chinese and Western medicine in preventing and treating dyslipidemia and atherosclerosis. In addition to highlighting statins in directly intervening low-density lipoprotein cholesterol, we should make full use of the superiority of Chinese medicine in overall regulation and individualized treatment to promote the self-healing capacity of the patients, which further regulates abnormality of both concentration and function of the whole blood lipid family to equilibrium. This new strategy for modulating dyslipidemia with mutual complement of advantages from Western and Chinese medicines will no doubt play an important role in future therapies.

KEYWORDS atherosclerosis, high-density lipoprotein, dyslipidemia, integrative medicine

For over 100 years, people have fully realized that dyslipidemia contributed greatly to the formation and progression of atherosclerosis. It also plays an important role in leading cardiovascular events. Modulating dyslipidemia actively is very crucial to prevent atherosclerosis and reduce the morbidity and mortality of cardiovascular diseases. With in-depth researches on lipid and atherosclerosis, high-density lipoprotein cholesterol (HDL-C) is paid more attention and great expectation, especially when the lipid studies targeting at low-density lipoprotein cholesterol (LDL-C) turned into its plateau phase. However, the failure of ILLUMINATE study targeting at raising HDL-C level disappointed cardiologists all over the world and raised doubts on regarding HDL-C as a new antiatherogenic target. Under these circumstances, it has undoubtedly important significance for us to reevaluate traditional understanding and future intervention strategy on HDL-C along the track of lipid studies.

LDL-C Reduction and Residual Cardiovascular Risk: the Discrepancy between Ideality and Reality

In the initial stage of lipid researches, people did not know which component, cholesterol or triglyceride, had more impact on atherosclerosis. When elevated cholesterol was defined as a risk factor of atherosclerosis, reducing LDL-C level to the normal range became the dominant goal of lipid-lowering therapy. A large number of epidemiological, experimental, and clinical investigations identified that increased cholesterol, especially LDL-C, was the most important risk factor for coronary heart disease (CHD), and decreasing LDL-C level actively could significantly reduce the morbidity and mortality of CHD. Along with continuous upgrading of statins remedies and the generally accepted conception of aggressive lipid-lowering therapy, LDL-C level is reduced to the lower limit of the normal range (<1.8 mmol/L). Nevertheless, statins could only reduce events by 25%–40%; there are still 60%–75% events that cannot be prevented by decreasing LDL-C level alone. In the ENHANCE trial, with simvastatin combined with ezetimibe, the lower LDL-C level was achieved compared with those with simvastatin plus the placebo group, although there was no additional benefit as for the surrogate endpoint of intima media thickness (IMT). Thus, the new concept of "residual cardiovascular risk" was
Increasing HDL-C: A New Target for the Prevention and Treatment of Atherosclerosis and CHD

With the in-depth understanding of blood lipids, HDL-C came into researchers' sight. In 1977, Gordon, et al. first reported that low HDL-C level was correlated to the coronary diseases. Thereafter, a meta-analysis of four prospective epidemiological investigations indicated that every 0.03 mmol/L (1 mg/dL) increment in HDL-C was associated with a significant CHD risk decrement of 2% in men and 3% in women. Low serum level of HDL-C was established to be a critical determinant risk factor for cardiovascular diseases, independent of levels of LDL-C. Meanwhile, a series of experimental studies demonstrated various cardioprotective effects of HDL. Apart from the anti-atherosclerosis effect by reverse cholesterol transport, HDL exhibits favorable effects on preventing LDL oxidation, inflammation and thrombosis of the vessel wall, protecting the vascular endothelial function, inhibiting apoptosis of the macrophage, as well as increasing endothelial progenitor cells. In Adult Treatment Panel III (ATP III) for the National Cholesterol Education Program (NCEP) expert panel on the detection, evaluation, and treatment of HDL in adults, low HDL-C is defined categorically as a level <40 mg/dL and is used as an important risk factor for individuals to estimate 10-year risk of CHD. Lipid-regulating therapy was changed gradually from simple LDL-lowering strategies to strategies targeting at raising HDL-C as an adjunctive therapy so as to further reduce the incidence of cardiovascular events and reverse atherosclerosis.

The Disappointing Results of Clinical Trials for Raising HDL-C: Did We Choose A Wrong Therapeutic Target?

The debates have never been suspending on whether available drugs for elevating HDL-C have independent anti-atherosclerotic effects. Several randomized clinical trials showed that elevating HDL-C level was beneficial to CHD prevention, although it was hard to identify whether the benefit came from elevating HDL itself or not since the involved HDL-regulating drugs in these studies also affected other lipid component including LDL-C and triglyceride.

Torcetrapib, an inhibitor of cholesteryl ester transfer protein, may block lipid exchange among lipoproteins and specifically elevating HDL-C level, which makes it possible for answering this question. In ILLUSTRATE, RADIANCE 1, and RADIANCE 2, the three clinical trials of surrogate end-point, torcetrapib raised HDL-C significantly but failed to reduce the progression of coronary or carotid atherosclerosis.

ILLUMINATE was a clinical end-point study for evaluating the additional effect of torcetrapib on reducing the risk of major cardiovascular events in the patients of CHD or CHD equivalents. A total of 15,067 patients at high cardiovascular risk were enrolled and randomly assigned to receive either torcetrapib combined with atorvastatin or atorvastatin alone. The primary outcome was the time to the first major cardiovascular event, which was defined as death from coronary heart disease, nonfatal myocardial infarction, stroke, or hospitalization for unstable angina. At 12 months in the patients who received torcetrapib, there was an increase of 72.1% in HDL-C. However, the trial was terminated prematurely because of an increased risk of death and cardiac events in the patients received torcetrapib. These results disappointed cardiologists all over the world, and inevitably challenged the theory of taking HDL-C as an antiatherogenic target.

Focus on HDL Function: from Quantitative Changes to Qualitative Changes

The plasma HDL-C concentration, which is primarily measured by the concentration of cholesterol in HDL, could represent the circulated HDL level to some extent. However, along with further studies on HDL construction and its relationship with HDL nature, people realized that the plasma HDL-C level itself did not convey the full picture of atheroprotective function of HDL. Some hereditary diseases, such as lecithin-cholesterol acyltransferase deficiency and familial alpha-lipoprotein deficiency disease (Tangier disease), are both characterized as low HDL-C level but without increased morbidity of cardiovascular diseases. Nearly 40% of the CHD event in the Framingham cohort occurred in subjects with normal HDL-C concentration.

HDL function correlates not only with serum HDL concentration but also with its structural integrity. HDLs are a heterogeneous class of lipoproteins. Generally speaking, HDLs are organized...