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Editorial

Modulation of High-Density Lipoprotein Function via Cardiac Rehabilitation

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Currently, cardiac rehabilitation (CR) is regarded as one of the most important and indispensable therapies for coronary artery disease (CAD)[1, 2]. The effect of CR on the secondary prevention of CAD was established in meta-analyses in terms of improving total mortality, hospitalization rate, exercise capacity, and quality of life. Additionally, a large number of studies support the ameliorating effects of CR on coronary risk factors, such as hypertension, impaired glucose tolerance, and dyslipidemia. CR was reported to increase the high-density lipoprotein cholesterol (HDL-C) level and decrease the triglyceride level. However, the mechanism underlying the beneficial effect of CR has been insufficiently understood. In particular, it is unclear whether CR can modulate the lipoprotein quality. Although there are a certain number of studies investigating the effects of CR on the HDL function[3, 4], the clinical effects remain controversial. The most plausible reason for inconsistent results in previous studies could possibly be attributed to the small sample size, probably because a number of participants had issues in completing the CR programs. For instance, HF-ACTION, the largest multicenter randomized controlled trial investigating the efficacy and safety of CR in patients with chronic heart failure[5], could not reveal any significant reduction in the risk for all-cause mortality or all-cause hospitalization, which was explained by the low rate (only 30%) of the patients who accomplished the target exercise training. Another possible explanation for the discordance is that the methods of exercise training in previous studies were different. Because the mode of exercise, intensity, duration, and frequency were not standardized in the previous research, it is not appropriate to compare the clinical outcomes. Thus, an optimal and unified method for CR should be developed.

In this issue of the Journal of Atherosclerosis and Thrombosis, Furuyama *et al*. investigated the effect of CR on the cholesterol efflux capacity (CEC) of HDL[3]. They showed that a five-month outpatient CR of the patients with acute coronary syndrome improved the CEC without a significant change in the plasma HDL-C level. The increase in the CEC was correlated with that of the anti-oxidative arylesterase activity (AREA), whereas the correlations with other biomarkers were considerably different between the CEC and AREA. The rate of change in apoA-I had higher correlation with that in the CEC and AREA than that in HDL-C.

Although this study is a single-center retrospective analysis based on a relatively small sample size, it has a potential clinical significance because it first demonstrated the beneficial effects of CR on both the CEC and AREA in CAD patients, irrespective of the use of statins. The CR program was appropriately conducted in accordance with the Japanese Circulation Society guidelines[1] with a high achievement rate (87%) of CR[3], which could have considerably influenced the HDL function. Although the correlation between peak VO_2 and the CEC was not significant, there was a marked association between peak VO_2 and the AREA. Thus, CR might have ameliorating effects, mainly by enhancing the paraoxonase1 (PON1) enzymatic activity and the apoA-I expression. PON1 protects various components in the HDL particles from oxidative modification, which may result in an improvement in the CEC.

The molecular mechanisms of PON 1 activation by exercise training have not yet been clarified. It has been reported that physical exercises induce various types of myokines in skeletal muscles, such as IL-6,

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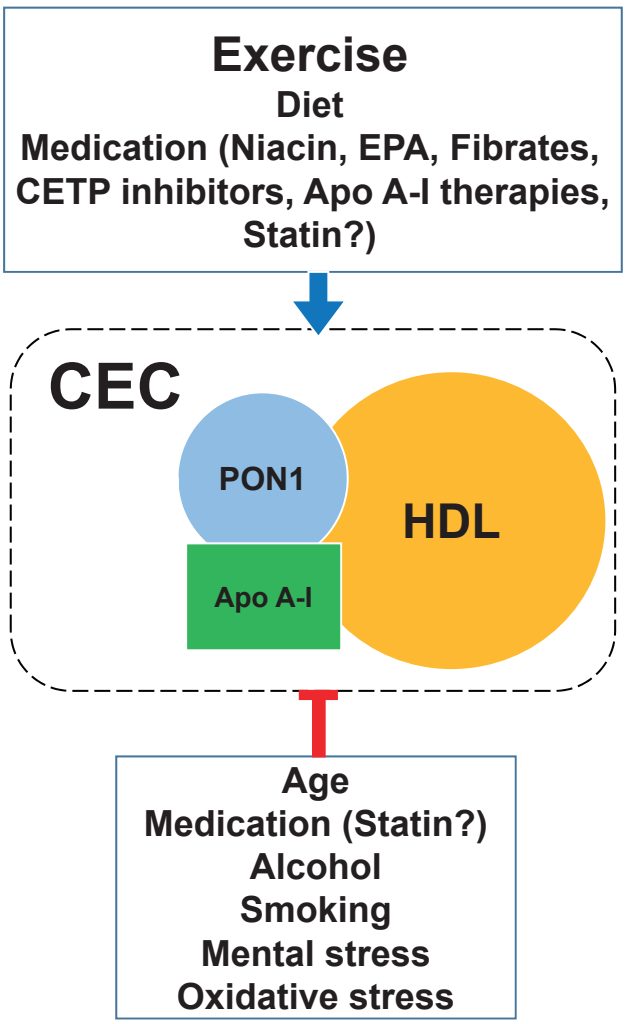

Fig. 1. Modulation of the CEC

PON1 is a serum HDL-associated enzyme binding apoA-I on HDL, which is stabilized and catalytically activated by apoA-I. PON1 and apoA-I are considered to regulate the CEC, which is an aspect of the pleiotropic functions of HDL. The CEC is reported to be ameliorated by some medications, such as niacin, EPA, fibrates, CETP inhibitors, and apoA-I therapies. The effect of statin remains controversial. Aging, alcohol, smoking, mental stress, and oxidative stress are considered to exacerbate the CEC. The positive modulation of the CEC by exercise and diet is plausible but with insufficient evidence.
PON1: paraoxonase1, HDL: high-density lipoprotein, apoA-I: apolipoprotein A-I, CEC: cholesterol efflux capacity, EPA: eicosapentaenoic acid, and CETP: cholesteryl ester transfer protein.

IL-15, and irisin[6]. Because some of these myokines are known to affect lipid metabolism[7] or lipid-related gene expression[8], there may be some regulatory interaction between the myokines and PON1 in the liver[9].

The current regulatory factors of the HDL function are shown in **Fig. 1**. Among these factors, exercises appear as one of the most promising regulators for the HDL function because they have multiple pleiotropic effects not only on atherosclerosis but also on the prevention of cancer, osteoporosis, mental disorder, and cognitive function. In addition, exercises are highly cost effective. Given the increasing importance of CR in CAD, it is greatly desired that the large multi-centered trial with standardized CR protocol and high achievement rate will explore the effectiveness of CR on the prognosis of cardiovascular diseases in the near future.

Disclosure

Tatsuro Ishida has received lecture honoraria from MSD and Mochida Pharmaceutical Co., Ltd.

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