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Cholesterol-Overloaded HDL Particles Are Independently Associated With Progression of Carotid Atherosclerosis in a Cardiovascular Disease-Free Population

A Community-Based Cohort Study

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ABSTRACT

BACKGROUND Cholesterol-overloaded high-density lipoprotein (HDL) particles exert a negative impact on the antiatherogenic function of HDL in experimental studies. However, it remains unclear whether cholesterol-overloaded HDL particle is involved in the development of atherosclerosis in humans.

OBJECTIVES The objective of this study was to explore whether cholesterol-overloaded HDL particles are associated with the progression of carotid atherosclerosis in a cardiovascular disease-free population.

METHODS Baseline HDL particle number was measured using nuclear magnetic resonance spectroscopy in 930 participants ages 45 to 74 years in a community-based cohort study. An estimate of cholesterol molecules per HDL particle (HDL-C/P ratio) was calculated as the ratio of HDL cholesterol to HDL particles. HDL-C/P ratio was categorized as $<$41.0 (lowest), 41.0 to 46.9, 47.0 to 52.9, and $\geq$53.0 (highest) using a fixed increment method. Modified Poisson regression was used to assess the association between HDL-C/P ratio and 5-year progression of carotid atherosclerosis as indicated by progression of carotid plaques and change in total plaque area (TPA).

RESULTS Mean baseline HDL-C/P ratio was 46.4 $\pm$ 9.3 (range 23.8 to 86.9). Baseline HDL-C/P ratio was significantly associated with 5-year progression of carotid atherosclerosis. Participants with the highest HDL-C/P ratio had 1.56-fold (95% confidence interval: 1.14 to 2.13; $p = 0.006$) increased progression compared with those with the lowest level. Among participants without baseline plaque, TPA in re-examination was larger by 9.4 mm^2 in the subgroup with the highest level when compared with the lowest level.

CONCLUSIONS Our findings suggest that cholesterol-overloaded HDL particles are independently associated with the progression of carotid atherosclerosis. This may explain why in recent trials raising HDL cholesterol was not beneficial. This study strongly suggests that the combination of cholesterol content and particle number determines the antiatherogenic function of HDLs, rather than either parameter alone. (J Am Coll Cardiol 2015;65:355-63) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

BMI = body mass index

BP = blood pressure

CETP = cholesteryl ester transfer protein

CI = confidence interval

CVD = cardiovascular disease

FBG = fasting blood glucose

HDL-C = high-density lipoprotein cholesterol

HDL-C/P ratio = the ratio of HDL-C to HDL-P number

HDL-P = high-density lipoprotein particles

hs-CRP = high-sensitivity C-reactive protein

LDL-P = low-density lipoprotein particle

NMR = nuclear magnetic resonance

RR = relative risk

TPA = total plaque area of maximum plaques

Although observational studies have suggested high-density lipoprotein cholesterol (HDL-C) as an independent inverse predictor for atherosclerotic cardiovascular diseases (ASCVDs) (1), several large randomized controlled trials in which plasma HDL-C was raised failed to show benefit for cardiovascular disease (CVD) events or progression of atherosclerosis (2,3). Recent updated American Heart Association/American College of Cardiology and European Society of Cardiology guidelines do not recommend raising HDL-C as a means to prevent ASCVD (4).

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However, debate regarding the value of HDL-C in CVD prevention continues (5–7). A core question is whether HDL-C fully represents cholesterol reverse transport, an underpinning of the antiatherogenic function of HDL. Experimental studies point out that the concentration of HDL particles (HDL-P), rather than the cholesterol carried by these particles, might be the appropriate parameter for assessing the function of HDL (8,9). Several observational studies have proven HDL-P number to be more strongly associated with CVD risk than HDL-C (10,11). Indeed, cholesteryl ester transfer protein (CETP) inhibitor or niacin was found in recent randomized controlled trials to have little effect on HDL-P number. This was true even if HDL-C was substantially increased, thus resulting in increased cholesterol-overloaded HDL-P (5,12). There is evidence that cholesterol-overloaded HDL-P may be harmful because experimental studies observed that cholesterol-overloaded HDL-P not only exerted a negative impact on the efflux potential of cholesterol from extrahepatic cells (7,13) but also reduced hepatic selective uptake of cholesterol mediated by scavenger receptor class B member 1 (SR-BI) (14–16). However, it remains unclear whether cholesterol-overloaded HDL-P is involved in the development of atherosclerosis in humans.

In this study, we calculated the ratio of HDL-C to HDL-P number (HDL-C/P ratio) to estimate the cholesterol content per HDL-P in a CVD-free population. Specifically, a high HDL-C/P ratio indicates cholesterol-overloaded HDL-P. We therefore tested the hypothesis that cholesterol-overloaded HDL-P may be associated with the progression of carotid atherosclerosis in asymptomatic individuals from a community-based cohort study of the Chinese Multiprovincial Cohort Study (CMCS)-Beijing Project.

MATERIALS AND METHODS

STUDY PARTICIPANTS. Study participants were recruited from the CMCS-Beijing Project, which is a generally healthy population-based study (17). Of 1,982 participants originally enrolled from a community in Beijing in 1992, a total of 1,324 participants ages 45 to 74 years completed examinations on demographic characteristics, measurements of traditional risk factors, and carotid ultrasound from September to November 2002. After excluding participants with established CVD (n = 68), unavailable blood samples (n = 7), and incomplete data (n = 14) at baseline, 1,235 participants were followed up for the occurrence of CVD and then invited to repeat examinations for risk factors and carotid ultrasound in 2007. Sixty-two participants were lost to follow-up, 15 died, and 228 did not participate at re-examinations. Thus, 930 (418 men and 512 women) participants with complete data from 2 examinations were eligible for final analysis.

All participants gave written informed consent, and this study was approved by the ethics committee of Beijing An Zhen Hospital, Capital Medical University, and was performed in accordance with the Declaration of Helsinki.

RISK FACTOR SURVEY. This study complied with the protocol of the World Health Organization-MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease). Demographic characteristics and personal medical history were collected by a standard questionnaire. Anthropometric measurements and blood pressure (BP) levels were recorded during physical examination. Body mass index (BMI) was calculated as weight in kilograms divided by height squared in meters. The survey method and definition of risk factors, including hypertension, diabetes, and current smoking, were previously described (17).

LABORATORY ASSAYS. Venous blood samples were drawn from the antecubital vein and collected in lavender-top tube(s) containing EDTA anticoagulant in the morning after fasting at least 8 h. Lipid profiles, fasting blood glucose (FBG), and high-sensitivity C-reactive protein (hs-CRP) were measured on fresh samples at the same day of collection in 2002 according to previous reports (17). HDL-C levels were measured by homogeneous assays (Daiichi, Tokyo, Japan). The remaining samples were aliquoted and stored at −80°C. Plasma lipoprotein particle numbers were measured in 2013 using a commercially available nuclear magnetic resonance (NMR) spectroscopy assay at LipoScience (Raleigh, North Carolina). Briefly, samples for lipoprotein particle analysis using