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EDITORIAL COMMENT

HDL Cholesterol/HDL Particle Ratio

A New Measure of HDL Function?*

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In this issue of the *Journal*, Qi et al. (1) describe a potentially important advance in cardiovascular biomarker testing related to high-density lipoprotein cholesterol (HDL-C), the so called "good cholesterol." The story of how cholesterol is causally related to cardiovascular disease (CVD) started more than 100 years ago with the pioneering studies by N. Anitschkow, who first showed that feeding rabbits a high-cholesterol diet induced atherosclerosis (2). Later John Gofman, MD, PhD, in the 1950s, found by analytical ultracentrifugation that cholesterol on low-density lipoprotein (LDL) was a positive risk factor for CVD, whereas cholesterol on HDL was inversely related to CVD risk (3). This began the modern era of lipoprotein research and was the genesis for measurement of the cholesterol content of HDL (HDL-C) as the main metric for HDL. Subsequently, diagnostic testing for HDL-C has become so ingrained in medical practice that it is often incorrectly viewed as being synonymous with HDL.

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Recent improvements in technology related to HDL proteomics and lipidomics have revealed its compositional complexity. Besides cholesterol, HDL is now known to carry more than 100 different types of lipids (4), many of which are potent bioactive signaling molecules (4,5). Besides apolipoprotein A-I, its main structural protein, approximately 80 different proteins have been described to be associated with HDL (6). Perhaps not surprisingly, given its complexity, HDL has been proposed to have numerous biological functions (7). This has raised the important issue about whether our current HDL-C test provides a full assessment of HDL composition and function (8). Compounding this concern are the results of several recent clinical trials of different types of drugs for raising HDL-C that have not shown so far the expected decrease in CVD events (9). Large genome-wide association studies of common gene polymorphisms that modulate HDL-C levels have also failed to show a clear association with CVD risk (10). As a consequence, there is great interest in developing alternative measures of HDL both as diagnostic tests for assessing CVD risk and as novel biomarkers for drug development.

In the paper by Qi et al. (1), they investigate whether the ratio of HDL-C to high-density lipoprotein particles (HDL-P) can be used as a predictor of atherosclerosis progression. HDL-P refers to the particle count of HDL. In other words, it represents the total number of HDL particles per volume of plasma and is typically expressed as μmol/liter. The term HDL-P was originally coined by Dr. Jim Otvos from LipoScience (Raleigh North Carolina), who first developed a nuclear magnetic resonance (NMR)-based method for quantifying lipoproteins (11). HDL-P is now used as a more general term and can also be determined by other analytical methods (12). The NMR HDL-P test, which was used in this study, is based on the detection of the proton signal from the terminal methyl group of lipids on lipoproteins. This signal can be used, not only to quantify the amount of a lipoprotein present, but also its size, because different-size lipoprotein particles have different chemical shifts in their NMR spectra (11). A spectral deconvolution algorithm based on the known NMR spectrum of isolated lipoproteins of different sizes is used to calculate the number of lipoprotein particles

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present for each designated size class. In the case of HDL, the NMR method can report 3 different size classes (small, medium, and large), but these are aggregated for calculating the total HDL-P count. Similarly, one can also measure by NMR the other major lipoprotein fractions, such as the low-density lipoprotein particle (LDL-P) count. In fact, several studies have shown LDL-P to be superior to the cholesterol content of LDL (LDL-C) and apolipoprotein B as a positive risk marker for CVD (13). The NMR LDL-P test was cleared by the U.S. Food and Drug Administration (FDA) in 2008, and it is available through LipoScience and other reference laboratories. In 2012, the FDA cleared the Vantera clinical analyzer, a 400-MHz NMR spectrometer produced by LipoScience, for the high throughput measurement of LDL-P, HDL-C, and triglycerides in routine hospital laboratories. The NMR HDL-P test is not yet approved by the FDA, but in several large studies (MESA [Multi-Ethnic Study of Atherosclerosis] [14], JUPITER [Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin] [15], and HPS [Heart Protection Study] [16]), it appeared to be superior to HDL-C as a negative CVD risk marker.

The main hypothesis examined in this study by Qi et al. (1) was whether HDL enriched in cholesterol was less atheroprotective. This was determined by calculating the ratio of HDL-C/HDL-P in 930 healthy individuals from China. On the basis of this ratio, HDL particles were estimated to contain on average approximately 46 cholesterol molecules per particle, but this differed by more than 3-fold in test subjects, and the overall correlation between HDL-P and HDL-C was relatively poor ($r = 0.378$). Individuals in this study were followed for 5 years, and atherosclerosis progression was observed in approximately one-half of the subjects, as determined by comparing results from a baseline carotid ultrasound measurement to one performed at the end of the study. Participants were divided into 9 categories, depending on whether they had low, medium, or high HDL-P and HDL-C. Interestingly, HDL-C levels did not appear to be inversely related to the risk for atherosclerosis progression except for those in the lowest HDL-P subgroups. By contrast, high HDL-P appeared to be inversely related to atherosclerosis risk progression regardless of the HDL-C level, but this association did not reach statistical significance except for those in the highest HDL-C subgroups. Individuals with the highest HDL-C/HDL-P ratios (>53) had a significant 1.5-fold increase risk for atherosclerosis progression compared with individuals with the lowest HDL-C/HDL-P ratio (<41). This relationship held even after adjustment for other routine cardiovascular biomarkers, including LDL-P, and other risk factors, as well as after adjustment for the use of lipid-lowering medications.

The reason for the association of atherosclerosis progression with higher HDL-C/HDL-P ratios was not assessed in this study, but several plausible mechanisms were proposed. The most likely one is that cholesterol enrichment of HDL decreases its ability to promote the efflux of cholesterol from cells, which is believed to be one of its main antiatherogenic functions and has been shown to be inversely related to CVD risk (17). It has also already been demonstrated in vitro that adding exogenous cholesterol to HDL limits its capacity to bind additional cholesterol effluxed from cells (18). It is also known that phospholipid-rich, but cholesterol-poor, HDL subfractions, such as pre-beta HDL, are especially good at effluxing cholesterol from cells, particularly by the ABCA1 transporter (8,13,18). When HDL is enriched in cholesterol, it may, in fact, turn into a net donor of cholesterol to cells. This normally happens when HDL delivers cholesterol to the liver for excretion or to the adrenal gland for steroid hormone biosynthesis, but it has been proposed that HDL, under certain pathological conditions, may become dysfunctional and can lead to the net deposition of cholesterol into atherosclerotic plaque (19).

Although the results of this study are quite promising and could be readily implemented with existing routine clinical laboratory assays, it is, of course, important to replicate these results in larger studies with longer observation periods. A more careful assessment will also have to be made to show that HDL-C/HDL-P ratio provides additional independent predictive information over other currently used cardiovascular biomarkers, particularly for those subjects at intermediate CVD risk, a population on which the test is most likely to be first used. Finally, it will eventually be important to demonstrate, not only an association with atherosclerosis progression, but that the HDL-C/HDL-P ratio is predictive of future CVD based on clinical events, such as myocardial infarction, revascularization, and stroke.

It has been a long and winding road in unraveling the link between cholesterol and atherosclerosis, but recent progress in understanding the complexity of HDL coupled with new analytical procedures, such as NMR-based lipoprotein testing, may lead to better HDL-based biomarkers for drug development and CVD risk assessment.

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