Revisiting “Good” and “Bad” Cholesterol

The Battle over Flow through Arteries Now Shifts to Flow through Airways

Several decades ago, plasma levels of high-density lipoprotein cholesterol (HDL-C) were found to be inversely related to atherosclerotic cardiovascular disease (ASCVD) in the general population, and low-density lipoprotein cholesterol (LDL-C) levels were found to be directly related (1, 2). This led to positing of the HDL hypothesis: that HDL defends against LDL-induced atherosclerotic lesions by promoting reverse cholesterol transport from vessel walls (2). It also led to the colloquial, but misplaced, equation of plasma HDL particles with their cholesterol content (i.e., so-called “good cholesterol”) among patients and many physicians alike. The HDL hypothesis has been challenged in recent years by the results of Mendelian randomization studies and trials of HDL-C-raising drugs, both of which have dissociated HDL-C from ASCVD (1). At the same time, there has been renewed interest in noncholesterol components of HDL that may underlie its beneficial functions in cardiovascular and other diseases.

HDL particles are highly complex multimolecular conglomerates of more than 80 different proteins, numerous lipid species, microRNAs, and other cargo (3). Adding further complexity, HDL particles are highly heterogeneous, with at least five compositionally distinct subcategories that can be distinguished by density, but with the recognition that there is a further spectrum of heterogeneity, likely at the particle level, within subcategories (3, 4). In addition to inducing cholesterol efflux from cells, HDL is now recognized to trigger cellular signals that underlie a remarkably wide suite of biological effects, including antiinflammatory, antioxidant, antiapoptotic, antiplatelet, vasodilatory, endocrine, and antimicrobial effects (4). Many of these functions arise from bioactive lipids in HDL, including sphingosine-1-phosphate, whereas others may arise from the ability of HDL to reprogram gene expression via transcellular delivery of microRNAs (5) and induction of antiinflammatory transcription factors (6). Interestingly, the composition and function of HDL are both remodeled during disease states, including inflammation, insulin resistance, and obesity (7), suggesting HDL may be both a biomarker of, and a shape-shifting mediator in, disease.

In recognition of the limited information provided by lipoprotein cholesterol, the cardiovascular sciences have recently sought to validate the predictive value of advanced lipid testing methods, including measurement of the plasma concentrations of HDL and LDL particles (proton nuclear magnetic resonance spectroscopy) and apolipoproteins associated with HDL (apoA-I) and LDL (apoB) (3, 8). Although some studies have suggested improved prediction of ASCVD, the superiority of these methods over traditional measures, such as total cholesterol/HDL-C ratio, remains unclear (2). Moreover, challenges remain over method standardization and measurement variability. Direct *in vitro* studies of HDL function

have been validated in prediction of ASCVD and may be the ultimate gold standard (2, 4), but they will face even larger challenges in standardization, cost-effectiveness, and throughput.

So, what do lipoproteins have to do with the lung? One of the hallmark functions of the lung is, of course, surfactant lipid synthesis. Conversely, the alveolus is a reservoir of lipids that are subject to environmental oxidation and that must be cleared. Viewed in this light, it should be unsurprising that key roles have been identified for lipoproteins in lung biology. Circulating lipoproteins are taken up by the lung *in vivo* (9), promote surfactant production by type II cells (10), and attenuate airway inflammation (9). Remarkably, apoE-null mice have reduced developmental alveologenesis and abnormal lung function (11), and apoA-I-null mice have increased oxidative stress, inflammation, and resistance in the airways (12). HDL is also the major source of the antioxidant vitamin E for the lung (13) and a major vehicle for α_1 -antitrypsin delivery to the lung (9). Moreover, HDL mimetics attenuate experimental asthma in mice (14), whereas diet-induced hypercholesterolemia enhances disease (15). Asthma is interestingly associated with reduced airspace apoA-I (16), increased plasma oxidized LDL (17), and deficient antiinflammatory function of HDL (18), suggesting lung disease may itself dysregulate local and systemic lipid metabolism, potentially in ways that may feed forward to promote disease.

In recent years, several studies have sought to define the relationship between traditional lipoprotein cholesterol measures and human asthma. A wide and divergent variety of relationships has been reported among total cholesterol, LDL-C, and HDL-C on the one hand and asthma diagnosis on the other (19). In this issue of the *Journal*, Barochia and colleagues (pp. 990–1000) provide a substantial step forward by evaluating the relationships of both traditional and advanced serum lipoprotein measures to lung function in 159 subjects with objectively confirmed atopic asthma and 154 controls without asthma (20). No significant relationships were found between traditional lipoprotein measures and FEV₁% predicted in the control group. In contrast, among atopic patients with asthma, an atherogenic lipid profile was found to correlate with reduced FEV₁. Specifically, serum HDL-C and apoA-I were positively correlated with FEV₁, whereas serum LDL-C, triglycerides, apoB, and apoB/apoA-I ratio were negatively correlated with FEV₁. Advanced testing with nuclear magnetic resonance spectroscopy revealed consistent findings. Positive correlations were found between FEV₁ and HDL particle size, as well as between FEV₁ and concentration of large HDL particles. In contrast, LDL particle size, LDL particle concentration, and very LDL particle concentration were all negatively correlated with FEV₁.

This is the first comprehensive characterization of lipoprotein particle profile by nuclear magnetic resonance spectroscopy in

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asthma and has the further strength of correlating lipid measures to objectively measured lung function. As large HDL particles are more cholesterol laden than small HDL particles and correlate better with HDL-C (7), the authors' traditional and advanced findings on HDL are consistent, and together may suggest that large HDL particles possibly mediate airway protective effects in asthma. This is generally consistent with the cardiovascular literature, where large HDL particles have been associated with cardioprotection in some, but not all, reports (7, 21).

The authors themselves acknowledge a few limitations of their study that may point the way for future efforts. The cross-sectional study design prevents conclusions on temporality and causality. On that note, given that inflammation has been associated with reductions in HDL-C and remodeling of HDL (7, 21), reverse causality between advanced lung disease and HDL cannot be excluded. It would be interesting to know whether inflammatory measures such as C-reactive protein either confound or modify the HDL- FEV_1 relationship. Future longitudinal trials may also allow study of lipoprotein changes during asthma exacerbations. As also acknowledged by the authors, the modest size of the study prevented a meaningful analysis of lipoprotein relationships in the subset of clinically severe patients with asthma. Finally, the authors show that serum triglyceride, a determinant of HDL size, does not confound the HDL- FEV_1 relationship, but it would be interesting to also know whether other factors that are related to both lung function and HDL, such as body mass index and physical activity (8), affect the relationship.

In summary, the article by Barochia and colleagues offers critical steps forward in understanding serum lipids in asthma and also identifies new key questions for the field. Among these, it will be interesting to consider whether systemic disorders that affect asthma pathogenesis and also modify HDL composition (e.g., obesity) communicate molecularly with lung-resident cells via delivery of altered HDL cargo to the lung. Moreover, as further functional assays of HDL and biomarkers of HDL dysfunction (e.g., HDL proteomic changes) are validated in ASCVD, this will create new opportunities for translation to pulmonology. Last, multiple HDL-increasing and HDL-mimetic strategies are currently in the development pipeline for ASCVD (2). Predictably, some of these novel agents will warrant testing in asthma, and perhaps other lung diseases. A relative latecomer to the lipoprotein scene, pulmonology may now find itself ideally positioned to rapidly benefit from past and ongoing discoveries made in the cardiovascular sciences. ■

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