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HDL modification: recent developments and their relevance to atherosclerotic cardiovascular disease

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Abstract

Purpose of review—In the last 2 years, significant advances in the understanding of HDL particle structure and the associations between particle structure, function, and atherosclerosis have been made. We will review and provide clinical and epidemiological context to these recent advances.

Recent findings—Several recent studies have analyzed the associations between HDL particle size distribution, number, and particle function and specific environmental, behavioral, and pharmacologic exposures. Detailed phenotyping of HDL-associated protein complements, particularly apolipoproteins, strongly suggests structural subspecies of HDL exist with differential associations with HDL function and ASCVD risk.

Summary—The recent data on biological and structural variation in HDL suggests the existence of relatively discrete particle species, which share a similar structure and function. We propose that the classical taxonomy that clusters HDL particles by cholesterol content is incomplete. Detailed phenotyping of HDL subspecies in clinical and epidemiological research may yield insights into new risk markers and biochemical pathways that could provide targets for atherosclerotic cardiovascular disease (ASCVD) therapy and prevention in the future.

Keywords

HDL; modifications; particle number; particle size; proteome

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Conflicts of interest

There are no conflicts of interest.

INTRODUCTION

HDL is a heterogeneous group of lipoprotein particles with a density above 1.063g/ml and size ranging from 7 to 12nm [1]. Some of the broadly accepted characteristics of HDL particles include: the presence of apolipoprotein A-I (APOA-I) as its major structural and binding ligand protein [2], a phospholipid outer layer with a dynamic combination of associated proteins from a highly complex proteome composed of up to 95 different protein species in variable stoichiometry within and between individuals, and a variable lipid core of mostly esterified cholesterol, especially in larger HDL subspecies [3].

Characterization of HDL in the plasma compartment has revealed significant structural and chemical heterogeneity. Analyses by ultracentrifugation, gel electrophoresis, mass spectrometry, immunoassays, and nuclear magnetic resonance have shown a host of HDL subspecies, which differ in size, charge, shape, protein, and lipid content [3]. The nomenclature of these fractions is often variable depending on the technique used to separate the fraction. The smallest size sub fraction, small or 'prebeta' HDL particles are lipid-deplete, discoidal in structure, and have the smallest complement of associated proteins [4]. Medium or 'alpha-3' particles are larger, more spherical in shape, and have a larger core of esterified cholesterol and a larger associated proteome than the prebeta fraction. The third, and largest, size sub fraction are described as large or 'alpha-2' particles. This sub fraction contains the highest amount of esterified cholesterol and likely the most diverse proteome of all HDL subfractions. Given the structural heterogeneity, differential proteome, and cholesterol content, many researchers have hypothesized that the overall quantity and relative distribution of small, medium, and larger HDL particles are differentially associated with and may mediate atherosclerotic cardiovascular disease (ASCVD).

There remains a debate over the lifecycle of HDL size subfractions, which is relevant to understanding the mechanisms through which HDL is associated with atherosclerosis. Animal models suggest that there is a distinct lifecycle of HDL particles that begins with lipid-deplete prebeta particles that become enriched with esterified cholesterol, become spherical, and enlarge over time into larger, alpha particle species. These particles ultimately interact with cholesteryl ester transfer protein or with the SRB-1 receptor in the liver or steroidogenic tissues to deliver their lipid component and complete the process of reverse cholesterol transport. However, more recent kinetic studies in humans suggest that at least some medium and large HDL particles are synthesized *de novo* from the liver and do not originate from lipid-poor prebeta particles [5]. These findings have particular significance to understanding epidemiological data that demonstrate associations between HDL particle distributions and ASCVD risk. For example, in some individuals, a high small HDL particle concentration may represent a failure of maturation of small particles, whereas in others, it may represent increased *de novo* synthesis of prebeta particles. One could hypothesize that a high prebeta fraction caused by decreased maturation and one caused by increased synthesis could have contrasting associations with ASCVD risk.

Several classic epidemiological studies demonstrated strong, inverse associations between the cholesterol content of HDL particles, HDL-C, and coronary heart disease risk [6]. Although this association persists, more recent Mendelian randomization and randomized

clinical trials call into question the causal role of the HDL-cholesterol fraction in CHD risk development [7,8]. Moreover, for years, researchers have hypothesized that the functional properties of these particles, especially the ability of HDL particles to transport cholesterol from the periphery to the liver for excretion, are the actual atheroprotective feature of this fraction, not the cholesterol contained within HDL particles. Several contemporary studies strongly support this hypothesis as they demonstrated robust inverse associations between HDL efflux capacity, an index of reverse cholesterol transport (RCT), and ASCVD risk that were independent of HDL-C [9■]. Thus, it may be the function of these particles that is in fact atheroprotective, and measurement of HDL cholesterol concentration may not adequately capture the rate at which an individual is able to perform RCT.

Furthermore, the atheroprotective functions of HDL may extend well beyond RCT. Examination of the HDL proteome strongly suggests that HDL particles have inflammatory properties, direct immunologic effects, antithrombotic, antiapoptotic, antioxidant effects, and they may mediate release of nitric oxide (NO) from smooth muscle cells, resulting in vasodilation [10].

With the emerging understanding of the role of HDL functionality in ASCVD, there is growing interest in understanding the structural characteristics of HDL particles and how these structural characteristics may affect HDL function and relate to ASCVD. Thus, in this review, we will discuss recent published developments in the field of human HDL biology that have enhanced our understanding of the spectrum of HDL structural and functional modification and the potential role of these variants in the pathobiology of ASCVD. Specifically, we will review recent studies that enhance our understanding of: how HDL particle number and size are related to environmental exposures; how the HDL proteome varies across individuals; and how this structural and functional variation in HDL particles may be relevant to ASCVD. We will focus on the outcome of ASCVD, though it is important to note that compelling hypotheses that HDL mediates other pathologic processes (e.g. dementia, autoimmune disorders) exist. However, there are limited data to support or reject these hypotheses at this time, thus they are outside the scope of this review.

HDL-CHOLESTEROL PARTICLE NUMBER, SIZE, AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

Several contemporary epidemiological and clinical trial-based studies have enhanced our understanding of the interconnectedness of HDL particle number, size, and function with environmental exposures that likely mediate ASCVD. Specifically, associations between air pollution, diet, healthy aging, and statin medication use and metrics of HDL particle number, size, and function have been reported and will be discussed below.

Interestingly, a cross-sectional analysis from the Multi-Ethnic Study of Atherosclerosis (MESA) demonstrates significant inverse associations between particulate air pollution and HDL particle number [11]. This analysis included 6654 white, African American, Hispanic, and Chinese American cohort participants aged 45–84 years. A 5mg/m² higher exposure to ambient fine particulate air pollution was associated with a 0.64mmol/l lower HDL particle number, but was not associated with lower HDL-C. These data suggest that air pollution

may partially mediate HDL metabolism and, if HDL particles are causally related to ASCVD, the associations between increased air pollution and ASCVD risk could be mediated, in part, by alterations in HDL particle metabolism. Alternatively, changes in HDL particle number may be markers of overall environmental and metabolic exposure serving as integrative markers of vascular health. Regardless, these data indicate that HDL particles are responsive to a variety of environmental exposures, several of which (like air pollution) are not routinely measured in clinical and epidemiological research, thus further complicating observational epidemiological research into this dynamic and highly heterogeneous class of lipoprotein. Longitudinal data on the associations between air pollution and HDL structure and function are needed to further clarify the accuracy, directionality, and consequences of these associations.

Adoption of a Mediterranean diet eating pattern has been shown to reduce ASCVD risk whenever compared with a low-fat diet. The mechanisms through which dietary modification reduces ASCVD risk are partially, but incompletely, understood. Certainly, alterations in blood pressure, blood glucose, and favorable changes in lipid profiles are likely one mechanism through which healthy diets reduce ASCVD risk. The extent to which HDL functional characteristics are altered by healthy eating patterns was recently reported in a substudy performed in the PREDIMED study [12[■]]. Researchers reported that a Mediterranean diet pattern enriched with virgin olive oil was associated with improvement in HDL esterification index, PON1 acyltransferase activity, HDL vasodilatory capacity, and an increase in HDL phospholipid content. This study is one of the most comprehensive assessments of the effects of dietary modification on a variety of HDL-related structural and functional characteristics. Furthermore, the fact that this study was imbedded in a randomized clinical trial enhances our confidence that the effects reported are in fact because of the dietary intervention and not a confounder. However, this study does not prove that the protective effects of a Mediterranean diet work through changes in HDL function, as the changes observed could have been markers but not mediators of improved cardiometabolic health and reduced ASCVD risk.

The extent to which HDL structural and functional characteristics predict the presence of subclinical atherosclerosis is not clear. Interestingly, in the Dallas Heart Study, HDL efflux strongly predicted ASCVD events, but it had a null association with coronary artery calcium [9[■]]. Furthermore, the extent to which HDL efflux is explained through HDL particle number and HDL size variance across individuals remains incompletely understood. A study performed in the Chicago Healthy Aging Study (CHAS), explored the associations between HDL efflux, HDL particle number, and a lipid-rich necrotic core plaque in the carotid arteries [13]. Of note, CHAS intentionally oversampled healthy aging adults, as it was designed to understand long-term outcomes in this group. Thus, findings reported in this study may not be generalizable to the general population and individuals with high cardiometabolic risk. Interestingly, in CHAS, all markers of HDL structure and function were associated with lipid-rich necrotic core plaque in unadjusted models, but the associations were attenuated by multivariable adjustment for traditional risk factors, suggesting that HDL particle number and function were integrative makers of risk factor burden in this subsample. The authors also reported that a higher concentration of medium and large HDL particles was positively associated with HDL efflux and a higher

concentration of small particles was inversely associated with HDL efflux. At the least, these findings add to previous data that suggest that differences in HDL structure may explain some of the interindividual differences in HDL efflux.

In high-risk primary and secondary prevention patients, the absolute residual risk for events remains elevated despite maximal statin therapy [14]. Thus, the identification of markers of residual risk and targets for ASCVD risk reduction in these patients is of significant clinical importance. Data from the JUPITER study assessed the associations between HDL efflux, HDL particle number, and HDL cholesterol at baseline at 12 months with ASCVD risk. Interestingly, the authors report that HDL particle number was the only HDL structural or functional index obtained at trial baseline that was associated with ASCVD risk. After 12 months of therapy, HDL efflux did not change, but HDL-C and HDL particle number increased modestly with statin therapy. At 12 months, HDL efflux and HDL particle number were both inversely associated with ASCVD risk in statin-treated patients. These data suggest that the relationships between HDL function and ASCVD risk may be complex and mediated by statin therapy. They also add to previous observations the HDL particle number and HDL efflux are positively associated, suggesting that the HDL particle may be the actuator of HDL-associated cardioprotection. Lastly, these data suggest that measures of HDL particle number and/or function could become useful tools to guide residual risk assessment.

In summary, significant advances in our understanding of the associations between HDL structure, function, environment, behavior, and pharmacologic exposures have been reported in the last year and a half. All of these studies suggest that HDL metabolism has complex associations with multiple environmental and behavioral exposures. Further-more, the data strongly support the linkages between HDL structural characteristics and HDL function.

THE HDL PROTEOME AND CARDIOMETABOLIC RISK FOR ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

Proteins compose 35–65% of the molecular weight of HDL particles [15]. Thus far, there have been 95–100 protein species reproducibly associated with HDL particles. Among the most commonly observed major protein groups are apolipoproteins, enzymes, lipid transfer proteins, acute-phase-response proteins, proteins of the complement cascade, and protease inhibitors. Although this proteomic diversity suggests a multiplicity of functions for HDL particles, several of the HDL-associated proteins are expressed in plasma molar concentrations below that of HDL itself, suggesting that they are present in only a fraction of the particles [16]. Thus, there may be HDL particles with distinct proteomic profiles and distinct biochemical functions.

In order to characterize protein distribution across HDL particles, multiple proteomic studies have analyzed the proteome of prefractionated HDL subspecies. Results suggest specific protein species cluster to ranges of HDL particles defined by size, charge or presence of a specific apolipoprotein. Iteratively, the field is defining several proteome variants, which are roughly reproducible across studies. Furthermore, the apparent clustering of proteins components of similar metabolic pathways in specific HDL proteome variants has been

posited to be a key marker and driver of the heterogeneity of HDL functions [16,17]. Thus, there is hope that stratification of HDL by its proteome might lead to better understanding of the pathways connecting HDL functions to atheroprotection and ultimately contribute to the development of effective HDL-targeted therapeutic interventions. In that sense, several studies have sorted HDL particle subspecies by the presence or absence of specific apolipoproteins, notably apoC-III. This type of study has its advantages, as it facilitates separation and/or detection, which can be done by immunoassays, and it decreases analytical complexity by focusing on the effect of one molecular factor. Several lines of research strongly suggest that the presence of apoC-III on HDL particles modulates HDL function and the associations between HDL-C and ASCVD risk. For example, in the Diet, Cancer, and Health (DCH) study, researchers quantified the associations between HDL-containing apoC-III and measures of adiposity and sedentariness. They found that for each 15cm higher waist circumference, the percentage of HDL that contained apoC-III was 2.8% higher. Similarly, each 20 metabolic equivalents, higher physical activity was associated with 0.9% higher percentage of HDL-containing apoC-III [18]. Furthermore, in the DCH study, baseline concentrations of apoC-III were strongly associated with the risk for incident diabetes with a hazard ratio of 3.43 when the top quartile of HDL with apoC-III was compared with the bottom. However, HDL-C that contained apoC-III was not significantly associated with incident diabetes mellitus, suggesting that apoC-III may alter any possible antidiabetic properties of HDL [19].

Not only does the presence of apoC-III on HDL particles seem to co-vary with cardiometabolic risk but also it appears to modify the associations between HDL-C and ASCVD risk. The associations between HDL with and without apoC-III and ASCVD were examined in the Nurses' Health Study, MESA, DCH, and the Health Professional's Follow-Up study. The authors report that HDL species that contain apoC-III had positive associations with CHD risk [risk ratio (RR) 1.09 per standard deviation (SD) increase in HDL with apoC-III] whereas HDL without apoC-III was associated with an inverse association with CHD risk (RR 0.76) [20]. In aggregate, the recently emergent research on HDL-containing apoC-III supports the hypothesis that HDL subgroups – variable in structure, function, and their associations with ASCVD – are present in humans. Certainly, these data suggest that apoC-III may be the central constituent of the HDL proteome that modifies ASCVD risk.

Work is ongoing to 'sub-speciate' HDL particles by the proteomic profiles, with particular focus on apolipoproteins. Reports of the presence of apoA-II and apoE on HDL particles being associated with distinct proteomic signatures also suggest that the apolipoprotein complement of HDL particles is not random and serves distinct roles in constitutive function and in ASCVD risk development [21]. Specifically, in the DCH study, the inverse association between apoE on HDL particles and CHD risk was modified by the co-presence of apoC-III, such that HDL particles with apoE and apoC-III did not have inverse associations with CHD risk [22]. Thus, these data suggest that apolipoprotein profiles, and potentially interactions between the apolipoproteins, are modifying the function, and thus the associations between HDL particles and ASCVD.

The determinants of proteome function are certainly more complex than the presence or absence of one or more apolipoproteins. It is likely that multiple other protein–protein interactions also mediate HDL function and its role in atherosclerosis. Swertfeger *et al.* [15] broadly surveyed the spectrum of lipoprotein subspecies, analyzing multiple HDL and LDL size fractions for their proteome and for metrics of two key HDL atheroprotective functions: cholesterol efflux and antioxidation. Peaks of activity for each function were observed in different parts of the size spectrum and whereas none of the proteins quantified in this study were associated with either function individually, distinct groups of proteins were associated with the different activity peaks, highlighting the importance of the proteome in aggregate rather than a single protein for activity.

Posttranslational modification (PTM) of HDL-associated proteins adds another layer of complexity to understanding the HDL proteome. Innovative translational work from Huang *et al.* [23], identified an abundant oxidized form of apoA1 (oxTrp72-apoA1) in surgically explanted human atheroma. This specific molecular variant was associated with lower HDL efflux and higher ASCVD risk in a small clinical cohort when present in the serum. These data provide a possible pathway through which chronic inflammation may lead to reductions in HDL function. They also suggest that characterization of HDL-associated PTMs may enhance our understanding of the pathobiology of ASCVD. Early data from the CHAS support this hypothesis as well. Researchers found that molecular apoA-I variants with fatty acids bound to the lysine88 residue were more abundant in individuals with high HDL efflux when compared with individuals with low HDL efflux capacity [24]. However, the sample size used for this analysis was quite modest, thus these data require replication in a much larger sample.

CONCLUSION

There has been substantial progress made towards understanding the structural complexity of HDL particles and the linkages between HDL structure and function. In aggregate, recently published work suggests that the currently used taxonomy of HDL is incomplete and that HDL-C is an inadequate measure of HDL biology. The proteome of HDL particles is exceptionally complex, appears to be nonrandom, and likely results in different subspecies of HDL with distinct functional properties. Furthermore, evidence continues to support the associations between these HDL functional properties and ASCVD risk. In total, it is clear the measurement of HDL-C alone neither captures the structural and functional complexity of HDL nor does it adequately explain HDL-associated ASCVD risk. Hopefully, further investigations into HDL structural variation will lead to improvements in ASCVD risk assessment and identification of novel pathways to treat and prevent atherosclerosis.

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KEY POINTS

- HDL particles are highly complex lipoproteins with substantial variability in size, cholesterol content, and their associated proteomes.
- Recently, measures of HDL function have been shown to have strong, independent associations with ASCVD risk. However, the determinants of difference in HDL function are not completely understood.
- Differences in HDL particle size and number are associated with multiple environmental exposures, HDL function, and ASCVD risk.
- The proteome of HDL particles is complex with up to 100 HDL-associated proteins. The HDL proteome is variable within and between individuals. Furthermore, the distribution of proteins appears to be nonrandom and suggests the existence of HDL particle subspecies with distinct functional properties.
- Distinct profiles of HDL-associated apolipoproteins, notably apoC-III, appear to significantly modify the associations between HDL-C and CVD risk factors and ASCVD events.
- Identifying the optimal structural and functional characteristics of HDL-associated proteins is needed to more completely understand the role of this highly prevalent lipoprotein species in states of health and disease.