Curr Atheroscler Rep (2016) 18: 71
DOI 10.1007/s11883-016-0623-0

GENETICS (A. MARIAN, SECTION EDITOR)

HDL as a Causal Factor in Atherosclerosis: Insights from Human Genetics

Liam R. Brunham [1,2,3]

Published online: 26 October 2016

Abstract High-density lipoprotein cholesterol (HDL-C) levels are inversely related to risk of atherosclerotic cardiovascular disease (ASCVD). However, the simplistic assumption that HDL-C levels directly and causally impact atherogenesis has been challenged in recent years. The purpose of this article is to review the current state of knowledge regarding genetically determined HDL-C levels and ASCVD risk and determine what insight these studies provide into the causal relationship between HDL and atherosclerosis.

Keywords HDL · Atherosclerosis · Genetics · Lipids · Lipoproteins

Introduction

Epidemiological studies over the past six decades have established an inverse relationship between plasma levels of high-density lipoprotein cholesterol (HDL-C) and the risk of atherosclerotic cardiovascular disease (ASCVD) [1, 2]. A large body of experimental data has established a number of anti-atherosclerotic properties of HDL particles [3, 4], fuelling interest in the concept of HDL-based therapeutics to prevent or reverse ASCVD. However, the "HDL hypothesis" [5] has fallen on hard times over the past several years [6], and uncertainty has developed surrounding the causal role of HDL in atherosclerosis. Several lines of evidence have conspired to cast doubt on a causal role of HDL in atherogenesis [6], including the failure of clinical trials of drugs aimed at raising HDL-C levels [7–12] and Mendelian randomization studies that have brought into question whether genetically determined changes in HDL-C levels impact ASCVD risk [13–15].

Human genetics has been one of the major sources of our knowledge of HDL metabolism and function [16]. The purpose of this review is to summarize what has been learned from human genetic studies regarding a causal role for HDL in atherosclerosis.

Mendelian Disorders of HDL

Pathogenic mutations in three genes, namely *ABCA1*, *APOA1*, and *LCAT*, cause rare Mendelian disorders of low HDL-C [16, 17]. Each of these is characterized by near absence of HDL in blood and in theory should serve as ideal experiments of nature to determine the role of HDL in atherogenesis. However, the rarity of these conditions, as well issues related to selection basis in terms of the patients that come to clinical attention, has made accurate estimation of the risk of ASCVD in these conditions challenging.

Most series of Tangier disease patients have reported an increased prevalence of ASCVD relative to population controls [18–20]. However, it is apparent that Tangier disease does not confer the dramatically elevated risk of premature ASCVD that is seen in Mendelian condition of high LDL-C, such as familial hypercholesterolemia (FH) [21]. There is tremendous inter-individual variability among patients with TD

This article is part of the Topical Collection on *Genetics*

✉ Liam R. Brunham
Liam.brunham@ubc.ca

[1] Department of Medicine, University of British Columbia, Vancouver, Canada

[2] Centre for Heart Lung Innovation, Providence Health Care Research Institute, University of British Columbia, St. Paul's Hospital, Room 166-1081 Burrard Street, Vancouver, BC V6Z 1Y6, Canada

[3] Translational Laboratory in Genetic Medicine (TLGM), Agency for Science, Technology and Research (A*STAR), Singapore, Singapore

in susceptibility to ASCVD [22], which may relate to differences in the severity of the underlying mutation and the corresponding impairment in cholesterol efflux [23]. Studies of individuals heterozygous for mutations in *ABCA1* have generally reported increased prevalence of clinical [24, 25] or subclinical ASCVD [26, 27]. Certain variants in *ABCA*1 also impact ASCVD risk in the general population [28], though somewhat paradoxically, this effect appears to be independent of HDL-C levels.

Early studies of *APOA1* deficiency suggested that these patients develop premature ASCVD [29, 30]. In general, the risk of ASCVD in *APOA1* deficiency is thought to be higher than in Tangier disease or familial LCAT deficiency [20]. One reason for this difference may be that plasma LDL-C levels, which are reduced in Tangier disease, are relatively normal in *APOA1* deficiency. Combined mutations in *ABCA1* and *APOA1* have been reported to be associated with premature ASCVD in very rare cases [22].

While data are conflicting, the bulk of evidence appears to suggest that familial *LCAT* deficiency does not increase the risk of ASCVD [20, 31–33]. Imaging studies have also reported conflicting result regarding subclinical atherosclerosis in heterozygous carriers of *LCAT* mutations [34–36].

Genome-Wide Association Studies and Mendelian Randomization

Genome-wide association studies (GWAS) have identified 71 loci associated with HDL-C levels [37]. Of these, 46 loci are associated with HDL-C without statistically significant associations with other lipid parameters. In addition to their role in identifying genetic variants that are associated with plasma lipids and risk for ASCVD, human genetic studies also provide an opportunity to infer the causal relationship between an exposure (genetically determined HDL-C levels) and outcome (ASCVD risk). Such Mendelian randomization studies have consistently reported that genetic risk scores constructed from variants that associate with HDL-C levels from GWAS, or individual variants that associate with HDL-C levels, do not impact ASCVD risk [13–15, 38, 39, 40•, 41, 42]. Collectively, these studies provide one of the strongest arguments against a causal role for HDL-C in atherosclerosis.

While these studies provide strong evidence that genetically determined elevations in HDL-C do not impact ASCVD risk, there are a number of caveats. Firstly, the magnitude of change in HDL-C conferred by these genetic variants are often very small, typically in the range of 0.01–0.1 mmol/L (0.38–3.8 mg/dL). Whether such small changes in HDL-C are enough to modify risk in an individual patient is uncertain. Secondly, the use of genetic risk scores is problematic in that the biological function of most of the variants included is unknown. As a result, predicting what effect these genetic variants may have on ASCVD risk is challenging. This is critical because the complexity of HDL metabolism means that not every variant that raises plasma HDL-C levels can be assumed to reduce ASCVD risk. This is highlighted by the fact that the genetic risk score used in one of the seminal Mendelian randomization studies included a variant in *SCARB1* [13], which raises HDL-C but based on its biological function would be expected to *increase* ASCVD risk (see below). If these genetic risk scores include a combination of variants with varying effects on ASCVD risk (increase, decrease or no effect), it could explain why the genetic risk score as a whole does not appear to modulate ASCVD risk.

One exception to this relates to the cholesterol ester transfer protein (*CETP*) gene. A number of Mendelian randomization studies have used variants in the *CETP* gene that associate with increased HDL-C as an instrument to determine the impact of high HDL-C on ASCVD risk [43, 44]. These studies consistently report a reduction in ASCVD risk in patients with genetically reduced *CETP* activity and increased HDL-C. However, in addition to raising HDL-C levels, these genetic variants also reduce LDL-C, TG, and non-HDL-C. Whether the reduction in ASCVD risk is due to the increased HDL-C, decreased non-HDL-C, or a combination of both is unknown.

Rare Variant Association Studies

The availability of very large cohorts of patients that have been genotyped or sequenced has created new opportunities to investigate the impact of rare genetic variants that influence HDL metabolism on atherosclerosis. This approach was powerfully demonstrated in a recent study of the scavenger receptor B1, *SCARB1*, gene [45••]. Pioneering studies in mice had established that *SCARB1* plays a key role in HDL metabolism and functions as a hepatic HDL-C receptor [46, 47]. Despite having elevated HDL-C, mice with deletion of *Scarb1* have increased atherosclerosis [48, 49]. Mechanistically, this is explained by impaired reverse cholesterol transport in these mice due to reduced hepatic HDL-C uptake [50].

Until recently, the extent to which these observations could be extrapolated to humans was unknown. In 2011, the first humans with heterozygous mutations in *SCARB1* were described [51, 52]. These patients have elevated HDL-C, exactly as predicted from studies in mice. However, the number of patients with these rare mutations was too small to assess the risk of ASCVD. In 2016, Zanoni et al. described a patient homozygous for a rare variant in *SCARB1* (p.P376L) which resulted in loss-of-function of the encoded protein [45••]. This patient had significantly elevated HDL-C levels and evidence of subclinical atherosclerosis. Leveraging the availability of large case–control cohorts of patients with ASCVD, the authors then investigated the role of p.376 L in ASCVD risk in ~137,000 individuals. They found that p.376 L conferred an

increased risk for coronary heart disease with an odds ratio of 1.79, $P = 0.018$ [45••], providing clear evidence that this rare genetic variant in a hepatic HDL receptor leads to elevated HDL-C and increased risk of ASCVD.

While it is possible that *SCARB1* may impact ASVCD risk independently of its effect on HDL metabolism, this study provides one of the most compelling examples of human genetic variation in an HDL-related gene that impacts susceptibility to ASCVD. Unexpectedly (although presaged by studies in mice [46, 47]), this variant causes *increased* HDL-C and *increased* ASCVD, which would seem to be in contrast with the inverse epidemiological relationship between HDL-C levels and ASCVD risk. This example therefore establishes the crucial importance of what impact a genetic variant has on flux through the HDL pathway rather than simply the HDL-C level, and cautions against simplistic interpretations between the HDL-C level and ASCVD risk. This study also demonstrates the tremendous opportunity offered by large cohorts of genotyped cases and controls for identifying rare genetic variants that affect ASCVD in humans.

Rare variants in *APOA1* also appear to impact ASCVD risk. A large re-sequencing study of *APOA1* reported an increased risk for myocardial infarction in (HR 1.7) among individuals with non-synonymous variants in this gene [53]. A rare variant study of ~33,000 ASCVD cases and 236,000 controls identified five genetic variants that were associated with lipid levels and coronary artery disease [40•]. One of these was a novel missense variant, p.V43L, in *APOA1* with an allele frequency of 0.7 %. This variant was associated with a 0.17 mmol/L (6.5 mg/dL) increase in HDL-C levels and a 26 % reduction in risk for coronary artery disease. These data are consistent with the concept that p.V43L is a gain-of-function variant in *APOA1* that raises HDL and reduces risk for ASCVD. While this variant was also associated with both triglycerides and non-HDL-C levels [40•], the strongest association with blood lipids was with HDL-C, and the known biological role of apolipoprotein A-I as the principal apolipoprotein of HDL supports that its effect on ASCVD is via its role in HDL metabolism. Additional studies will be needed to confirm this association and determine the mechanism by which this variant raises HDL-C levels.

Making Sense of HDL and ASCVD Risk

How can we reconcile the seemingly disparate findings from human genetic studies regarding HDL and atherosclerosis? Certain Mendelian disorders of HDL appear to impact ASCVD risk (*APOA1* deficiency and Tangier disease), whereas others seemingly do not (familial *LCAT* deficiency). Mendelian randomization studies consistently show no impact of genetically determined changes in HDL-C levels on ASCVD risk. Rare variant studies have identified specific mutations that impact key proteins in HDL biology and do modulate ASCVD risk.

One important factor in interpreting these results is the interactions between different lipoprotein classes as part of normal lipid physiology and the pleiotropic effects of genetic variants on lipid levels. For example, most loss-of-function mutations in *ABCA1* result in not only low HDL-C but also low LDL-C, and indeed, patients with Tangier disease typically have a ~40 % reduction in LDL-C levels [54]. These changes in lipid levels would be predicted to have conflicting results on ASCVD risk, which may partially explain the less-than-anticipated increase in ASCVD rates in patients with Tangier disease. Mendelian randomization studies have attempted to address this by focusing on genetic variation for which there is statistically significant associations with HDL-C levels and not other lipid levels [13, 38]. However, in so doing, these studies typically use genetic variants in genes for which the functional role in lipid metabolism is unknown. Consequently, predicting how they might impact ASCVD risk is problematic.

A critical theme to emerge from these studies is that the level of HDL-C may be considerably less important than the mechanism by which that HDL-C level was achieved. This concept explains why some genetic variants that impact HDL-C do influence ASCVD risk [40•] whereas others do not [13]. The primacy of mechanism over static HDL-C level is perhaps most clearly demonstrated by loss-of-function variants in *SCARB1* that raise HDL-C and increase ASCVD risk [45••]. Whereas a simplistic interpretation based on observational epidemiology is that raised HDL-C should lower ASCVD risk, a deeper understanding of the role of *SCARB1* in HDL biology, based on a large body of work in animal and cellular models, predicts that blocking a critical step in hepatic HDL uptake and thereby impairing flux through the reverse cholesterol transport pathway would be expected to increase ASCVD risk. The implications for drug development are that attention should be focused on pharmacological targets predicted to increase flux through the HDL pathway, rather than on those that simply raise HDL-C levels.

A limitation in the field remains our inability to accurately measure HDL function or flux and the inadequacy of HDL-C levels as a metric of atheroprotection. Improved biomarkers of HDL functionality, such as efflux potential [55, 56], may help provide additional insight into the function of specific genetic variants on HDL function. Rare variant studies in large cohorts of patients, such as those performed for variants in *SCARB1* [45••] and *APOA1* [40•], provide an outstanding opportunity to investigate the impact of pathogenic variants in genes that impact HDL through established mechanisms. Such studies may well yield additional examples of genetic variants that influence HDL-C and ASCVD risk.

Conclusions

Human genetics provides a complex and, at times, discordant picture of the relationship between HDL and atherosclerosis. Although many outstanding questions remain, recent developments have helped to fill in some of the gaps and allow a more complete picture to emerge. While genetically determined alterations in HDL-C levels do not appear to influence ASCVD risk as a whole, specific genetic mechanisms that impact key steps in HDL metabolism do modulate ASCVD risk in ways that are predictable based on an understanding of HDL biology. Sufficient examples from human genetics now exist whereby alterations in HDL-C levels are associated with changes in ASCVD risk to support the body of evidence from epidemiology and preclinical studies that HDL is a causal factor in atherogenesis. What is clear is that the relationship between HDL and atherosclerosis is complex, intriguing, and that the final chapter has not yet been written.

Acknowledgments LRB is supported by a Heart & Stroke Foundation of Canada National New Investigator Award and is a Canadian Institute of Health Research New Investigator. His laboratory is supported by an Emerging Research Leaders Initiative grant from the Heart & Stroke Foundation of Canada.

Compliance with Ethical Standards

Conflict of Interest Liam R. Brunham declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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