HHS Public Access

Author manuscript

Atherosclerosis. Author manuscript; available in PMC 2015 June 17.

Published in final edited form as:

Atherosclerosis. 2014 December ; 237(2): 838–839. doi:10.1016/j.atherosclerosis.2014.10.026.

High-density lipoprotein and endothelial function in patients with myocardial infarction: Pieces in a puzzle

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Keywords

High-density lipoprotein; Nitric oxide; Endothelial function; Myocardial infarction

Like the colorful lights of the aurora borealis, high-density lipoproteins (HDLs) are full of character and inspire wonder. Their extremely heterogeneous polymolecular complexity and multidimensional functionality demands careful scrutiny, or else their wondrous nuances could go unappreciated [1–3]. Indeed, while epidemiological observations have suggested an important role of HDL in protection from cardiovascular disease (CVD), recent clinical trials have tempered enthusiasm over simply raising the quantity of cholesterol within HDL [4–7]. The lack of positive clinical trials in this space has only increased motivation for a deeper understanding of how pieces of the puzzle fit together in the HDL-CVD relationship.

Over the life course of an HDL particle, there is continual remodeling of the lipidome and proteome, and these dynamic structural changes appear to dictate functionality. Reverse cholesterol transport is the classic function, but not necessarily the most important one. Other described HDL functions include platelet reactivity, heme metabolism, vitamin binding, insulin secretion, immunity, and as addressed in this issue by Carvalho et al. [7]– antioxidative/anti-inflammatory activity and regulation of endothelial function.

Translational mechanistic studies like Carvalho et al.'s are important to bridging the space between basic science and outcomes research. In a prospective cohort design, the Brazilian Heart Study investigators examined 180 consecutive patients with ST-elevation myocardial infarction (STEMI). Embracing the dynamic nature of HDL, assessments were performed at admission and again at day 5 and day 30. The analysis showed that those with higher admission HDL cholesterol levels (third tertile >42 mg/dL) had a ~50% lower acute increase in plasma nitric oxide levels compared to those with HDL cholesterol levels <33 mg/dL and relatively less favorable endothelial function (~40% lower) at day 30 by flow-mediated dilatation (FMD). The study team performed a parallel anti-oxidative/anti-inflammatory protocol involving a subset of 9 non-diabetic STEMI patients and 9 age- and sex-matched

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healthy volunteers. Within 24 h of STEMI admission, HDL showed similar capacity for preventing LDL oxidation relative to healthy subjects, but STEMI patients then demonstrated significant impairment at day 5. It appeared that the acute inflammatory response with STEMI brought dynamic structural changes in HDL (reduction in apoA-I content) associated with impaired antioxidant/anti-inflammatory activity, which may underlie the observed relationship between HDL-C and FMD.

Guidelines view FMD as a research tool for non-invasive assessment of vascular endothelial function [8]. After release of arterial compression, blood flow stimulates nitric oxide release in healthy endothelium, inducing vasodilation that can be quantified by ultrasound. Generally considered a technically-challenging technique, FMD is best performed by experienced research teams like the Brazilian Heart Study investigators. When measured in expert laboratories, brachial artery FMD has been linked with invasive coronary endothelial function testing and long-term cardiovascular risk. However, standardizing FMD measurement across individual patients and research labs poses a challenge given the operator-dependency of the technique and possible variations in measurement at different times of day or temperatures, for instance. While FMD as a surrogate end-point is important and interesting, hard outcome data are critical, a lesson that has been learned the hard way in the HDL therapy world [2, 6].

Regarding hard clinical outcomes, the authors noted the recent report of a null predictive value for HDL-C in secondary prevention. We [9] along with two other groups [10, 11] have reached compatible findings. In addition, it is worth noting that two Mendelian randomization studies were not able to establish a causal role for HDL-C in risk of myocardial infarction [12, 13]. This may come as a surprise to many given the widely ingrained beliefs about HDL cholesterol's inverse relationship with risk.

Taking the line of investigation a step beyond total HDL cholesterol, in secondary prevention patients, we examined the risk associations of its two major subclasses: HDL_2-C and HDL_3-C [9]. Participants were from two modern, prospective, cohort studies: Translational Research Investigating Underlying disparities in acute Myocardial infarction Patient's Health status (TRIUMPH) registry and Intermountain Heart Collaborative Study (IHCS). The complementary nature of the study populations enhances their generalizability; TRIUMPH included STEMI and non-STEMI patients from 24 hospitals across the United States while the IHCS involved patients undergoing cardiac catheterization for a spectrum of coronary indications. Although HDL_2-C was not significantly associated with risk, those in the lowest tertile of HDL_3-C had an approximately 50% higher risk of long-term mortality after accounting for potential confounding variables. The smaller, denser, protein-rich HDL_3 subclass tends to carry about three-fourths of HDL cholesterol [9] and most closely relates to the broad range of atheroprotective HDL functions [1]. As Carvalho et al. discuss, an acute inflammatory surge related to myocardial infarction may induce endothelial lipase and phospholipases, and attenuate lecithin-cholesterol acyltransferase activity, in turn, resulting in denser, cholesterol-depleted HDL particles. However, to what extent this explains our results is unclear as blood specimens were drawn near discharge in TRIUMPH and at the time of cardiac catheterization in IHCS, and similar findings were reached.

Similar results were also reached in diverse primary prevention populations inclusive of Caucasian and African-American men and women from the Framingham Offspring Cohort and Jackson Heart Studies, where evidence supports HDL_3-C as the primary link to coronary risk and mortality [14, 15]. The longest available follow-up (53 years) comes from Gofman's Livermore Cohort wherein analytic ultracentrifugation was performed at baseline to measure HDL subclass mass [15]. In an analysis of 1144 men, 34% survived to age 85, and the odds of survival were 70% higher for men above the lowest quartile of HDL_3-C compared to men within that lowest HDL_3-C group, a finding that persisted after adjustment for standard risk factors.

Given that low HDL_3-C relates to risk similarly at different time points in the context of secondary prevention, and also in primary prevention, one cannot conclude that the acute HDL changes in the context of myocardial infarction primarily explain the connection between low HDL_3-C and poor prognosis. Still, as the authors point out, evidence indicates that HDL_3 in myocardial infarction patients is especially susceptible to oxidation. We can thus speculate that one reason for the link of low HDL_3-C to higher mortality risk may be poor reserve in the oxidative buffering function of HDL and greater vascular injury that may result. However, we suspect that this would be one of multiple important mechanisms of injury and risk.

Overall, we believe that there has been a long-standing challenge in the HDL field to connect different lines of evidence. From basic research to translational studies to population science to clinical trials, we submit that there is a strong need to work together to build the evidence in a collaborative and complementary fashion. Once pieces of the puzzle start fitting together, then we may start making sense of the mystery that is HDL. It is important to consider how patient characteristics may impact results. The present study population was predominantly composed of Brazilian men, with a large portion of smokers, who were treated with chemical revascularization. Whether the findings would have been similar, for instance, in American women who are non-smokers and treated with percutaneous coronary intervention is not certain. Also, given statin therapy has an impact on both HDL-C and inflammation, it will be important to carefully scrutinize the relevance of this to the findings. Of course none of the healthy volunteers in this study were taking statins.

In conclusion, Carvalho et al.'s documentation of dynamic structural and functional changes in HDL during STEMI, and connection of these changes with FMD, are an important addition to the literature that further support the growing movement towards a more sophisticated structural-functional characterization of HDL. We look forward to following the Brazilian Heart Study and learning how the findings in this study eventually map to hard clinical outcomes. If our research community continues to be inspired by the complexity of HDL and collaboratively embrace the challenge of trying to understand it, we may fit together the pieces of the puzzle with this intricate lipoprotein and clarify whether it is a viable therapeutic target in CVD.

Acknowledgments

Support

SSM is supported by the Pollin Cardiovascular Prevention Fellowship, *Marie-Josée* and Henry R Kravis endowed fellowship, and a National Institutes of Health training grant (T32HL07024). PHJ is supported by the Pollin Cardiovascular Prevention Fellowship and a National Institutes of Health training grant (T32HL007227).

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