High-density lipoprotein and inflammation in cardiovascular disease

MARGERY A. CONNELLY, IRINA SHALAUROVA, and JAMES D. OTVOS

RALEIGH, NC

Great advances are being made at the mechanistic level in the understanding of the structural and functional diversity of high-density lipoprotein (HDL). HDL particle subspecies of different sizes are now known to differ in the protein and lipid cargo they transport, conferring on them the ability to perform different functions that in aggregate would be expected to provide protection against the development of atherosclerosis and its downstream clinical consequences. Exacerbating what is already a very complex system is the finding that inflammation, via alteration of the proteomic and lipidomic composition of HDL subspecies, can modulate at least some of their functional activities. In contrast to the progress being made at the mechanistic level, HDL epidemiologic research has lagged behind, largely because the simple HDL biomarkers used (mainly just HDL cholesterol) lack the needed complexity. To address this deficiency, analyses will need to use multiple HDL subspecies and be conducted in such a way as to eliminate potential sources of confounding. To help account for the modulating influence of inflammation, effective use must also be made of inflammatory biomarkers including searching systematically for HDL-inflammation interactions. Using nuclear magnetic resonance (NMR)-measured HDL subclass data and a novel NMR-derived inflammatory biomarker, GlycA, we offer a case study example of the type of analytic approach considered necessary to advance HDL epidemiologic understanding. (Translational Research 2016;173:7–18)

Abbreviations: Apo = apolipoprotein; BMI = body mass index; CAD = coronary artery disease; CHD = coronary heart disease; CVD = cardiovascular disease; HDL = high-density lipoprotein; HDL-C = HDL cholesterol; HDL-P = HDL particle concentration; HPS = Heart Protection Study; hsCRP = high-sensitivity C-reactive protein; IRAS = Insulin Resistance Atherosclerosis Study; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL = low-density lipoprotein; LDL-C = LDL cholesterol; LDL-P = LDL particle concentration; LP-IR = lipoprotein insulin resistance index; MESA = Multi-Ethnic Study of Atherosclerosis; MPO = myeloperoxidase; NMR = nuclear magnetic resonance; PON1 = paraoxonase-1; PREVEND = Prevention of Renal and Vascular End-stage Disease; RA = rheumatoid arthritis; SAA = serum amyloid A; T2D = type 2 diabetes; VLDL = very low-density lipoprotein

From the LipoScience, Laboratory Corporation of America Holdings, Raleigh, NC.

Submitted for publication December 9, 2015; accepted for publication January 11, 2016.

Reprint requests: James D. Otvos, LabCorp, 2500 Sumner Boulevard, Raleigh, NC 27616; e-mail: otvosj@labcorp.com.

1931-5244/$ - see front matter

http://dx.doi.org/10.1016/j.trsl.2016.01.006

HIGH-DENSITY LIPOPROTEIN PARTICLES AND THE IMMUNE SYSTEM

On the basis of the various functions ascribed to high-density lipoprotein (HDL), HDL particles can be considered to be an integral part of the innate immune system. The best known function of HDL is facilitation of the reverse cholesterol transport pathway: the efflux of excess unesterified cholesterol from peripheral cells and subsequent transport of cholesterol and cholesteryl esters to the liver

for biliary secretion.[1-4] However, additional activities have been attributed to HDL particles including anti-inflammatory, antioxidant, antithrombotic, endothelial repair, angiogenesis, and most recently, antidiabetic.[5-12] HDL particles also play a role in host defense against microbial infection.[13,14] Many of these activities have been invoked to explain the inverse relationship between HDL cholesterol (HDL-C) and cardiovascular disease (CVD).[15-17] HDL particles have been referred to as "dysfunctional" in various inflammatory diseases when they exhibit reduced anti-inflammatory or reverse cholesterol transport activities and provide less of a protective role in CVD. However, such HDL particles may, in fact, remain functional but serve very different roles during inflammation.

The many roles HDL particles play in the immune system are evident by its protein and lipid cargo.[18] The Davidson laboratory at the University of Cincinnati compiled a list of proteins that were found on HDL particles using 17 published mass spectrometry–based studies.[19] The current list, called the HDL Proteome Watch, reveals 95 proteins confirmed in multiple studies to be carried by HDL (http://homepages.uc.edu/~davidswm/HDLproteome.html).[19] Besides containing proteins that are involved in lipid metabolism such as apolipoprotein A-I (apoA-I), apoA-II, and apoE, HDL particles also carry proteins that are part of the immune system.[19,20] For example, the HDL proteome includes proteins involved in (1) complement activation (complement factors C3, C4A, and C4B), (2) microbial killing (apoL1 and haptoglobin-related protein), and (3) regulation of inflammation (α1-acid glycoprotein, α1-antitrypsin, haptoglobin, and α1-antichymotrypsin).[19,21-23] The HDL lipidome is also heterogeneous and reflects the many functions of HDL.[24] Depending on the disease state, HDL particles may contain lipids that are either proinflammatory or anti-inflammatory in nature.[24] HDL is also known to transport hormones, water insoluble vitamins, steroids, carotenoids, bile acids, and microRNA, which have biologically diverse functions, some of which include immune modulation.[18]

INFLAMMATION MODULATES HDL COMPOSITION AND FUNCTION

The composition and structure of HDL particles are modified in patients with chronic low-grade inflammation or severe inflammatory diseases.[25,26] A number of studies revealed that small HDL particles from subjects with coronary artery disease (CAD) were selectively enriched in apoE, apoA-IV, apoC-IV, complement C3, and paraoxonase-1 (PON1).[21,27,28] Another study showed significant differences in serum amyloid A (SAA), apoA-IV, and complement C3 concentrations in control subjects compared with subjects with either stable CAD or acute coronary syndrome.[29] Similar changes were noted in subjects with psoriasis and rheumatoid arthritis (RA) where there were notable reductions in apoA-I and concomitant increases in apoA-II and acute phase proteins.[26,30] Compared with patients with anti-inflammatory HDL, RA patients with proinflammatory HDL particles had significantly higher levels of HDL-associated haptoglobin, hemoglobin, apoA-I, and myeloperoxidase (MPO).[31] Reductions in HDL phospholipid content were also noted in subjects with psoriasis.[30]

HDL metabolism is altered in subjects with increased inflammation, which is typically revealed by alterations in HDL subclass distribution. Subjects with metabolic syndrome and type 2 diabetes (T2D) have increased levels of small HDL and LDL particles, largely because of decreased lipoprotein lipase and increased hepatic lipase–mediated lipolysis.[32] In contrast, in subjects with enhanced inflammation, higher endothelial lipase activity leads to increased HDL phospholipid hydrolysis and increased elimination of HDL particles, thereby reducing HDL particle concentrations.[33] These changes are evident in subjects with RA, where there are distinct inflammation-mediated alterations in the lipoprotein profile.[34,35] For example, concentrations of small HDL particles were found to be lower in RA patients compared with controls and in RA patients with coronary calcification compared with those without.[36] Furthermore, small HDL particle concentrations in RA patients were inversely related to measures of inflammatory disease activity.[36]

Inflammation-mediated modifications of the HDL proteome, lipidome, and subclass distribution lead to altered HDL functionality.[5,31,37-40] For example, HDL particles with increased oxidized phospholipid content exhibit reduced PON1 activity.[41,42] Additionally, MPO was found to interact with PON1 on HDL particles, leading to site-specific oxidative modification of PON1 and reduced PON1 antioxidant activity.[43] ApoA-I has also been shown to be a target of MPO, leading to altered HDL function.[44,45] Recent studies revealed that changes in the HDL proteome in patients with CAD were associated with alterations in the ability of HDL particles to activate endothelial antiapoptotic and proapoptotic pathways.[46] Moreover, inflammatory remodeling of the HDL proteome has been shown to reduce cholesterol efflux capacity, a measure of the initial step in the reverse cholesterol transport pathway.[47,48] For example, acute phase proteins such as SAA and α1-acid glycoprotein bind HDL particles leading to a reduction in HDL-associated apoA-I and apoM and reduced cholesterol efflux.[39,49] Furthermore, anti-inflammatory agents that modify