Editorial

High-density lipoprotein: does it have a dark side?

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See related review article by Hahn *et al*., http://arthritis-research.com/content/10/4/213

Abstract

There are proven pleiotropic anti-atherogenic actions of high-density lipoprotein (HDL). However, in systemic inflammation, HDL can have pro-inflammatory properties that may contribute to accelerated atherosclerosis, likely mediated by a change in the structure of HDL to pro-inflammatory HDL (PiHDL). Validation of the technically challenging assay for PiHDL, and confirmation of an association of PiHDL in multiple populations with known risk for atherosclerosis will eventually provide a useful biomarker. Identification of PiHDL in patients with rheumatic disease may help identify patients at risk of accelerated atherosclerosis, and focus our therapeutic interventions.

In the previous issue of *Arthritis Research & Therapy*, Hahn and colleagues [1] provided a comprehensive review of altered lipoprotein metabolism in chronic inflammatory states, and proposed that this altered metabolism may be important in the pathogenesis of accelerated atherosclerosis in rheumatic disease. Cardiovascular morbidity and mortality have been associated with chronic rheumatic diseases, most notably systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Although co-morbidities may frequently co-exist in patients with RA and SLE as a complication of disease or treatment, both SLE and RA have been identified as independent risk factors for atherosclerotic cardiovascular disease [2,3]. What factors or group of factors increase that risk is under intense investigation. Lipids and lipoproteins have been extensively studied, but have not been shown to be a primary risk factor in SLE and RA. In cohorts of SLE patients studied, cholesterol has not been an independent predictor of atherosclerotic cardiovascular disease [4,5]. Additionally, although there has been a consistent pattern of lower high-density lipoprotein (HDL) cholesterol levels seen in RA patients compared with age- and sex-matched controls, the picture is more mixed with regard to total cholesterol and low-density lipoprotein (LDL) cholesterol levels [6,7]. Therefore, if cholesterol metabolism and transport contribute to the presence and progression of atherosclerosis in these inflammatory states, it is reasonable to consider altered lipoprotein states. In their review, Hahn and colleagues present the accumulated data on pro-inflammatory HDL as a novel biomarker for increased risk of atherosclerosis in patients with SLE and RA.

HDL-cholesterol is considered among the best predictors of cardiovascular disease in large populations. However, in the original Framingham study approximately 44% of the events in men and 43% in women occurred in persons with normal HDL-cholesterol levels [8]. Research has proven the pleiotropic anti-atherogenic actions of HDL, and Hahn and colleagues review the three major protective mechanisms by which HDL prevents atherosclerosis: through its role in reverse cholesterol transport; through its antioxidative function, especially with apoA-1 and apoE; and through direct interactions with endothelial cells.

However, more than a decade ago, Van Lenten and colleagues [9] reported that during an acute phase response in animals or in humans following surgery, the properties of HDL changed dramatically, and became pro-inflammatory. These observations have spawned studies evaluating the pro-inflammatory properties of HDL. The processes that account for the modification of normal HDL to pro-inflammatory HDL (PiHDL) are also reviewed in Hahn and colleagues' article and include: oxidation of lipoproteins in the HDL particle; decreased synthesis of protective lipoproteins, especially ApoA-1; and replacement of cholesterol transporting proteins with pro-oxidants, including serum amyloid A and ceruloplasmin. When an acute phase response occurs, non-specific immunity producing an oxidative environment takes place. Thus, HDL appears to be part of the innate immune system and can be either pro-inflammatory or anti-inflammatory depending on the presence or absence of an

CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PiHDL = pro-inflammatory HDL; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

acute phase response and the presence or absence of systemic inflammation.

The assay used to measure PiHDL is a cell-free assay using LDL as the fluorescence-inducing agent and is technically challenging [10]. Replication has been difficult because of the nuances of the assay. Nevertheless, this assay has been used to study at least two populations, the first, an SLE and RA population reported by Hahn's group, and more recently, a South Asian immigrant group.

MacMahon and colleagues [11] reported that SLE patients had more PiHDL than matched controls (mean ± standard deviation score of 1.02 ± 0.57 versus 0.68 ± 0.28 in controls ($p < 0.0001$)) and that SLE patients with coronary artery disease (CAD) had significantly higher PiHDL scores than patients without CAD ($p < 0.001$). PiHDL was associated with elevated levels of oxidized LDL.

Dodani and colleagues [12] studied a cohort of South Asian immigrants, who have a higher risk for CAD compared to Caucasians, and measured sub-clinical CAD using carotid intima media thickness as a surrogate marker of atherosclerosis. On logistic regression analysis, positive carotid intima media thickness was found to be associated with PiHDL after adjusting for age, family history of cardiovascular disease, and hypertension ($p = 0.030$).

These two studies suggest that HDL structure and function may predict atherosclerotic cardiovascular disease better than HDL-cholesterol levels. Although there is a need to replicate and validate these findings in other populations, measurement of PiHDL, along with other markers that correlate with atherosclerotic cardiovascular disease such as homocysteine [4,5], may help us better identify patients with rheumatic disease who are at risk of cardiovascular events. Identification of these patients will facilitate therapeutic interventions to prevent the morbidity and mortality associated with accelerated atherosclerosis in rheumatic diseases.

Competing interests

The author declares that they have no competing interests.

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