High-Density Lipoprotein Functionality in Coronary Artery Disease

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Abstract: The role of high-density lipoprotein (HDL) in cardiovascular atheroprotection is well established. Epidemiological data have clearly demonstrated an inverse relationship between HDL levels and the risk for coronary artery disease, which is independent of the low-density lipoprotein levels. However, more recent data provide evidence that high HDL levels are not always protective and that under certain conditions may even confer an increased risk. Thus, a new concept has arisen, which stresses the importance of HDL functionality, rather than HDL concentration per se, in the assessment of cardiovascular risk. HDL functionality is genetically defined but can also be modified by several environmental and lifestyle factors, such as diet, smoking or certain pharmacologic interventions. Furthermore, HDL is consisted of a heterogeneous group of particles with major differences in their structural, biological and functional properties. Recently, the cholesterol efflux capacity from macrophages was proven to be an excellent metric of HDL functionality, because it was shown to have a strong inverse relationship with the risk of angiographically documented coronary artery disease, independent of the HDL and apolipoprotein A-1 levels, although it may not actually predict the prospective risk for cardiovascular events. Thus, improving the quality of HDL may represent a better therapeutic target than simply raising the HDL level, and assessment of HDL function may prove informative in refining our understanding of HDL-mediated atheroprotection.

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The role of low-density lipoprotein cholesterol (LDL-C) in the pathophysiology of atherosclerosis is well known, and the use of LDL-lowering medications has led to a significant reduction of cardiovascular risk in both primary and secondary prevention.[1,2] Of note, though, a significant cardiovascular risk remains even after optimal LDL level has been achieved, and among the major statin trials, the maximum relative risk reduction was no higher than 47%.[3] This is especially true for patients with cardiometabolic disease, and current evidence implicates elevated triglyceride-rich lipoproteins and their remnants and low levels of high-density lipoprotein cholesterol (HDL-C) in this excess cardiovascular risk.[4]

However, epidemiological data have clearly demonstrated an inverse relationship between HDL-C levels and the risk for coronary artery disease (CAD), which is independent of the LDL-C levels and remains relevant even when LDL-C levels are below 70 mg/dL.[5,6] In addition, the absolute benefits of lowering LDL-C seem to be greater in patients with low HDL-C concentrations.[7] However, more recent genetic studies and clinical investigations have come to challenge the hypothesis that lower HDL levels are always detrimental and that higher HDL levels are always beneficial.[8–15]

In a genetic study, approximately 30% lower HDL levels, associated with functional mutations in ATP-binding cassette transporter A1 (ABCA1), did not predict cardiovascular risk in the general population and in patients with cardiovascular disease.[8] Moreover, 3 functional variants of hepatic lipase, associated with a modest rise in HDL levels, did not change the risk of cardiovascular disease.[8] In another genetic study, carriers of a single nucleotide polymorphism in the endothelial lipase gene had higher HDL-C by 5.4 mg/dL but similar levels of other lipid and nonlipid risk factors for myocardial infarction compared with noncarriers. However, this increase in HDL-C was not associated with a decreased risk of myocardial infarction.[9] In addition, recent large-scale genome-wide association studies do not support a direct causal relation between molecularly defined HDL disorders and atherosclerosis per se.[10]

On the other hand, in a recently published large meta-analysis of 12,292 participants, it was shown that the inverse relationship of HDL with cardiovascular mortality was actually weakened in patients with CAD.[11] Moreover, in a clinical study that included a consecutive series of 1548 patients with CAD undergoing coronary artery bypass grafting, higher preoperative HDL levels were not associated with reduced risk of vascular events.[12] More importantly, the increased cardiovascular risk associated with very high HDL levels or very large HDL particles and the detrimental or neutral effects of the cholesteryl ester transfer protein (CETP) inhibitors anacetrapib and dalcetrapib (which will be discussed in more detail later in this review) strengthen the notion that high HDL levels are not always protective.[13–15]

Thus, given the above genetic and clinical data, a new concept has arisen, which stresses the importance of HDL functionality, rather than HDL concentration per se, in the assessment of cardiovascular risk.

This review aims to provide the current evidence pertaining to the importance of HDL functionality over the actual HDL levels in mediating the favorable effects on the cardiovascular system.

Biological Activities of HDL

HDL has a central role in reverse cholesterol transport, the primary mechanism by which excess cholesterol is removed from peripheral vessels and delivered to the liver.[16] Furthermore, HDL seems to have anti-inflammatory, antioxidant, anticoagulant and profibrinolytic actions that may provide additional protection against CAD.[17,18] HDL inhibits LDL oxidation through transfer of oxidation products from LDL to HDL, reduces endothelial cell inflammatory activation through

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inhibition of the expression of monocyte chemoattractant protein-1 and through promotion of efflux of 7-ketocholesterol at sites of inflammation, inhibits apoptosis of endothelial cells induced by both death receptor–mediated and mitochondrial-mediated apoptotic pathways, and stimulates endothelial repair processes after vascular injury.[19] Moreover, HDL impacts the endothelial function by activating endothelial nitric oxide (NO) synthase through binding to scavenger receptor class B type 1 (SR-B1), thus increasing the production of nitric oxide.[18,19] Whereas, mass spectrometry studies have shown that the HDL particles carry multiple proteins, which are not only involved in lipid metabolism but also play a role in complement regulation, acute phase response and proteinase inhibition.[20] Lipidomic approaches have provided initial insights into the HDL lipidome with identification of more than 200 molecular lipid species in normolipidemic HDL, including phospholipids, sphingolipids, steroids, cholesteryl esters, triglycerides, as well as diacylglycerides, monoacylglycerides and free fatty acids.[21] In addition, it has to be stressed that HDL is consisted of a group of particles with high levels of structural, compositional and functional heterogeneity and with major differences in their biological activities. (Figure 1).[21,22]

Apolipoprotein A-1 Milano

The 1st evidence to imply the importance of HDL functionality came from a clinical observation that was made in Italy in the early 1980s. Researchers from the University of Milan described a case series of 33 patients with very low levels of HDL and moderate hypertriglyceridemia but no clinical evidence of premature atherosclerosis.[23] Subsequent genetic analysis revealed that those patients were carriers of a rare genetic mutation, the apoA-1 Milano. This genetic mutation leads to the substitution of arginine for cysteine in the 173 position of apoprotein A-1. Subsequent studies proved that apoA-1 Milano carriers have no signs of preclinical atherosclerosis in their coronary or carotid arteries.[24] Those observations led to the assumption that the HDL particles in those patients are highly functional and/or have enhanced capacity for reverse cholesterol transport.

Based on that assumption, Nissen et al studied the effects of recombinant apoA-1 Milano on atheroma burden in patients with acute coronary syndrome (ACS). Recombinant apoA-1 Milano or placebo were administered by weekly infusions to ACS patients, and the coronary atheroma burden was measured by intravascular ultrasound, which was initially performed within 2 weeks after ACS and was then repeated after 5 weekly treatments. At the 5-week interval, patients receiving recombinant apoA-1 Milano had significant regression of coronary atherosclerosis compared with placebo.[25] Furthermore, a recent animal study showed that recombinant apoA-1 Milano exerts greater anti-inflammatory, antioxidant and plaque-stabilizing effects than wild-type HDL.[26]

Cholesteryl Ester Transfer Protein Inhibitors

The role of the CETP is to promote the transfer of cholesteryl esters from HDL to other lipoproteins, and therefore CETP inhibition raises HDL cholesterol levels and decreases LDL cholesterol levels. Torcetrapib is a CETP inhibitor that has

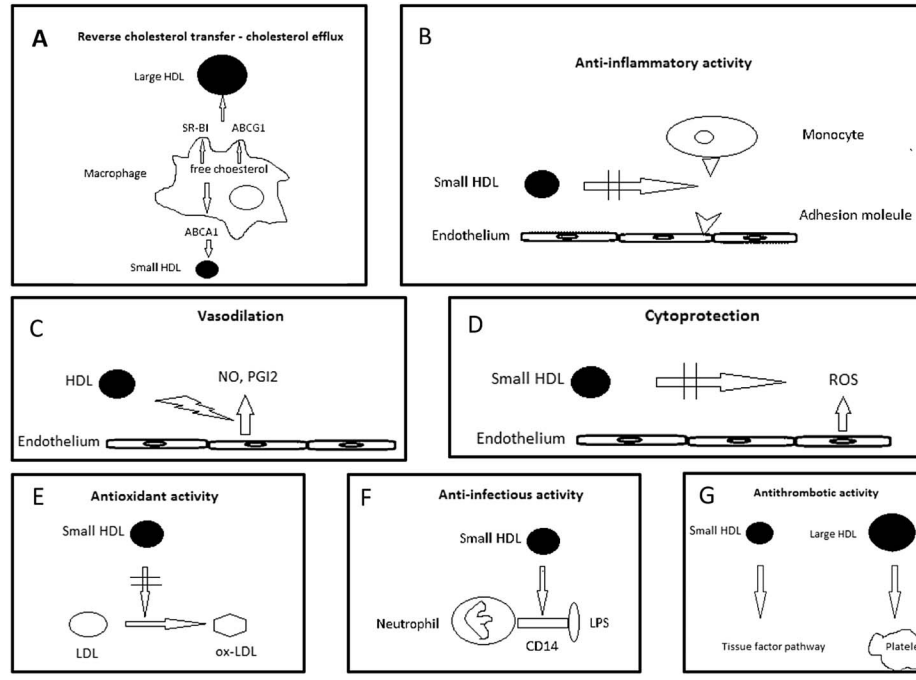

FIGURE 1. Biological activities of HDL. (A) Reverse cholesterol transfer—cholesterol efflux: small HDL particles efflux free cholesterol from macrophages through the ATP-binding cassette A1 (ABCA1) transporter, whereas efflux of large HDL particles is mediated through scavenger receptor class B type I (SR-BI) and the ATP-binding cassette G1 transporter. (B) Anti-inflammatory activity: small HDL particles inhibit the expression of vascular adhesion molecules on the endothelial surface. (C) Vasodilatory activity: HDL promotes the production of the vasoactive molecules NO and PGI2. (D) Cytoprotection: small HDL particles inhibit the production of reactive oxygen species (ROS) from the endothelial cells. (E) Antioxidant activity: small HDL particles inhibit the oxidation of the LDL particles. (F) Anti-infectious activity: small HDL particles, through interaction with the CD14 receptor on the neutrophils, promote the clearance of circulating lipopolysaccharides (LPS). (G) Antithrombotic activity: small HDL particles have anticoagulant properties through inhibition of tissue factor pathways, whereas large HDL particles inhibit platelet aggregation.