HDL Function as a Target of Lipid-Modifying Therapy

Karol E. Watson, MD, PhD, Benjamin J. Ansell, MD,
Andrew D. Watson, MD, PhD, Gregg C. Fonarow, MD, FACC

Division of Cardiology, The David Geffen School of Medicine at UCLA, Los Angeles, CA

High-density lipoprotein (HDL) is conventionally believed to possess many features that protect against atherosclerosis. However, these lipoproteins may be modified in certain individuals and/or circumstances to become pro-inflammatory. The ability of HDL to inhibit or paradoxically to enhance vascular inflammation, lipid oxidation, plaque growth, and thrombosis reflects changes in specific enzyme and protein components. The anti-inflammatory and pro-inflammatory functional properties of HDL can now be assessed using cell-based and cell-free assays. Acute or chronic systemic inflammation and the metabolic syndrome appear to render HDL pro-inflammatory. In contrast, statins and experimental agents such as apolipoprotein A-1 mimetics render HDL more anti-inflammatory. The 2 main classes of existing drugs for HDL modification are fibric acid derivatives, also known as "fibrates," and niacin-containing compounds. In several controlled and prospective intervention studies, patients with low HDL-C and additional risk factors benefited from treatment with fibrates or niacin. However, an increase in HDL-C did not lead to a decrease in cardiovascular events in all trials.

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Multiple epidemiology studies and population-based investigations have established that the concentration of high-density lipoprotein (HDL) cholesterol is an independent predictor of atherosclerotic events. These data have stimulated tremendous interest in the structure, function, and therapeutic potential of HDL.

The best-known anti-atherogenic function of HDL is reverse cholesterol transport—the ability to remove cholesterol from the artery wall and transfer it to the liver for metabolism and/or excretion. However, recent investigations have revealed that HDL likely protects against atherosclerosis by other mechanisms as well. HDL has antioxidant, anti-inflammatory, and antithrombotic properties, and it is likely that all of these features contribute to its anti-atherosclerotic effects. Even more recently, it has also been recognized that HDL can both moderate and enhance inflammation in atherogenesis. The anti-inflammatory functions of HDL include limiting lipid peroxidation, influencing expression of cytokines, modulating recruitment/adhesion of monocytes, and altering other aspects of endothelial function.[1] Paradoxically, HDL particles can also assume pro-inflammatory, pro-atherogenic characteristics, especially when an acute phase or chronic systemic inflammatory response is present.[2]

Dietary and exercise strategies can lead to modest improvements in HDL-cholesterol (HDL-C) concentrations and, in fact, may be associated with greater antioxidative potential of HDL.[3] Lipid-modification with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, can favorably impact the anti-inflammatory/pro-inflammatory potential of HDL.[4] Functional characterization of HDL may allow for enhanced accuracy in assessing cardiovascular risk as well as provide a therapeutic target for risk reduction. In this article, we will review the current understanding of HDL function, its role in atheroprotection, and the potential clinical utility of assessing HDL function.

HDL Structure and Functions

HDL particles consist of an outer layer of free cholesterol, phospholipid, and several apolipoproteins, along with an inner portion that contains triglyceride and cholesterol-ester. Apolipoprotein (apo) A-1 is the principal protein of HDL. HDL particles also carry enzymes, such as paraoxonase, platelet-activating factor–acetylhydrolase (PAF-AH), lecithin cholesterol acyltransferase (LCAT), and cholesteryl ester transfer protein (CETP). HDL particles have been categorized into several subtypes on the basis of several analytical properties, including density, electrophoretic mobility, or size (via nuclear magnetic resonance). The differences in HDL particles result mainly from the species and abundance of apolipoproteins per HDL and the volume of the cholesterol ester in the core of the particle.[5]

The antiatherogenic function of HDL particles that is most commonly appreciated relates to their ability to promote the efflux of cholesterol from cells of the artery wall, a capacity that initiates reverse cholesterol transport and is generally attributed to apoA-1. Efflux of cholesterol can occur by several mechanisms, including 1) passive diffusion of free cholesterol from the macrophage, with subsequent esterification by lecithin:cholesterol acyltransferase associated with HDL, 2) transport of cholesterol to HDL via scavenger receptor B1 on the vessel wall surface, and 3) most significantly, binding of lipid-poor apoA-1 to the adenosine triphosphate-binding cassette (ABC) A1 transporter in the vessel wall, where it accepts free cholesterol, forming pre-beta HDL that matures through esterification to alpha-migrating HDL.[6] In addition to its role in reverse cholesterol transport, HDL also has potent antioxidant, anti-inflammatory, and antithrombotic properties that may play important roles in the anti-atherogenic effects of HDL

Lipid Oxidation in Atherosclerosis

Oxidation is central to the initiation and propagation of atherosclerosis.[4] Oxidation of phospholipids within low-density lipoproteins (LDL) leads to the production of minimally modified LDL (mm-LDL) that initiates a sequence of events that lead to the initial fatty streak.[7] Lipid hydroperoxides can also decrease nitric oxide production and thus decrease the vasomotor response of the arterial wall in vitro.[8] Oxidized LDL is also associated with aggregation of LDL in vivo and coronary artery cell toxicity in vitro.[9] It is thus likely that a progressive cycle of lipid oxidation and nitric oxide depletion can contribute to the accelerated development of atherosclerosis.[10]

Lipid oxidation contributes to vascular inflammation and is more likely to occur when systemic inflammation is present. Leukocytes from patients with either systemic lupus erythematosus or rheumatoid arthritis can cause enhanced lipid peroxidation[11,12] and LDL oxidation.[13] These altered lipids are called *lipid hydroperoxides* and are products of the 5-lipoxygenase pathway.[12] LDL oxidation and plasma lipid hydroperoxides are increased during systemic infection[14] and in patients with the metabolic syndrome.[15]

HDL as an Antioxidant

HDL plays an important role as an antioxidant both by inhibiting phospholipid oxidation within LDL and by reducing the activity of mm-LDL.[16] Several components of HDL contribute to this antioxidant effect, including apoA-1 and antioxidant enzymes such as paraoxanase, PAF-AH, and LCAT.[17] Watson and colleagues[16] demonstrated that paraoxanase prevents the formation of lipid

hydroperoxides and oxidized phospholipids and hydrolyzes them once they are formed. In vitro, apoA-1 also reduces lipid hydroperoxides within LDL, independent of paraoxonase.[18] Graham and associates[19] have shown that phospholipids in the HDL-3 fraction are especially capable of retarding LDL oxidation.

In Certain Circumstances, Rather Than Being Antioxidant, HDL Can Become Pro-Oxidant

In many patients with atherosclerosis, it appears that HDL is not only ineffective as an antioxidant, but, paradoxically, it increases lipid peroxide formation. HDL from patients with a history of coronary heart disease (CHD) is not only unable to prevent LDL oxidation, but it enhances the oxidation of LDL and phospholipids in LDL.[20] Although oxidation of HDL is usually harmful, it does not always generate ineffective HDL. Macdonald and colleagues[21] reported that tyrosyl radical oxidation of mouse HDL enhances its ability to promote cholesterol efflux in vitro and inhibits aortic lesion development in vivo.

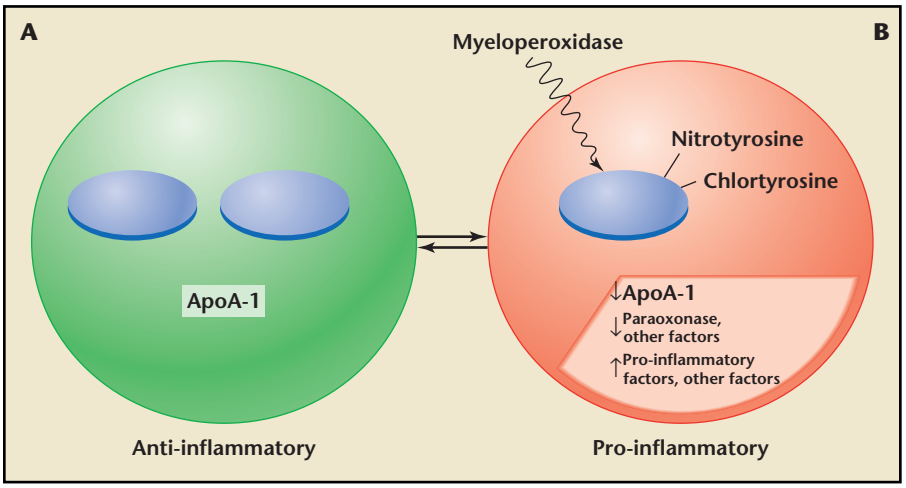


Figure 1. *Model of bidirectional conversion of HDL from anti-inflammatory* (**A**) *to pro-inflammatory* (**B**)*, and the role of myeloperoxidase in catalyzing oxidative modification of HDL, rendering it unable to effect ABCA1-mediated cholesterol transport. In association with these changes, apoA-1 and paraoxanase levels decrease, while proinflammatory factors such as lipid oxidation products increase. Apo, apolipoprotein; HDL, high-density lipoprotein; ABC, adenosine triphosphate-binding cassette transporter. Adapted by permission from Macmillan Publishers Ltd:* Nat Med. *Fogelman AM.[2] 2004.* www.medreviews.com

In many patients with atherosclerosis, it appears that high-density lipoprotein (HDL) is not only ineffective as an antioxidant, but, paradoxically, it increases lipid peroxide formation.

While tyrosyl radical oxidation of HDL may augment cholesterol efflux, oxidation and subsequent nitration of HDL has the opposite effect. An antioxidant under normal conditions, endothelial nitric oxide can be altered by myeloperoxidase produced by macrophages to create nitric oxide–derived oxygen species that can promote oxidative stress and atherosclerosis.[22,23] Zheng and colleagues[22] identified apoA-1 as a specific target of myeloperoxidase that, when oxidized and nitrated, impaired ABCA1-dependent cholesterol efflux.

Furthermore, exposing HDL or apoA-1 to the myeloperoxidase product hydrochlorous acid almost entirely abolishes ABCA1-dependent reverse cholesterol transport.[24] Figure 1 summarizes the role of myeloperoxidase in catalyzing oxidative modification of HDL, rendering it unable to employ ABCA1-mediated transport.

Analogous to its adverse effects on HDL function, myeloperoxidase may also inhibit endothelial cell function, given the strong inverse relationship between flow-mediated dilation of the brachial artery and serum myeloperoxidase levels.[25] Based on the enzyme's potential linkage between oxidation and vascular inflammation, Nicholls and Hazen[23] have suggested that myeloperoxidase itself may be an important biomarker of atherosclerotic risk as well as a target for therapeutic intervention.

HDL as an Anti-Inflammatory Agent

In response to the production of oxidized phospholipids within the subendothelial space of a developing atherosclerotic plaque, monocyte chemotaxis protein-1 is produced by the vascular endothelial cells.[26] There is therefore a close association between oxidation and inflammation, and HDL appears to moderate both of these processes.

Another important anti-inflammatory role of HDL is to limit the expression of cytokines, such as tumor necrosis factor-α and interleukin-1, that mediate up-regulation of leukocyte endothelial adhesion molecules. Cockerill and colleagues[27] have shown that human endothelial cells, when pretreated with HDL, show markedly reduced expression of leukocyte adhesion molecules when stimulated by these inflammatory cytokines.

Pro-Inflammatory HDL

Under certain circumstances, rather than being anti-inflammatory, HDL can act in such a way as to amplify vascular inflammation.[28] Ansell and colleagues[20] demonstrated that the HDL from a majority of patients with CHD or CHD–risk equivalents enhanced LDL-induced recruitment of monocytes in an experimental coculture of endothelial and smooth muscle cells—and thus was pro-inflammatory. None of the age- or sex-matched controls without CHD had pro-inflammatory HDL. In other patient cohorts and circumstances, HDL also appears to have pro-inflammatory effects, as discussed below.

Relationship of Anti-Inflammatory/ Pro-Inflammatory Properties of HDL to Reverse Cholesterol Transport

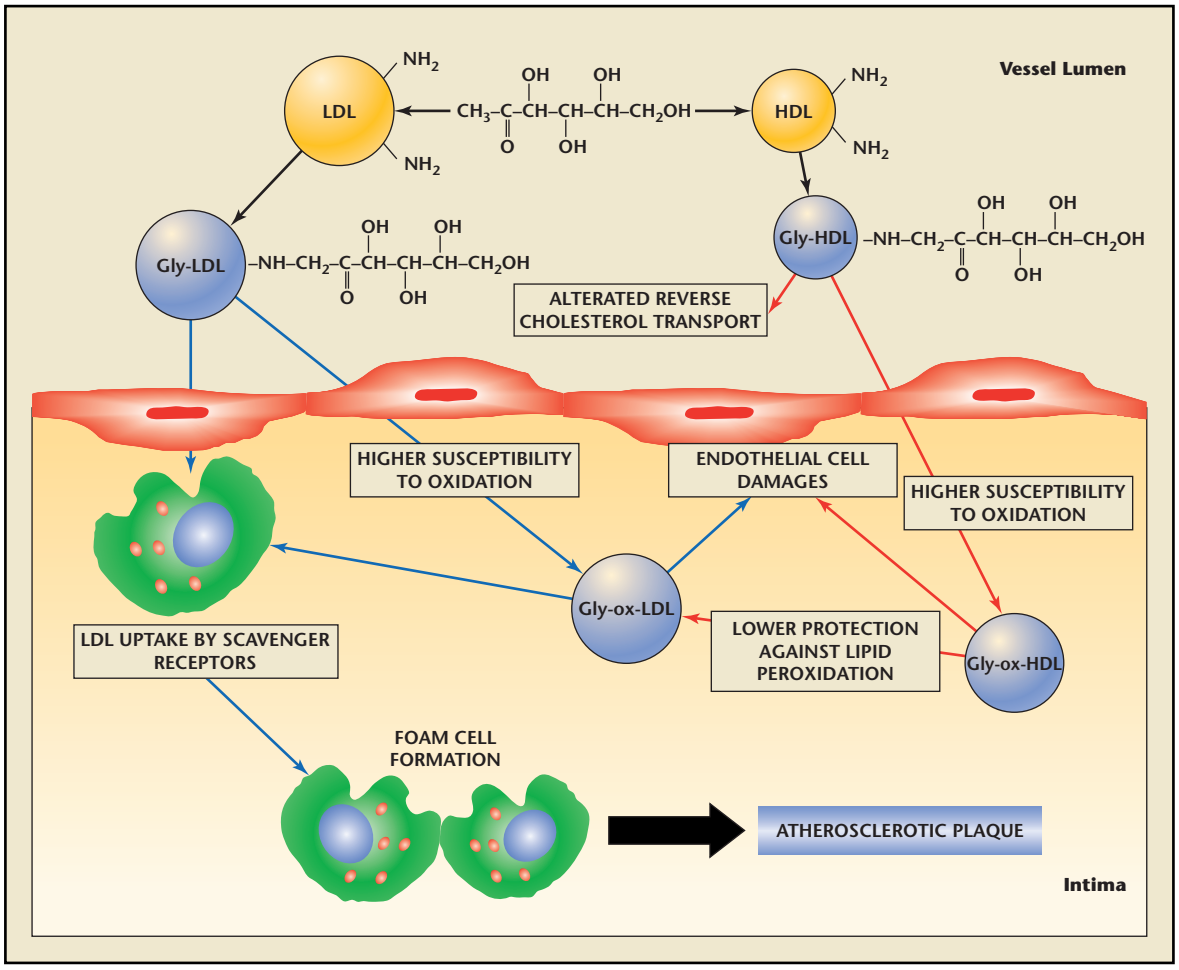
The ability of HDL to facilitate cellular cholesterol efflux may be directly related to its anti-inflammatory/ inflammatory properties. In the study by Ansell and colleagues[20] mentioned above, the ability of a subject's HDL to inhibit inflammation was highly correlated with its capacity to promote cholesterol efflux. Impaired reverse cholesterol transport by HDL leads to increased levels of atherogenic lipoproteins and increased levels of oxidized lipids, which are themselves pro-inflammatory (Figure 2).[29]

Modifiers of HDL Anti-Inflammatory/ Inflammatory Activity

The potential for HDL to inhibit lipid oxidation and/or inflammation appears to be modifiable by the acute phase response, medications, and HDL mimetics.

The acute phase response has both quantitative and qualitative effects on HDL and its constituents.[30] Rohrer and colleagues[31] reported

Figure 2. *Atherogenic effects of glycation of high-density lipoprotein (Gly-HDL), including impaired reverse cholesterol transport, increased susceptibility to oxidation (GLY-ox-HDL), and decreased ability to slow oxidation of low-density lipoprotein (LDL), which itself is rendered more susceptible to oxidation by glycation. Reproduced with permission from Ferretti G et al.*[44] www.medreviews.com



that inflammation reduces HDL-C by increasing the activities of endothelial lipase and soluble phospholipase A2 and by replacing apoA-1 in HDL with serum amyloid A. As examples, sepsis or influenza infection can decrease the concentration of HDL-C in humans by as much as 50%.[32]

Inflammation also causes significant changes in the protein and lipid composition of HDL.[33] In humans undergoing elective laparoscopic cholecystectomy, levels of paraoxanase and LCAT fell 24% and 44%, respectively, to a nadir 3 to 6 days postoperatively.[34] These alterations in antioxidative capacity allow for increased production of oxidized-LDL that contributes to the production of inflammatory cytokines by smooth muscle and endothelial cells.

In contrast to the effects of systemic inflammation, statin therapy appears to lessen the pro-inflammatory potential of HDL. Although statin treatment is associated with a relatively minimal effect on HDL-C concentration, it may have greater influence on HDL's functional potential.

In the study by Ansell and colleagues,[20] after 6 weeks of treatment with simvastatin 40 mg/d, 46% of CHD and CHD–risk equivalent patients showed anti-inflammatory HDL (versus 23% at baseline). This change suggests that conventional statin treatment in CHD patients is associated with increased anti-inflammatory ability of HDL. However, it must be mentioned that the inflammatory capacity of HDL from these statin-treated patients still did not reach the very profound anti-inflammatory capacity seen in the normal control patients.[20]

Dietary Effects

A recent study indicates that dietary composition can affect HDL's anti-inflammatory capacity. In a crossover design, Nicholls and colleagues[35] compared the effects of 2 high-fat meals that contained either predominantly polyunsaturated fat (safflower oil) versus saturated fat (coconut oil) sources in 14 healthy volunteers who were about 30 years old. The high-fat meals were administered in a random order, separated by 1 month and (in the case of female subjects) timed at 7 days following menstruation. HDL was isolated from the subjects in a fasting state, then at 3 and 6 hours following each high-fat meal. Brachial artery reactivity was also assessed at the same time points.

Nicholls' group[35] then assessed the effect of HDL on expression of the intercellular adhesion molecule-1 (ICAM-1) and vascular cellular adhesion molecule-1 (VCAM-1) on the surface of human umbilical vein endothelial cells that were activated by tumor necrosis factor-alpha. The expression of these inflammatory cellular adhesion molecules was significantly lower at both time points following the polyunsaturated fat meal compared with the fasting state. In contrast, the saturated fat meal increased the expression of ICAM-1 and VCAM-1 at 6 hours compared with fasting. Importantly, the protein, cholesterol, and phospholipid content; particle size; and electrophoretic pattern of HDL were not significantly changed from the fasting state by either meal. The researchers also reported a modest decrease in post-hyperemic flow–mediated dilatation in the subjects after the saturated fat meal, but not the polyunsaturated fat meal.[35]

Synthetic HDL and Mimetics

Infusions of HDL and apoA-1 have been associated with enhanced reverse cholesterol transport, decreased proinflammatory characteristics of HDL, and atherosclerotic regression, mostly in animal models.[36-38] Five weekly infusions of recombinant apoA-1 Milano, the natural form of which is protective against coronary disease, was associated with short-term atherosclerotic regression (4.2% from baseline) in contrast to an ineffective placebo ($P < .001$), in a clinical trial reported by Nissen and colleagues.[38] The study assessed the change in atheroma volume as assessed by intravascular ultrasound in 47 subjects with acute coronary syndromes. The characteristics of the individuals' HDL have not been reported, but the study provides proof-of-concept that HDL-mediated therapies can have remarkable impact on atherosclerosis.

ApoA-1 contains 243 amino acids and must be administered by intravenous infusion, presenting practical barriers to its use as a major therapeutic intervention. However, several different orally active peptides with characteristics similar to native HDL are currently in preclinical investigation. One of these is D-4F, an 18-amino acid peptide that forms an amphipathic helix like apoA-1, but whose *dextro* peptide bond orientation prevents its degradation by human digestive enzymes. The sequence of amino acids is critical to D-4F's activity.[39]

Navab and colleagues[36] reported that D-4F ingested twice daily by LDL-receptor null ($LDLR^{-/-}$) and apoE-null ($apoE^{-/-}$) mice decreased atherosclerotic lesion size by 79% and 75%, respectively, without changing cholesterol or HDL-cholesterol levels. Analysis of the plasma of treated $apoE^{-/-}$ mice 20 minutes after D-4F administration revealed small micelle-like cholesterol-containing particles that migrated in a pre-beta chromatographic pattern and were enriched in apoA-1 and paraoxanase activity. HDL and these small particles

Table 1
Therapeutic Interventions and Disease States Associated With Pro-Inflammatory and Anti-Inflammatory HDL

Pro-Inflammatory Effect	Anti-Inflammatory Effect (Proven)
Coronary atherosclerosis	ApoA-1 mimetics
Diabetes mellitus	Statins
Systemic lupus erythematosus	High dietary polyunsaturated fat content
Rheumatoid arthritis	**Anti-Inflammatory Effect (Possible)**
Hemodialysis	ApoA-1 Milano
Infection	Cholesteryl ester transferase protein inhibitors
Surgery	Delipidated HDL
High dietary saturated fat content	Anti-rheumatic biologicals

HDL, high-density lipoprotein; Apo, apolipoprotein. Reprinted with permission from Ansell BJ et al.[45] *Curr Atherscler Rep*. Philadelphia, PA: Current Medicine Group, LLC; 2007.

were both very anti-inflammatory and enhanced cholesterol efflux following D-4F treatment, in contrast to the corresponding liquid chromatography fractions prior to treatment. D-4F also appears to offer protection against the inflammatory response to viral infections. Control $LDLR^{-/-}$ mice that were infected with influenza A developed severe pneumonia that was associated with proinflammatory HDL and decreased paraoxanase levels. In contrast, when $LDLR^{-/-}$ mice were pre-treated with oral D-4F prior to influenza exposure, the pulmonary inflammatory response was minimal, HDL remained anti-inflammatory, and paraoxanase levels increased.[40] Increased macrophage entry into the aortae was seen in the control group, but not in the D-4F-treated mice.[40]

A combined therapeutic approach using both statin and D-4F treatment may offer synergy in generating anti-inflammatory HDL and retarding atherosclerosis. In both a monkey model and a mouse model, separately administered low doses of pravastatin and D-4F had no measurable impact on HDL or its function, but simultaneous treatment with both drugs led to increased levels of HDL-cholesterol, apoA-1, and paraoxanase.[41] In mice, treatment with a combination of both agents compared with placebo was associated with a 79% reduction ($P < .0001$) in aortic lesion formation, regression of existing plaque, and decreased lesion macrophage content.[41] In monkeys on the combination therapy but not those taking the agents separately, HDL became more anti-inflammatory as indicated by the monocyte chemotaxis assay.[41] Table 1 lists clinical conditions that are associated with pro-inflammatory and anti-inflammatory changes in HDL, as well as potential and proven anti-inflammatory HDL-based strategies.

One of the recently developed strategies to raise HDL-C to a greater extent than currently possible was that of CETP inhibition. The first agent tested in man was torcetrapib, which alone or in combination with atorvastatin increased quantitative levels of HDL by 40% to 61%. It was known that the relationship between CETP and atherosclerosis was complex, with both proatherogenic and antiatherogenic effects suggested. It has been reported that torcetrapib increased the risk of cardiovascular events and all-cause mortality by more than 50%, leading to termination of its development. It is not known whether CETP inhibition affects HDL quality and function. It is possible that treatment with torcetrapib did not produce HDL of good quality, but this has not yet been studied.[42] It also remains to be seen whether the increased risk was related to torcetrapib itself or will be seen with other CETP inhibitors as well.

Clinical Implications

Clinicians should continue to measure HDL-C levels and treat according to the most current national guidelines.[43] HDL levels have been shown to increase with regular aerobic exercise, modest alcohol consumption, weight loss, a high-fat diet, and smoking cessation. HDL levels decrease with smoking, obesity, menopause, and high-carbohydrate diets. Pharmacological agents that increase HDL include statins, niacin, fibric acid derivatives, phenytoin, and hormone replacement therapy. However, the magnitude of HDL elevation with clinically available drug therapy is generally small and highly variable. Although statins and dietary modification have been demonstrated to improve HDL function, determination of the impact of other therapies on HDL function requires further study. In the future, there may be more widely available testing to assess the functional properties of HDL, and if large-scale clinical trials prove that modulation of HDL function improves outcomes, it may one day become a target of lipid-modifying therapy.

Conclusion

HDL has a variety of functional effects, including both pro-inflammatory and

anti-inflammatory properties. The serum HDL-C level does not assess HDL's functional properties. HDL from patients with CHD or CHD–risk equivalents is significantly pro-inflammatory, likely contributing to their atherosclerosis risk even in the setting of normal HDL-C levels. Even in normal individuals (without atherosclerosis or not at high risk), HDL may become transiently pro-oxidant in the presence of systemic infection. Further understanding of the nature of HDL's protective capacity against atherosclerosis is essential in order to develop more effective treatments for this complex disease. ■

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Main Points

- Functional characterization of high-density lipoprotein (HDL) may allow for enhanced accuracy in assessing cardiovascular risk as well as provide a therapeutic target for risk reduction.
- In addition to its role in reverse cholesterol transport, HDL also has potent antioxidant, anti-inflammatory, and antithrombotic properties that may play important roles in the anti-atherogenic effects of HDL.
- HDL from patients with a history of coronary heart disease is not only unable to prevent low-density lipoprotein (LDL) oxidation, but it enhances the oxidation of LDL and phospholipids in LDL.
- Under certain circumstances, rather than being anti-inflammatory, HDL can act in such a way as to amplify vascular inflammation.
- Although statins and dietary modification have been demonstrated to improve HDL function, determination of the impact of other therapies on HDL function requires further study.

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