New Strategies in Managing and Preventing Atherosclerosis: Focus on HDL

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The development of atherosclerosis is a complex process whose central elements include the entrapment of low-density lipoprotein in the vessel wall, its subsequent oxidative modification, and the stimulation of proinflammatory gene expression leading to inflammatory cell recruitment, infiltration, and activation. High-density lipoprotein interacts with this process at multiple points, and these interactions could provide therapeutic targets to prevent, stabilize, or even promote the regression of atherosclerosis. High-density lipoprotein may retard atherosclerotic progression by promoting cholesterol efflux from the arterial wall, thereby reducing plaque lipid content as well as potentially inhibiting nascent fatty streak formation. A growing body of evidence derived from clinical trials supports the contention that the raising of high-density lipoprotein levels may confer significant cardiovascular benefit independently of low-density lipoprotein lowering. An antiatherogenic strategy focusing on high-density lipoprotein and its apolipoproteins represents a new frontier in the management of atherosclerosis. [Rev Cardiovasc Med. *2002;3(3):129–137*]

Key words: Atherosclerosis • High-density lipoprotein • Cholesterol • Plaque • Gemfibrozil

Elevated non–high-density lipoprotein (HDL) and low HDL levels are key risk factors for the development of atherosclerotic vascular disease.[1–5] Large-scale clinical trials have shown that reducing LDL levels confers a substantial relative risk reduction for major cardiac events.[6–10] However, 60%–70% of adverse cardiovascular events continue to occur despite LDL-lowering therapy. The next step in both prevention and therapy may center on HDL and its associated apolipoproteins. A large body of experimental evidence suggests

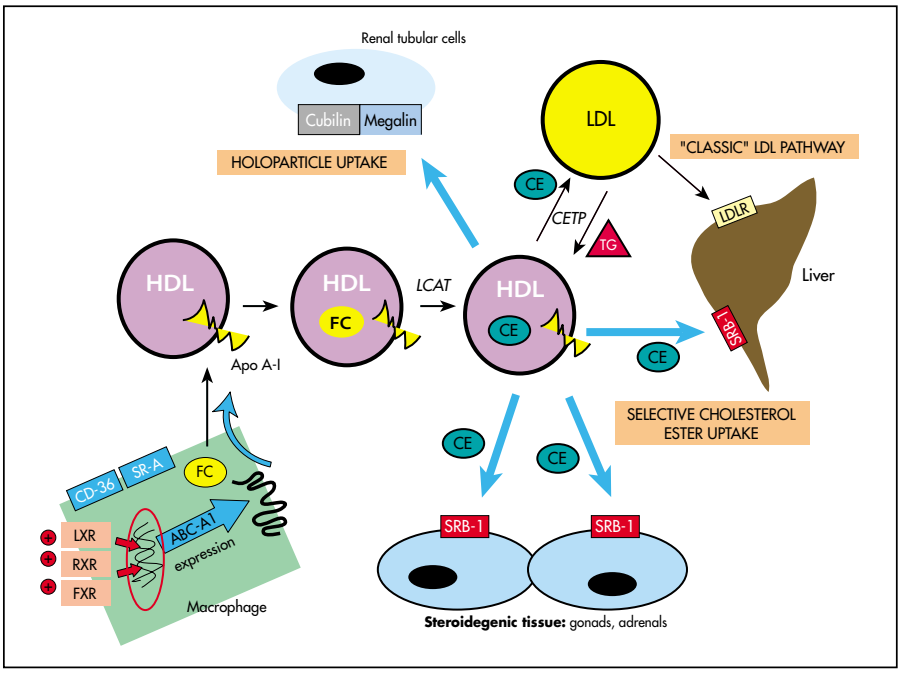

Figure 1. *The reverse cholesterol transport pathway. The ABC-A1 gene encodes transmembrane proteins which are critical, in addition to apolipoprotein A-I, for mobilization of free cholesterol from the macrophage to the apolipoprotein A-I–containing HDL. Activation of nuclear hormone receptors enhances the expression of ABC-AI. LCAT catalyzes the esterification of free cholesterol. The cholesterol ester of HDL has three possible fates: transfer to LDL by CETP for hepatic uptake by the classic LDL pathway; selective SRB-1–mediated CE uptake in the liver and steroidogenic tissue; or holoparticle uptake in the kidney via the cubilin and megalin receptors. CE, cholesterol ester; FC, free cholesterol; TG, triglycerides; ABC, ATP-binding cassette transporter; LCAT, lecithin cholesterol acyl transferase; LDLR, LDL receptor; RXR, retinoid X receptor; LXR, liver X receptor; FXR, farnesoid X receptor; CETP, cholesterol ester transfer protein. See text for details.*

that the HDL particle plays a crucial role in the mobilization of lipid from the arterial wall and exerts significant antioxidant and anti-inflammatory effects. In animal models of hypercholesterolemia and atherosclerosis, the manipulation of HDL, its associated protein apolipoprotein A-I, and their synthetic mimetics has resulted in lesion regression and lesion stabilization irrespective of non-HDL levels. Thus, an antiatherogenic strategy focusing on HDL and its apolipoproteins represents a new frontier in the management of atherosclerosis.

HDL: Potential Antiatherogenic Properties

The development of atherosclerosis is a complex process whose central elements include the entrapment of LDL in the vessel wall, its subsequent oxidative modification, and the stimulation of proinflammatory gene expression leading to inflammatory cell recruitment, infiltration, and activation.[11,12] HDL interacts with this process at multiple points, and these interactions could provide therapeutic targets to prevent, stabilize, or even promote the regression of atherosclerosis.

A major physiologic function of HDL is reverse cholesterol transport, which involves the mobilization of free cholesterol from the arterial wall and its delivery to the liver and steroidogenic tissues.[13] HDL may retard atherosclerotic progression by promoting cholesterol efflux from the arterial wall, thereby leeching the lipid content out of plaque as well as potentially inhibiting nascent fatty streak formation.[14,15] The components that play a key role in reverse cholesterol transport are apolipoprotein A-I, adenosine triphosphate (ATP)–binding cassette transporter protein, lecithin cholesterol acyl transferase (LCAT), cholesterol ester transfer protein (CETP), and phospholipid (Figures 1 and 2).[16] Paraoxonase and platelet-activating factor acetylhydrolase, two enzymes found within HDL, likely mediate in part HDL's ability to inhibit LDL oxidation.[17,18] Apolipoprotein A-I itself also removes seeding molecules for oxidation from the arterial wall.[19,20] Because the oxidative modification of LDL initiates the inflammatory process that in turn stimulates the development of atherosclerosis, HDL's ability to inhibit LDL oxidation may translate into an anti-inflammatory and antiatherogenic effect. Indeed, HDL and/or its components have been shown to decrease tumor necrosis factor release, inhibit cytokine-induced monocyte adhesion receptor expression by endothelial cells,[21–23] and reduce atherosclerotic plaque macrophage content.[24,25] In other words, HDL decreases inflammatory cell recruitment, adhesion, and infiltration. This may impede the monocyte's ability to act as a driving force for atherogenesis.

The next step in both prevention of and therapy for atherosclerosis may center on HDL and its associated apolipoproteins.

HDL: Potential Plaque Stabilization Properties

HDL may not only retard (or reverse)

the progression of atherosclerosis, but may also have a significant impact on plaque vulnerability. The relative stability of a given atherosclerotic plaque likely depends on the magnitude of its lipid core, the degree and activity of inflammatory infiltrate, and the thickness and smooth muscle content of its fibrous cap.[26] HDL-mediated cholesterol efflux reduces plaque lipid content; HDL-mediated inhibition of lipid oxidation and the interrelated inflammatory process may reduce plaque macrophage content and activity; and HDL-associated phospholipid scavenging of the toxic by-products of lipid oxidation decreases smooth muscle death,[27,28] potentially stabilizing or strengthening the atherosclerotic plaque's fibrous cap. Indeed, apolipoprotein A-I has been shown in animal models to decrease plaque cholesterol and macrophage content[24,25,29] and to increase plaque smooth muscle content.[25] All of these features may enable HDL to alter plaque composition to a more stable phenotype, preventing rupture and in turn decreasing the incidence of acute cardiovascular events.

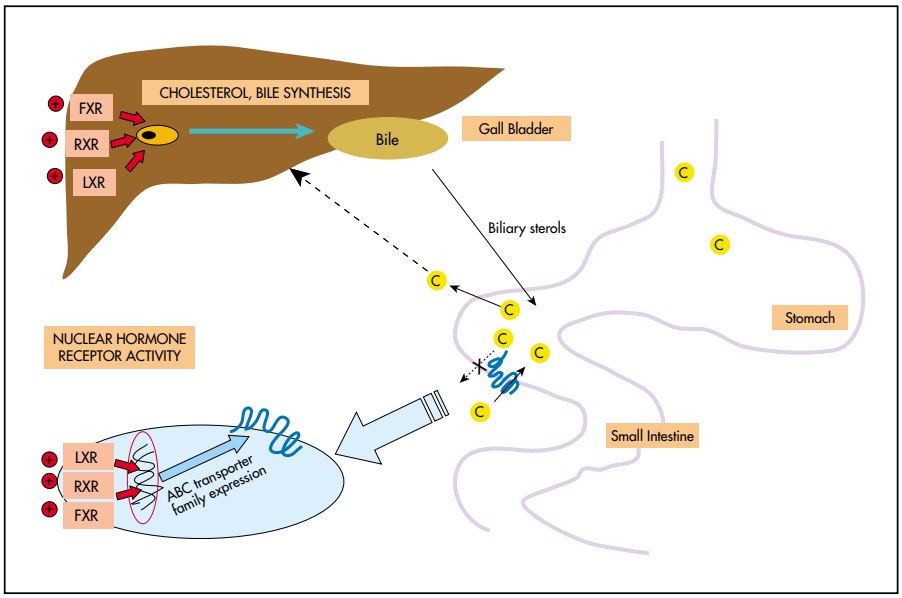

Figure 2. *Schematic of intestinal regulation of cholesterol transport. Ligand-mediated nuclear hormone receptor activation leads to activation of the ABC transporter family, leading to inhibition of cholesterol uptake in the gut and increased cholesterol efflux from peripheral tissues. Nuclear hormone receptor activation also stimulates biliary excretion of bile acids. C, cholesterol; RXR, retinoid X receptor; LXR, liver X receptor; FXR, farnesoid X receptor.*

HDL: Quality, Not Quantity

Although HDL has been demonstrated to have physiologic effects that are potentially antiatherogenic, the magnitude of these effects are determined in part by the qualitative function of the HDL species, not solely by its circulating levels. HDL is not always anti-inflammatory: during the acute phase, HDL loses its paraoxonase and apolipoprotein A-I content, and becomes pro-oxidant and proinflammatory.[12] Even outside of the acute phase, all HDL is not alike. Navab and colleagues found that the HDL from a group of patients with angiographically proven atherosclerosis, a normal lipid profile, and no other risk factors was dysfunctional in preventing the formation and inactivation of oxidized phospholipids in comparison to that of a control group.[30] Thus the successful therapeutic use of HDL likely depends on specifically manipulating its antiatherogenic components and the molecules with which they interact.

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It has been postulated that the cardioprotective effects of HDL can be attributed to one or more of its subfractions, HDL_2 or HDL_3. The circulating concentrations of HDL_2 and HDL_3 are for the most part determined by the simultaneous action of CETP, LCAT, lipoprotein lipase, and hepatic lipase.[31] Although cross-sectional studies support the hypothesis that the benefit of elevated HDL may be mediated by its HDL_2 subfraction, the results of prospective studies have been inconsistent.[32] The quantitative measurement of HDL subfractions likely does not provide incremental information above that provided by the measurement of total HDL alone. Instead, the ongoing development of functional assays will allow the clinician to determine the anti-atherogenic profile of an individual's HDL.[30]

From Potential to Practice: Therapeutic Strategies to Exploit HDL

Clinical Studies of HDL-Raising Therapies

Observational studies have demonstrated a strong inverse relationship between HDL levels and coronary heart disease.[33] A growing body of

evidence derived from clinical trials supports the contention that the raising of HDL levels may confer significant cardiovascular benefit independently of LDL lowering. In the primary prevention Helsinki Heart Study, 4081 asymptomatic men with elevated non-HDL cholesterol levels were randomized to either gemfibrozil or placebo.[34] Gemfibrozil therapy led to an 11% increase in HDL and a 34% relative risk reduction in cardiac endpoints; in those patients with high triglycerides and low HDL levels, gemfibrozil therapy led to a 78% relative risk reduction. An increase in HDL levels was an independent predictor of a reduction in clinical events.

The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT)[35] further elucidated the benefit of raising HDL with fibrates. In this secondary prevention trial, 2531 men with known coronary artery disease, normal LDL levels (≤140 mg/dL), and low HDL levels (≤40 mg/dL) were randomized to gemfibrozil therapy or placebo. At a median follow up of 5.1 years, LDL concentrations had not significantly changed, but HDL concentrations had increased by 6%. Gemfibrozil therapy resulted in a 22% relative risk reduction in the primary endpoint of nonfatal myocardial infarction (MI) or death from coronary heart disease. The degree of risk reduction in proportion to the magnitude of HDL increase was consistent with that observed in the Helsinki Heart Study.

The Bezafibrate Infarction Prevention (BIP) study[36] examined the effect of bezafibrate therapy in individuals with previous MI, LDL cholesterol less than 180 mg/dL and HDL less than 45 mg/dL. Bezafibrate increased HDL levels by 15% and, by post hoc analysis, resulted in a 40% risk reduction in the primary endpoint of nonfatal MI or cardiac death in the subgroup of patients with triglycerides levels greater than 200 mg/dL. Overall, however, the relative risk reduction was 7%, which was not statistically significant. A smaller trial, the HDL-Atherosclerosis Treatment Study (HATS), examined the angiographic and clinical benefits of combination therapy with simvastatin and niacin in 160 patients with coronary artery disease, normal LDL (≤145 mg/dL), and low HDL levels (≤45 mg/dL).[37] HDL levels were raised more dramatically than in the Helsinki Heart Study, VA-HIT, or BIP, with impressive clinical sequelae: combination therapy increased HDL concentrations by 26%, decreased LDL concentrations by 42%, led to regression of angiographic coronary atherosclerosis (by 0.4%, compared to progression by 3.9% in the placebo group), and resulted in a significant 60% relative risk reduction in the combined primary endpoint (cardiovascular death, MI, stroke, or revascularization for worsening ischemic symptoms) compared to placebo. These clinical benefits were greater than those expected from LDL lowering by statin therapy alone.

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The direct causality between increasing HDL and an improvement in cardiovascular outcomes is difficult to demonstrate, because the modification of HDL levels also affects the levels of non-HDL cholesterol. Moreover, a low HDL level is often accompanied by elevated triglycerides and insulin resistance, a triad referred to as the metabolic syndrome. Pharmacological or nonpharmacological modification of HDL levels may also have lipid-independent effects on cardiovascular risk. Laboratory investigation, however, has shown that the HDL molecule has broad antiatherogenic properties. The experimental manipulation of HDL concentration and activity in animal models of atherosclerosis and dyslipidemia has demonstrated powerful antiatherogenic effects.

Table 1
Current Interventions That Raise HDL Levels

Regular dynamic exercise
Moderate alcohol consumption
Weight loss
Smoking cessation
Diet high in saturated fat or carbohydrates
Phenytoin
Statins
Fibrates
Niacin
Estrogen

Current Therapies to Raise HDL Levels

Methods that are clinically available to elevate circulating HDL levels include lifestyle modification and pharmacological therapy (Table 1). The magnitude of impact on lipid concentrations with exercise depends on its type, duration, and intensity, and the baseline lipid profile, gender, and age of the patient.[38,39] Generally, moderate dynamic exercise at least three times a week results in a small but significant improvement in HDL levels, although the impact of exer-

cise on HDL levels may be less in women.[40] Weight loss in obese patients can increase HDL levels by as much as 0.8 mg/dL for every unit decrease in body mass index.[41]

Both the amount and the type of dietary fat content impact upon HDL levels. Saturated fats increase circulating HDL when dietary cholesterol intake is held constant; when cholesterol, total, and saturated fat intake is decreased, HDL levels decrease as well.[42] However, the substantial impact of reducing saturated fat intake on LDL levels and cardiovascular risk outweighs the negative effect of lowering HDL levels,[42] so in general a diet low in saturated fats should be recommended to patients. Modest alcohol consumption—1 to 2 glasses of wine per day for men, and 1/2 to 1 glass of wine per day for women—has been shown to have cardiovascular benefit. Potentially, part of this benefit may be due to alcohol's ability mildly to increase HDL. Cigarette smoking has a substantial negative effect on HDL levels; the impact is dose-dependent, and men who smoke more than 20 cigarettes a day have 11% lower HDL levels than nonsmokers.[43] Smoking cessation should thus be an initial step in any therapeutic approach to raise HDL levels.

The primary pharmacological means of raising HDL include estrogen, fibrates, statins, and niacin. Estrogen therapy in postmenopausal women significantly raises HDL levels.[44] In the Heart and Estrogen/progestin Replacement Study (HERS), combination therapy with estrogen and progesterone raised HDL levels by 10%, but there was no cardiovascular benefit, and a pattern of early increase in the risk of cardiovascular events was observed.[45] One should thus not select hormone replacement as a primary treatment for low HDL levels.

Fibrates, such as gemfibrozil and bezafibrate, raised HDL concentrations by 11% and 15%, respectively, in the VA-HIT and BIP trials. Statin therapy causes a modest rise in HDL levels in the range of 5%–10%.[46] One mechanism for this effect is statin-induced inhibition of the Rho signaling pathway, which activates the peroxisomal proliferator activating receptor-α (PPAR-α) and induces the transcription of apolipoprotein A-I gene.[47] The magnitude of HDL elevation varies among statins, as high-dose simvastatin produces a relatively greater elevation in HDL than high-dose atorvastatin.[48] Niacin can increase HDL levels as much as 15%–35% and is thus the most effective pharmacological agent in raising HDL. Its clinical utility may be limited secondary to its side effects, especially flushing, gastrointestinal complaints, hyperglycemia, hyperuricemia, and hepatotoxicity, the latter being more common in long-acting preparations.[41,49–51] Combination therapy with a statin and niacin has been shown to be safe, effective, and of significant cardiovascular benefit, as demonstrated in the prospective HATS trial mentioned above.[37,52] Low-dose phenytoin (goal blood level of 7.5–15 μg/mL) in nonepileptic patients raised HDL levels by 12% without affecting LDL or triglycerides levels.[53] The impact of phenytoin treatment on cardiovascular risk has not yet been determined.

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Novel Therapeutic Strategies

Current pharmacological and nonpharmacological interventions have therapeutic limitations because of the modest degree of elevation in HDL levels and the functional heterogeneity of the HDL itself.[54] One alternative is to directly administer functionally competent HDL, its associated protein apo A-I, or synthetic mimetics. Experimental evidence supports the contention that this may provide significant therapeutic benefit. Repeated parenteral administration of recombinant apo A-I_{milano}-phospholipid complex prevented the progression of aortic atherosclerosis in apo E–deficient mice despite severe hypercholesterolemia.[24,55] Injection of disks containing apo A-I and phosphatidylcholine increased in vivo production of small pre-β-HDL particles and increased the efflux and esterification of tissue-derived unesterified cholesterol in healthy male volunteers,[56,57] and injection in humans of liposomes containing a precursor of apolipoprotein A-I increased fecal excretion of cholesterol.[58] These data support the hypothesis that direct administration of HDL compounds can stimulate reverse cholesterol transport and potentially affect atherosclerotic progression. This potential was demonstrated recently by Navab and colleagues, who showed that treatment with an oral apolipoprotein A-I mimetic peptide reduced atherosclerotic lesion area by 79% in LDL receptor–null mice on a Western diet and by 75% in apo E–null mice.[59]

Direct administration of HDL components also favorably alters atherosclerotic plaque composition

Table 2
High-Density Lipoprotein, Antiatherogenic Properties, and Therapeutic Strategies

HDL Component/Associated Protein	Antiatherogenic/Vasculoprotective Effect	Therapeutic Strategy
Apolipoprotein A-I	Facilitates reverse cholesterol transport Removes oxidative seeding molecules Scavenges toxic products from arterial wall Reduces smooth muscle cell apoptosis/necrosis Reduces plaque lipid content Reduces plaque macrophage content Improves endothelial dysfunction	Direct IV/PO administration of plasma-derived wild-type apo A-I, apo A-I_{milano}, whole functional HDL, or synthetic mimetic peptides Apo A-I gene transfer
Phospholipid	Facilitates reverse cholesterol transport	Synthetic disks/liposomes
Paraoxonase, PAF-acetylhydrolase	Inhibits LDL oxidation	Increased activity by pharmacological/gene therapy?
Cholesterol ester transfer protein	Facilitates reverse cholesterol transport	Vaccination, pharmacological inhibitor
ATP-binding cassette transporter	Facilitates reverse cholesterol transport	Rexinoids, PPAR receptor family agonists, LXR agonists
SRB-1 receptor	Facilitates reverse cholesterol transport (hepatic HDL uptake)	Increased activity/expression by gene therapy, pharmacological therapy?

HDL, high-density lipoprotein; LDL, low-density lipoprotein; PAF, platelet-activating factor; PPAR, peroxisome proliferator activated receptor; LXR, liver X receptor.

to a more stable phenotype, as demonstrated by the observation that parenteral recombinant apo A-I_{milano}-phospholipid complex reduced plaque cholesterol by 40% and reduced macrophage content by 46% in apo E knockout mice.[24] Even acutely, a single high-dose administration resulted in a 40%–50% lower lipid content ($P < .01$) and 29%–36% lower macrophage content in aortic root plaques at 48 hours.[29] One could speculate that HDL administration could "cool off" "hot" plaques during acute coronary syndromes.

Other novel antiatherogenic therapies may be directed at key points in HDL metabolic pathways, either through pharmacological manipulation or, in the more distant future, via gene therapy (Table 2). Candidate targets are the HDL-associated proteins involved in reverse cholesterol transport. CETP inhibition may be potentially antiatherogenic in raising HDL concentrations, because CETP catalyzes the transfer of esterified cholesterol from the HDL particle to LDL and thus lowers circulating HDL levels and raises LDL levels. A vaccine against an epitope of CETP has been shown to inhibit CETP, increase HDL cholesterol levels, and reduce fatty streaks in cholesterol-fed rabbits.[60] However, CETP inhibition may also prove to be proatherogenic, because CETP facilitates the production of pre-β-HDL particles, which are efficient stimulators of reverse cholesterol transport.[61] This complex relationship between CETP activity and atherosclerosis makes CETP a less attractive candidate for therapeutic manipulation in humans.

ATP-binding cassette transporter, a transmembrane protein encoded by the gene ABC-A1, mediates the initial step of reverse cholesterol transport, the cholesterol efflux from cells to HDL particles.[62] ABC-A1 transcription is regulated by nuclear hormone receptors such as PPARα, PPARδ, PPARγ, liver X receptor (LXR), and the retinoid X receptor (RXR).[63–65] One strategy to enhance reverse cholesterol transport is to modulate ABC-A1 transcriptional regulation through ligands of these nuclear hormone receptors. Indeed, an orally administered selective agonist of PPARδ increases expression of the ATP-binding cassette transporter and induces apolipoprotein A1-specific cholesterol efflux, as well as dramatically increasing HDL levels, reducing small dense LDL, and correcting hyperinsulinemia in primates.[66] Ligands of LXR play a broad role in the regulation of lipid metabolism in the bile, peripheral tissues, and gut. PPARα and PPARγ activators, through the enhanced expression of LXR, induce the expression of ABC-A1 and increase cholesterol efflux from macrophages.[67] Oral administration of an RXR agonist dramatically inhibited atherogenesis in apo E–null mice in an LXR-dependent fashion.[68]

A novel hepatic receptor, SRB-1, has been identified that is responsible for hepatic HDL-associated cho-

lesterol uptake independent of the classic LDL pathway. SRB-1/apo-E double knockout mice demonstrate extensive cholesterol-rich coronary lesions and spontaneous MIs.[69] In contradistinction, adenovirus-mediated hepatic overexpression of SRB-1 in mice resulted in the virtual disappearance of plasma HDL and dramatically increased bile cholesterol[70]; transient adenovirus-mediated hepatic overexpression of SRB-1 in LDL-receptor–null mice led to regression of both early and advanced atherosclerotic lesions and a marked reduction in circulating HDL levels.[71] Thus the enhancement of SRB-1 activity and/or its expression represents a potential strategy significantly to promote reverse cholesterol transport and inhibit atherosclerosis.

Conclusion

A wealth of experimental data has demonstrated that HDL and apo A-I have significant antioxidant and anti-inflammatory properties, scavenge toxic products from the endothelium, ameliorate endothelial dysfunction, and mobilize cholesterol from the vessel wall. Qualitative HDL function may be crucial in addition to circulating HDL levels in exerting these effects. Elevations in HDL levels through statin, fibrate, niacin, or combination therapy may not be adequate to exploit the antiatherogenic and vasculoprotective potential of HDL and apo A-I. Direct administration of plasma-derived or recombinant HDL/apo A-I or their synthetic mimetics as a drug may provide significant clinical benefit. Activation of specific subtypes of nuclear hormone receptors, particularly the rexinoids, and pharmacological or gene therapy to enhance the expression and/or activity of the specific hepatic HDL-cholesterol scavenger receptor represent novel strategies for augmenting reverse cholesterol transport. This may inhibit the initiation and progression of atherosclerosis and promote its regression. LDL lowering through statin therapy has clearly made a major impact on cardiovascular morbidity and mortality. Now it is time to focus on HDL and its biological pathways as primary targets in the battle against atherosclerosis. ■

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Main Points

- A large body of experimental evidence suggests that the high-density lipoprotein (HDL) particle plays a crucial role in the mobilization of lipid from the arterial wall and exerts significant antioxidant and anti-inflammatory effects.
- HDL and/or its components have been shown to decrease tumor necrosis factor release, inhibit cytokine-induced monocyte adhesion receptor expression by endothelial cells, and reduce atherosclerotic plaque macrophage content.
- HDL may alter plaque composition to a more stable phenotype, preventing plaque rupture and decreasing the incidence of acute cardiovascular events.
- Observational studies have demonstrated a strong inverse relationship between HDL levels and coronary heart disease.
- In a study of 4081 asymptomatic men with elevated non-HDL cholesterol levels, gemfibrozil therapy led to an 11% increase in HDL and a 34% relative risk reduction in cardiac endpoints.
- Methods to elevate circulating HDL levels include lifestyle modification and pharmacological therapy.
- Cigarette smoking has a substantial negative effect on HDL levels; the impact is dose-dependent, and men who smoke more than 20 cigarettes a day have 11% lower HDL levels than nonsmokers.
- In women, combination therapy with estrogen and progesterone raised HDL levels by 10%, but there was no cardiovascular benefit, and a pattern of early increase in the risk of cardiovascular events was observed.
- Combination therapy with a statin and niacin has been shown to be safe, effective, and of significant cardiovascular benefit.

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