Cardioprotective Effects of High-Density Lipoproteins
The Evidence Strengthens

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The fact that a low level of high-density lipoprotein (HDL) cholesterol is highly predictive of future cardiovascular events has been established in population studies beyond all reasonable doubt. Furthermore, the evidence is overwhelming that the relationship is one of cause and effect rather than an epiphenomenon, with numerous studies in animals demonstrating that HDL-raising interventions translate into profound reductions in atherosclerosis. Such interventions have included the infusion of both native and reconstituted HDLs into rabbit models of atherosclerosis, the overexpression of apolipoprotein (apo) A-I (the major HDL protein) in transgenic mice and rabbits, and the inhibition of cholesteryl ester transfer protein (CETP) in rabbits.

Evidence that raising the level of HDLs is also antiatherogenic in humans is mounting, although there are still relatively few human studies that have directly tested the phenomenon. Fibrates, statins, and niacin all raise the level of HDL cholesterol, and treatment with each of these agents has been shown to be associated with a reduction in future cardiovascular events. Fibrates are especially effective in event reduction in people with insulin resistance or with other features of the metabolic syndrome, although the benefits cannot be explained in terms of the observed HDL raising. Statins are effective in reducing events in all subjects, but the benefits can be explained almost completely in terms of the observed HDL raising.1 Statins are effective in reducing events in all subjects, but the benefits can be explained almost completely in terms of the achieved LDL lowering; the contribution of a statin-induced elevation of HDL is difficult to evaluate. Niacin, the most effective of the currently available HDL-raising agents, has also been shown to reduce cardiovascular events, especially when coadministered with a statin; but again, other properties of niacin may contribute to the benefit. But, overall, the extent of HDL raising achieved with currently available agents is modest compared with the LDL lowering achieved with statins, and demonstration of the real benefits of HDL raising in humans may have to await the results of trials with a range of interesting new agents.

The first of these (a preparation of reconstituted HDL [rHDL] consisting of apoA-I Milano complexed with phospholipids) has already been put to the test in humans.4 This preparation was used in a proof of concept study in which intravenous infusions of the rHDL into humans with acute coronary syndromes were associated with a demonstrable reduction in atheroma burden as assessed by coronary intravascular ultrasound (IVUS). The most impressive aspect of this study was the rapidity of the effect. Five injections of the rHDL given at weekly intervals resulted in a statistically significant reduction in atheroma burden. Although the study was small and had some design problems, the result was completely consistent with an even more rapid regression of atheroma observed after a single injection of rHDL into rabbits.5

Another approach to HDL raising, currently under investigation in humans, involves the use of inhibitors of CETP. These agents are highly effective in raising the HDL concentration in humans and, in rabbits, are profoundly antiatherogenic.6 The results of studies investigating the effects of CETP inhibition on atherosclerosis and cardiovascular events in humans are awaited with great interest.

The current issue of this journal contains a report7 and a review8 by Navab and colleagues describing another intervention that may enhance the protective potential of the HDL fraction. They describe effects of a class A amphipathic helical peptide, D-4F, which, when given orally to mice and monkeys, has been found to promote the formation of pre-beta migrating HDLs, to improve HDL-mediated cholesterol efflux from cells, to reduce lipoprotein lipid hydroperoxides, to increase paraoxonase activity, and to promote the conversion of HDLs from proinflammatory to antiinflammatory agents.8 This group has also reported that D-4F reduces atherosclerosis in apoE-null and low-density lipoprotein (LDL) receptor–null mice.8 These findings are of interest and potential importance, although they should be regarded at this stage with two notes of caution: firstly, the precise mechanism(s) by which D-4F exerts these effects has not been established and secondly, the reported beneficial effects of D-4F remain to be confirmed by other workers.

In the research report presented in this issue of the journal,7 Navab et al describe synergistic effects of D-4F when administered with a statin. The two agents were given in combination at doses that had been shown previously to be ineffective when given as single agents. When given to apoE null mice, the combination of low dose D-4F and statin increased the concentrations of HDL cholesterol, apoA-I, and paraoxonase, enhanced the antiinflammatory properties of the murine HDL, and was markedly antiatherogenic. It was also found that the combination of D-4F and pravastatin increased the synthesis of apoA-I in the intestine.

In additional (more limited) studies in monkeys, it was found that the combination of low doses of D-4F and statin converted the monkey HDL fraction from a proinflammatory to an antiinflammatory state as assessed in an assay, widely...
used by this group, that depends on measuring effects on LDL-induced monocyte chemotactic activity. A conclusion that the treatment rendered a proinflammatory monkey HDL fraction into one that was antiinflammatory would have been greatly strengthened by confirmation in additional assay system, such as the ability of the HDLs to inhibit expression of MCP-1 or adhesion proteins in activated endothelial cells. Again, as with any new finding, unreserved acceptance of these reported beneficial effects of a combination of D-4F and statin on the antiinflammatory potential of monkey HDLs should await independent confirmation by other workers. And, ultimately, the agent will need to be put to the test in a human clinical trial.

But regardless of whether D-4F ever finds a place as an antiatherogenic agent in humans, it should be emphasized that the evidence provided by a large number of groups, using a variety of approaches, clearly identifies the HDL fraction as a major target for therapeutic intervention.

Accepting this fact, the obvious question arises: by what mechanism(s) do HDLs exert their protective effects?

The best-known function of HDLs relates to their ability to promote the efflux of cholesterol from cells. To the extent that HDLs deplete macrophage-foam cells of cholesterol, this action of HDL would clearly be protective. But it is difficult to explain the rapidity of the effects of HDLs in the infusion studies in both animals and humans. This raises the possibility that there may be additional effects of HDL that contribute to their protective role. Indeed, there is growing evidence that antioxidant, antiinflammatory, antithrombotic, and endothelial stabilizing properties of HDLs may play a major role in their ability to protect against atherosclerosis.9,10

The ability of HDLs to inhibit oxidation has been known for many years and appears to relate both to the paraoxonase transported by HDLs and to the fact that several of the HDL apolipoproteins, including apoA-I, apoA-II, and apoA-IV, have intrinsic antioxidant properties. HDLs also have antiinflammatory properties that extend beyond their ability to inhibit oxidation. Both native and reconstituted HDLs have been shown in vitro to inhibit the cytokine-induced expression of adhesion proteins by endothelial cells growing in tissue culture. And in more recent in vivo studies in a rabbit model of acute vascular inflammation, as few as three infusions of small amounts of rHDLs (or indeed of lipid-free apoA-I alone) have been shown to abolish almost completely both the neutrophil infiltration into the wall of the injured artery and the associated generation by the artery of reactive oxygen species.11 The rHDL infusions also greatly reduced expression of adhesion molecules by the endothelium of the injured arteries.

So, the evidence continues to mount that HDLs protect by multiple mechanisms (Figure). Furthermore, in addition to their ability to retard (and even reverse) the development of atherosclerosis, they appear to possess properties that have the potential to inhibit the acute vascular inflammation that may contribute to the clinical consequences of acute coronary syndromes and acute ischemic strokes. The advent of new approaches to enhance the protective properties of HDLs, whether by infusion of rHDLs, by inhibition of CETP, or, possibly, by the use of novel peptides such as D-4F (whether alone or in combination with a statin), herald a new era in the management of cardiovascular disease.

References

Key Words: HDL | atherosclerosis | inflammation

![Possible mechanisms by which Atherothrombosis](image-url)
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