High-Density Lipoprotein and Plaque Regression
The Good Cholesterol Gets Even Better
Hayes M. Dansky, MD; Edward A. Fisher, MD, PhD

Primary and secondary prevention of coronary heart disease (CHD) has focused on lowering the LDL fraction of blood lipids not only because of the strong epidemiological evidence linking LDL to CHD, but also because pharmacological interventions have made it a highly modifiable risk factor. In contrast, although there is compelling epidemiological evidence that a low plasma level of HDL is also a powerful independent risk factor, it has received comparatively less attention as a therapeutic target. Contributing factors for this relative neglect undoubtedly include our poor understanding of the mechanisms by which low HDL increases cardiovascular risk and the fact that the most commonly used lipid-lowering drugs produce small increases in HDL levels.

A variety of clinical and epidemiological studies have shown that apolipoprotein A-I (apoA-I), the major protein present on the surface of HDL particles, correlates with HDL cholesterol (HDL-C) levels, and like HDL, apoA-I correlates inversely with atherosclerosis susceptibility. Historically, experimental studies designed to directly investigate the antiatherogenic properties of apoA-I and HDL particles have been limited to in vitro models, given the limited ability to perform invasive studies in humans. The availability of transgenic and knockout mice and other animals has provided intact models of lipoprotein metabolism and atherosclerosis.

Studies of such models have provided direct proof in mammals that an elevated plasma level of apoA-I results in increased HDL and in the inhibition of atherosclerotic lesion formation. For example, 2 independent studies1,2 demonstrated that transgenic expression of human apoA-I in hyperlipidemic apoE knockout mice resulted in a 2-fold increase in HDL-C and a dramatic inhibition of atherosclerotic lesion formation without changing non–HDL-C. Similar results have also been obtained in atherosclerosis-prone mice after HDL levels were raised by adeno-virus-mediated expression of human apoA-I.3 Transgenic overexpression of apoA-I or weekly injection of purified apoA-I in cholesterol-fed rabbits also resulted in decreases in lesion formation.4,5 Although these studies demonstrate that apoA-I has a direct inhibitory effect on the initiation and progression of atherosclerotic lesions, they do not address what effects elevated HDL levels would have on established lesions. Because clinical and pathological studies have indicated that secondary and even primary prevention of CHD in humans most likely involves the stabilization or regression of existing coronary plaques, this question is of major clinical relevance.

In the current issue of Circulation, Tangirala et al6 report for the first time that in addition to the aforementioned retardation of lesion initiation and progression, increased levels of apoA-I can indeed induce atherosclerotic lesion regression. The authors used the LDL receptor knockout mouse, a mouse model of familial hypercholesterolemia. After 5 weeks of consuming an atherogenic Western diet, mice were injected with either control virus or with recombinant defective adenovirus harboring the human apoA-I gene. This resulted in short-term (≈1 week) elevations in total apoA-I levels and a 50% increase in HDL-C. Whereas atherosclerosis progressed over the next 4 weeks in mice injected with the control virus, mice injected with the apoA-I recombinant adenovirus had 46% to 70% regression of atherosclerotic lesions. Regressed lesions “appeared less rich in foam cells and more fibrotic.”6 Consistent with this was the quantitative analysis of immunocytochemical staining of lesions, which revealed a smaller percent area occupied by macrophages in mice that had received the apoA-I–containing adenovirus. These findings suggest that elevated levels of apoA-I and HDL-C can reduce the size and change the cellular composition of preexisting atherosclerotic lesions, at least those with complexity corresponding to American Heart Association types I and II (ie, fatty streaks).

It is remarkable that significant lesion regression occurred after only 4 weeks, because peak expression of apoA-I and HDL-C levels lasted a relatively short time after injection of adenovirus. One possible explanation for the rapid regression is that the majority of lesions undergoing regression were macrophage foam-cell–containing fatty streaks, the type of lesions likely to be achieved in LDL-receptor knockout mice maintained on a Western diet for 9 weeks. If the lesions had contained more advanced characteristics, such as fibrous caps and necrotic cores, a rapid time course might not have been observed. Nonetheless, the demonstration of HDL-mediated regression of any type of lesion is a significant achievement, but readers are cautioned against concluding that regression of lesions is simply a reversal of progression. As the authors imply, the mechanisms and temporal nature of regression...
may be entirely distinct from the pathways involved in lesion progression.

By what mechanisms did elevations in apoA-I and HDL-C induce regression in these studies? They are likely to be different from those involved in lowering LDL. For example, as the authors note, HDL particles contain potentially anti-atherogenic components not found on LDL, such as apoA-IV, apoE, and paraoxonase, as well as lipid-processing enzymes such as LCAT (lecithin-cholesterol acyltransferase) and CETP (cholesterol ester transfer protein). In addition to roles in cholesterol efflux, there are data implicating these proteins in metabolic, oxidative, or inflammatory processes affecting atherosclerosis. Although the mechanisms may differ, the findings by Tangirala et al6 are similar in some respects to what has been found in animal models in which regression is induced by LDL lowering. For example, in a recent study by Aikawa et al,8 LDL lowering induced by withdrawal of a high-cholesterol diet in rabbits with existing atherosclerotic lesions also resulted in regression with a decrease in macrophage number and an increase in the collagen content of the lesions. Relative decreases in macrophage number and increases in the fibrous content of lesions would be expected to result in clinical benefit, because human autopsy studies have demonstrated that the “vulnerable” plaques associated with acute coronary syndromes have increased numbers of macrophages, large lipid-rich necrotic cores, and thin fibrous caps.9

Historically, significant atherosclerotic lesion regression in humans has been quite difficult to demonstrate. A multitude of “angiographic regression trials” have demonstrated that although LDL lowering results in a substantial reduction in coronary events, changes in lesion size based on serial quantitative angiographic measurements have been quite minimal. This has led to the hypothesis that LDL-lowering therapy stabilizes vulnerable atherosclerotic plaques without necessarily changing plaque size. Unfortunately, coronary angiography measurements are poor indices of lesion burden or characteristics, considering that pathological studies have demonstrated that atherosclerotic lesions can increase substantially in size through extensive outward growth and remodeling without affecting luminal diameter. Therefore, an exciting area of clinical research is the characterization of atherosclerotic lesions by the application of imaging modalities, notably intravascular ultrasound and MRI, to assess lesion features, such as size and composition. Although intravascular ultrasound imaging of coronary arteries is excellent for this purpose, it is an invasive technique and needs to be further developed to become a more routine clinical tool. MRI has the advantage of being noninvasive, but technical improvements are still needed before high-resolution images of coronary arteries are an everyday capability.

In addition to providing insights into the relationship between HDL and lesion dynamics, the findings of Tangirala et al6 also support the goal to develop new therapeutic agents that induce long-lasting, large increases in apoA-I and HDL-C levels in humans. The desirability of this goal is also emphasized by the recently released Veterans Affairs HDL Intervention Trial,10 in which the modest raising of HDL-C by a fibric-acid derivative in patients with normal LDL levels resulted in a reduction in coronary events. An extremely attractive scenario for the future is the combination of imaging modalities (to allow the clinical evaluation of the effects on atherosclerotic lesions of agents that increase apoA-I and HDL-C levels) and model systems, such as the one presented by Tangirala et al,6 with which to explore the mechanisms of actions of HDL and these agents. In this way, perhaps the “good” cholesterol can be made even “better.”

References


Key Words: Editorials ■ cholesterol ■ lipoproteins ■ atherosclerosis
High-Density Lipoprotein and Plaque Regression: The Good Cholesterol Gets Even Better
Hayes M. Dansky and Edward A. Fisher

Circulation. 1999;100:1762-1763
doi: 10.1161/01.CIR.100.17.1762

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/100/17/1762

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/