EDITORIAL

High-density Lipoproteins, Cholesterol Transport and Coronary Heart Disease

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NUMEROUS INVESTIGATIONS in humans and experimental animals during the past 25 years have suggested that some plasma lipoproteins are atherogenic, and others are not. In many humans who are especially susceptible to development of atherosclerotic lesions, and in animals with diet-induced atherosclerosis, the level of low-density lipoproteins (LDL), very low-density lipoproteins (VLDL), or both are increased, while levels of high-density lipoproteins (HDL) are changed relatively little. Total plasma cholesterol levels vary widely among mammalian species, but only in humans and guinea pigs do cholesterol-bearing lipoproteins other than HDL normally predominate.1 In ruminants and carnivores in particular, HDLs carry all but a small fraction of the plasma cholesterol. In certain aquatic mammals, such as seals2 and other carnivores such as the mink,3 plasma cholesterol levels as high as 400 mg/dl reflect very high concentrations of HDL without evident atherogenic consequences. Chemically, HDLs differ from atherogenic lipoproteins in containing none of the protein known as apolipoprotein B, which gives lipoproteins the peculiar ability to bind to negatively-charged glycosaminoglycans, as are present in the arterial intima.4 For these reasons, HDLs have long been considered to be nonatherogenic.

In the 1950s, a few clinical studies of lipoproteins and atherosclerosis included quantitative measures of HDL-lipids (cholesterol or phospholipids). Invariably, HDLs were found not to contribute to hyperlipoproteinemia in patients with premature atherosclerosis, so that the ratio of LDL and VLDL (β lipoprotein) to that of HDL (α lipoprotein) was increased. In a few studies, the absolute concentration of HDL-lipids was found to be reduced.5,6 As more was learned about interrelationships among lipoprotein lipids, it became apparent that the level of one species of HDL (HDL4) and that of total HDL-cholesterol bear a strong inverse relationship with plasma or VLDL-triglyceride levels.7-9 Because VLDL-triglycerides are often increased in patients with premature atherosclerosis, it was thought that reduced HDL levels simply reflected the tendency to hypertriglyceridemia.10 In support of this view, it was found that the lipid composition of HDL changes as VLDL-triglyceride levels rise,9 due to interchange of cholesteryl esters and triglycerides between VLDL and HDL.11 These lipids comprise the nonpolar "core" of these spherical lipoproteins. In hypertriglyceridemia, the core of HDL becomes enriched in triglycerides at the expense of cholesteryl esters. Thus, in hypertriglyceremic individuals, reduction of HDL-cholesterol does not necessarily reflect a reduced concentration of circulating particles.9,12

What has brought about the renewed interest in HDL? First, continuing research on HDL has led to the hypothesis that this lipoprotein class participates in the removal of cholesterol from cells (including those in developing atheromas) and delivery of cholesterol to the liver for excretion in the bile. This concept developed primarily from the work of Glomset on the plasma enzyme, lecithin-cholesterol acyltransferase (LCAT). Glomset showed during the 1960s that LCAT acts upon cholesterol and phosphatidyl choline (lecithin) in HDL to produce cholesteryl esters and lysolecithin.13 The lysolecithin is transferred to albumin, while the cholesteryl esters (the cholesterol moiety having lost its polar alcohol group) leave the surface of the HDL particle and either enter its nonpolar core or are transferred to the core of VLDL or LDL. LCAT is actually responsible for formation of virtually all of the cholesteryl esters in human blood plasma in the postabsorptive state. The fate of cholesteryl esters in various lipoproteins is only partially understood, but at least some are transported to the liver. The role of HDL and LCAT was further clarified by the observation that the liver secretes a nascent HDL in the form of bilayer discs that initially contain almost none of the cholesteryl ester produced by the LCAT reaction14 (the liver also secretes the enzyme itself). Thus, the bulk of the HDL particles in plasma represent metabolic end products.
Although the sources of the cholesterol that provide the substrate for LCAT have not been quantified, it is thought that the action of the enzyme upon nascent HDL creates a gradient favoring movement of cholesterol from cells into the blood plasma. Discoidal complexes of HDL-apoproteins and phospholipids have been shown to accept cholesterol from cells in culture, but it has been difficult to demonstrate a role for LCAT in this process in vitro. In human LCAT-deficiency states (either genetic or secondary to liver disease), cholesterol does accumulate in cells, especially the plasma membrane of erythrocytes, but this excessive erythrocyte cholesterol may originate from triglyceride-rich lipoproteins secreted from the intestine or the liver, rather than from cells in other tissues. Three years ago, Miller, Nestel and Clifton-Bligh reported that the size of both the rapidly and the slowly exchanging pools of tissue cholesterol, measured by an isotope dilution method in hyperlipoproteinemic humans, is inversely related to the concentration of HDL-cholesterol, consistent with the hypothetical function of the HDL-LCAT system.

Second, epidemiological research has produced important new evidence about HDL and coronary heart disease (CHD). Four years ago, investigators in five centers in the United States analyzed data collected on HDL-cholesterol in men and women aged 40 years and older, as part of a long-term study of plasma lipoproteins and coronary disease in free-living populations. They reported that HDL-cholesterol levels were consistently lower in individuals who had clinical CHD than in those who did not, and, based on multivariate analysis, the lower HDL-cholesterol levels could not be explained by associations with other factors, such as plasma triglyceride level. Later, investigators of the Framingham Heart Disease Epidemiology Study reported that the risk of developing clinical CHD in a 4-year period in men and women aged 49–82 years was more strongly related to initial HDL-cholesterol levels than to levels of LDL-cholesterol. Similar findings were reported for men aged 20–49 years from the Tromsø Heart Study in Norway. Last year, Jenkins, Harper and Nestel reported, in a series of patients studied by coronary angiography, an inverse realtionship between severity of luminal narrowing and HDL-cholesterol levels.

This epidemiological validation of the proposed physiological role of HDL has led to widespread acceptance of the putative causative relationship between HDL and atherogenesis. The hypothesis is consistent with other clinical observations. For example, after puberty, females have higher HDL levels and develop arteriosclerotic lesions more slowly than men. Greenland eskimos, who eat considerable amounts of meat, have total plasma cholesterol levels comparable to those of men and women in Denmark, but have substantially higher HDL-cholesterol levels and much less CHD (other differences involving prostaglandin metabolism have recently been used to explain the paucity of CHD in these eskimos). HDL-cholesterol levels are increased in long-distance runners, consistent with evidence that a consistently high level of physical activity helps to prevent clinical CHD. Increased levels of HDL-cholesterol produced by alcohol are also consistent with evidence that alcohol ingestion may be anti-atherogenic. Finally, in families in which unusually high levels of HDL-cholesterol are common, premature CHD is rare and the average life span seems to be extended by several years.

If HDL-cholesterol levels reflect the activity of the process by which the HDL-LCAT system promotes removal of cholesterol from cells, much remains to be learned. First, does the level really reflect the activity of the removal process? Is HDL-cholesterol or HDL-particle concentration the important determinant? How does cholesterol leave cells and is it transferred to a particular molecular species of HDL? Can the process of cholesterol removal be accelerated by increasing synthesis of LCAT or of HDL-components (the major apoproteins of HDL are now known to be synthesized in the small intestinal mucosa as well as the liver)? Most of these questions are likely to be answered by research in animals and in model systems.

In future clinical investigations of HDL, it will be important to measure more than HDL-cholesterol. For example, the higher level of HDL in women than men reflects exclusively a greatly increased concentration of larger HDL particles (HDL₃) which have a lower density than the bulk of HDL (HDL₂). Measures of particle number as well as of components of subclasses of HDL should therefore be included. Measurements of the major apoprotein components of HDL may provide some of this information. In all studies, relationships between HDL and other lipoprotein classes, especially VLDL, must be evaluated carefully. In the recent proliferation of reports of HDL-cholesterol levels in various diseases, such as diabetes mellitus, the failure to consider the strong inverse relationship between VLDL-triglycerides and HDL-cholesterol has often caused confusion.

Meanwhile, how should the clinician use available techniques for measuring HDL-cholesterol to advise patients? HDL-cholesterol is usually determined, by automated methods, in supernatant serum after precipitation of cholesterol in LDL and VLDL with heparin and manganese ion. From Framingham data, a difference of 10 mg/dl in HDL cholesterol (from 55 mg/dl, as commonly found in women, to 45 mg/dl, as commonly found in men) is associated with as much as a twofold increase in CHD risk. Unfortunately, the methodological error of a single HDL-cholesterol measurement is around 5–10 mg/dl. Thus, without clear assurance of considerably better than average precision and accuracy, the HDL-cholesterol level should not be used to measure atherosclerotic risk in a patient. However, HDL-cholesterol does have an important use in practice. In a small fraction of women (about 6%) and fewer men (about 1%), elevated plasma-cholesterol levels reflect an unusually high HDL-cholesterol (greater than 100 mg/dl). For example, a man with a plasma-cholesterol of 270
mg/dl may have 100 mg of cholesterol in HDL and 170 in LDL + VLDL, while most men would have around 45 mg/dl in HDL and 215 mg/dl in LDL + VLDL. Because such differences may affect therapeutic recommendations, HDL-cholesterol should be measured at least once in individuals whose plasma-cholesterol level would lead to a recommendation for long-term treatment.

We have no information about the effects of interventions that increase HDL-cholesterol levels on the development of atherosclerosis in humans. It is therefore premature to include interventions aimed solely at HDL-cholesterol in medical practice.

References

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