The HDL: The Good Cholesterol Carriers?

The lipoproteins called HDL may help to protect against heart attacks, but there are some uncertainties about how they perform this role

Usually we hear about what is bad for us—about something that causes cancer, heart disease, obesity, or sometimes all of these. That may be one reason why research on high-density lipoproteins (HDL) has captured the medical and popular imagination. Because it looks as if the HDL, once thought to be minor carriers of cholesterol in the bloodstream, may actually be good for us.

A growing body of research suggests that the HDL protect against heart attacks. The evidence comes both from epidemiological studies linking increased concentrations of blood HDL with a decreased risk of heart attack and from biochemical studies that provide a plausible—even if unproven—mechanism to explain how the HDL may prevent the buildup of the arterial cholesterol deposits that cause heart attacks.

One implication of the HDL research has already been widely accepted. The concentration of this good cholesterol component, taken in conjunction with that of total blood cholesterol, ought to give a more accurate prediction of an individual's risk of heart attack than the total cholesterol value alone.

Predicting risk is only one aspect of the heart disease problem, however. The second part is determining whether high-risk patients can take steps to avoid the fate predicted for them by the epidemiological studies. Still unanswered is the question of whether people can improve their chances of avoiding a heart attack by raising their HDL concentrations.

The possibility that the HDL might protect against heart attacks did not attract much attention until about 1975, although, as it happens, the idea is not new. It first cropped up more than 25 years ago.

Researchers have known for some time that cholesterol is carried in the bloodstream in complexes with other lipids and proteins. The lipoprotein complexes are subdivided according to their density into four major classes: the chylomicrons, the very low density lipoproteins (VLDL), the low-density lipoproteins (LDL), and the HDL. The LDL carry the largest portion, about 80 percent, of the total blood cholesterol, with the HDL carrying most of the remainder. The chylomicrons and VLDL contain large quantities of the lipids called triglycerides, but carry little cholesterol.

In 1951, David Barr, who was then at Cornell University Medical College, found low concentrations of HDL (which is also known as alpha-lipoprotein) in men with coronary heart disease. Barr's observation was confirmed by several other investigators in the late 1950's and early 1960's. But the implication of this finding—that low HDL concentrations might somehow predispose people to heart attacks—received little attention as most clinicians focused on the evils of high concentrations of total blood cholesterol. High concentrations of total cholesterol or of LDL, the major cholesterol carrier, had been linked to an increased risk of heart attack or stroke in several studies.

The HDL were neglected, according to Robert I. Levy, director of the National Heart, Lung, and Blood Institute (NHLBI) and a leading figure in lipoprotein research, partly because there were no easy and reliable methods for measuring the concentrations of the various lipoproteins until about 10 years ago. Levy concedes, however, that "we were so focused on total cholesterol and LDL, we ignored HDL to an extent."

That situation changed, beginning in about 1975, when Norman Miller, who was then at the Royal Infirmary in Edinburgh, Scotland, and George Miller, at that time at Llandough Hospital in Pennarth, South Wales, reported an inverse correlation between blood concentrations of HDL and total body cholesterol. They suggested that the HDL might keep body cholesterol down by facilitating its excretion.

The Millers' suggestion was quickly reinforced by the results of a series of epidemiological studies of a half-dozen or so diverse populations, including participants in the Framingham (Massachusetts) study, Japanese-Hawaiian men, Israeli men, and black sharecroppers in Evans County, Georgia. The studies all found—again—that the risk of heart attack increases as blood HDL concentrations decrease. Statistical analyses of the data showed low HDL concentrations to be a risk factor independent of other known risk factors, including high LDL concentrations.

Says William Castelli, director of the Framingham study, a prospective study that has provided much information about the risk factors for heart attack and other cardiovascular disease, "For every 5 milligrams per deciliter of blood your HDL falls below the average value, your risk of heart attack increases by roughly 25 percent." The average value for men is 45 milligrams per deciliter. For women, who are at lower risk of coronary heart disease than men, the average is 55 milligrams per deciliter.

Another indication that decreased HDL and increased LDL concentrations are independent risk factors for coronary heart disease comes from studies conducted by Charles Glueck and his colleagues at the University of Cincinnati College of Medicine. They have identified two groups of people who are genetically endowed either with high HDL or low LDL concentrations—and with lifespans as much as 5 to 10 years longer than average. These people, who have what Glueck has christened the "longevity syndrome," rarely get atherosclerosis. "It does not seem to matter," he says, "whether the HDL are up or the LDL are down. Either way they are protected." And the people's life-styles—their diet or whether they smoke, for example—do not seem to matter either.

According to Castelli, the data coming from the Framingham study suggest a better way of assessing an individual's risk of heart attack. He maintains that just measuring total cholesterol concentrations, which is what most physicians still do, is not adequate. Two patients with similar concentrations may have far different risks if one has a low HDL value and the other a high one. This is especially true for people whose total blood cholesterol concentrations are average or elevated slightly. The finding of a low HDL value for these individuals would indicate a higher risk than that predicted by total cholesterol alone.

Finally, there is little correlation between total blood cholesterol and heart attack risk for people over age 50. But the Framingham data show HDL to be predictive of risk even for older people.

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Castelli recommends determining the ratio of LDL to HDL cholesterol or of total to HDL cholesterol, which is somewhat easier to do. The Framingham study found the latter ratio to be 5.0 for the average man and only 5.7 for the average male heart attack victim. (For women, the analogous values are 4.4 and 5.3.) Castelli suggests that any ratio above 4.5 is grounds for instituting efforts to lower it.

The ratio could be lowered by increasing HDL concentrations, lowering total or LDL cholesterol concentrations, or doing both. The problem is that there is not much information about how to raise HDL levels. Levy, who is otherwise delighted with the attention the HDL are now receiving, says, "It is embarrassing. We spent so much time concentrating on how to alter the bad lipoproteins, that we do not know as much about HDL."

Researchers have identified a number of factors that may influence HDL concentrations, however. In general, those things already thought to predispose to heart disease, including smoking, obesity, and lack of exercise, are associated with low HDL levels. Conversely, factors thought to decrease the risk of heart attack, such as being female, exercising, and consuming moderate amounts of alcohol, are correlated with higher levels.

Women, as everyone knows, have a much lower risk of heart attack than men at all ages, but especially before the age of menopause. They also have higher HDL concentrations than men at all ages after puberty. This difference may help to explain the greater resistance of women to coronary heart disease.

The cause of the different blood lipoprotein patterns of men and women is not completely understood, although the sex hormones estrogen and testosterone undoubtedly have something to do with it. Studies carried out by the Lipid Research Clinics, which are sponsored by the NHLBI, have found comparable HDL concentrations in males and females before puberty. During sexual maturation, when the sex hormones are produced in much greater quantities, the HDL concentrations of males fall below those of females and the male LDL levels rise, establishing the lipoprotein patterns seen in later life. The theory is that the male hormone testosterone decreases whereas the female hormone estrogen increases HDL. As further evidence for this hypothesis, Ronald Krauss and Frank Lindgren of the Donner Laboratory, University of California at Berkeley, find higher HDL concentrations in women taking estrogens for menopausal symptoms than in women of the same age who are not taking estrogens.

The relationship between estrogens, HDL, and heart attacks is far from clear, however. According to the theory, estrogens, by virtue of their effect on HDL, should protect against heart attacks. But HDL concentrations usually increase with age, even after menopause, when estrogen production falls off. At the same time, the incidence of coronary heart disease also increases with age. Moreover, estrogen use has been linked to an increased incidence of heart attacks in both men and women. (Estrogens are used to treat some forms of cancer in men.)

Use of contraceptive pills, most of which contain an estrogen plus a progestin (a synthetic mimic of the female sex hormone progesterone), has also been associated with an increased risk of heart attack. Krauss, with investigators from the Kaiser-Permanente Contraceptive Drug Study in Walnut Creek and the Center for Disease Control in Atlanta, surveyed the effects of a wide variety of oral contraceptives and other hormones on the HDL concentrations of women taking the drugs. They concluded that the effect depends on the formulation of the drug because progestins may lower HDL concentrations whereas estrogens raise them. Thus, it is hard to tell whether HDL alterations might contribute to the pill-users' increased risk of heart attack.

Genetic endowment and sex cannot be changed (at least not easily) but some of the other factors associated with high HDL concentrations are more amenable to manipulation. However, anyone who attempts to raise his or her HDL level needs to consider the possibility that making the appropriate change in the factors will not necessarily produce the desired effect. In fact, when some such modifications have been attempted they have met with mixed results.

Exercise is one of the factors associated with elevated HDL concentrations that can be controlled. At about the time the HDL story was coming to the fore, Peter Wood at Stanford University was comparing the lipoprotein patterns of runners and nonrunners as a follow-up of a fortuitous observation he had made some years before. Wood, who has been a long-distance runner for more than 40 years, had sometimes used his own blood as a control in his lipoprotein experiments. He had noted that it contained much more HDL than most other people's blood and decided to see if the same was true of runners in general.

He compared the blood lipoproteins of 45 male runners between the ages of 35 and 59 with those of 45 relatively sedentary men in the same age group. The HDL concentrations of the controls averaged 45 milligrams per deciliter of blood, the same as the average found in the Framingham study, whereas those of the runners, who all ran at least 15 miles per week, averaged 65 milligrams per deciliter. In a study of women, Wood found that the runners' HDL concentrations also were about 20 milligrams per deciliter higher than the nonrunners'.

Interpretation of studies such as these may be confounded by additional differences between the control and test groups. Runners, for example, smoke less (usually not at all), are leaner, and, for some reason, drink more alcoholic beverages than nonrunners. All three of these characteristics have been correlated with increased HDL concentrations. According to Wood, statistical analysis of the Stanford data indicates that the runners' leanness may partially, although not totally, explain their higher HDL concentrations, but that not smoking and higher alcohol consumption make little, if any, contribution.

The runners studied by the Stanford workers all had well-established exercise habits. Whether or not the sedentary person who takes up exercise will be rewarded with increased HDL and a reduced risk of heart attack is an unanswered question. Some studies have shown an HDL increase, whereas others have not.

Attempts to increase HDL concentrations by weight loss have also met with mixed results, even though obesity has been correlated with reduced HDL levels in several studies, including the one at Framingham. Wood found that the concentration of the lipoprotein actually declined slightly, but significantly, in 15 very obese women who lost weight. Meanwhile, Gustav Schonfeld of the Washington University Medical School found that the effect of weight loss on HDL might vary, depending on the subject's characteristics. There are conditions called hyperlipoproteinemias in which one or another of the various lipoproteins of blood is increased in concentration. Schonfeld found that weight loss did increase HDL concentrations in patients with one kind of hyperlipoproteinemia but not in those with another.

There is not much information about the effects of diet in general on HDL. Whether low cholesterol or high polyunsaturated fat intakes, both of which are recommended for decreasing total cholesterol concentrations, can alter HDL is largely unknown. This is one of those embarrassing areas, mentioned by

Levy, where we do not know as much about HDL as we would like.

One possible dietary component—namely alcohol—does apparently raise HDL levels. Joseph Barboriak of Wood Veterans Administration Center and the Medical College of Wisconsin found that alcoholics have HDL concentrations between 80 and 100 milligrams per deciliter of blood, almost twice the average concentration. If the alcoholics refrain from drinking, the concentrations drop to normal within 2 weeks.

In another study, Barboriak also observed that the degree of blockage of the coronary arteries of men undergoing diagnostic tests for coronary heart disease was inversely correlated with their alcohol intake and with the HDL concentrations in their blood, giving further support to the theory that alcohol may protect against heart disease by raising HDL levels. Moreover, in some epidemiological studies, moderate drinking, usually defined as one to two drinks per day, has been linked to a decreased risk of dying from a heart attack, although alcohol may increase deaths from all causes.

While the epidemiological studies have been building up a case suggesting that HDL might protect against coronary heart disease, studies of the basic biochemistry of the blood lipoproteins have been providing some clues as to how the HDL might be working. The evidence suggests that the LDL may carry cholesterol to the tissues and deposit it there. If more cholesterol were deposited than is needed by the cells, it would accumulate. Accumulation in the arterial linings could produce atherosclerosis and coronary heart disease. In contrast, the HDL may carry cholesterol away from the tissues to the liver, from which it can be excreted, thus reducing the body's cholesterol burden.

"You can raise the HDL but it does not mean a thing if it does not affect atherosclerosis."

The HDL appear to be produced both by the liver and the intestines. The HDL come from the liver as incomplete disk-shaped particles consisting mainly of protein and phospholipid but with little cholesterol. According to Antonio Gotto and his colleagues at the Baylor College of Medicine and Methodist Hospital in Houston, other incomplete HDL particles are formed from some of the components of the VLDL and chylomicrons. During the normal metabolism of these two lipoproteins, the triglycerides contained in them are broken down by the enzyme lipoprotein lipase. Some of the residual proteins and phospholipids then end up as newly formed HDL disks.

Such a conversion of VLDL to HDL would help explain the common observation that VLDL concentrations are elevated in situations where HDL levels are low, and vice versa. It might also help to explain how alcohol and exercise increase HDL concentrations. Both of these HDL raisers increase lipoprotein lipase activity and thus the conversion of VLDL to HDL.

Several lines of evidence suggest that the HDL may help to prevent cholesterol accumulation by cells. According to Olga and Yechezkel Stein of Hebrew University-Hadassah Medical School in Jerusalem, HDL can remove cholesterol from a variety of cell types, including arterial smooth muscle cells, in the test tube. Whether they can do the same in the living animal is unclear, but results from Norman Miller's laboratory, which is now at St. Thomas's Hospital in London, indicate that they may. After labeled cholesterol was incorporated into the adipose tissue of test subjects, the individuals went on a low-calorie diet that caused weight loss and movement of the labeled cholesterol into the bloodstream. All the label turned up in the HDL.

Work in John Glomset's laboratory at the University of Washington has identified a way in which the HDL may pick up cholesterol from cells. The newly formed, cholesterol-poor HDL disks are thought to remove cholesterol from the cell membranes. An enzyme called lecithin-cholesterol acyltransferase (LCAT) then transfers a fatty acid group from the phospholipid lecithin to the cholesterol to form a cholesterol ester. This material, which is highly nonpolar and hydrophobic, moves to the interior of the HDL particle, where it is sheltered from the watery environment of the blood by the more polar proteins and phospholipids on the particle surface. The HDL particle can continue to pick up and sequester cholesterol in this way, during which process it becomes spherical.

Another way HDL may prevent cholesterol buildup in cells is by directly blocking the uptake of LDL cholesterol. The Steins and also Thomas Carew and Daniel Steinberg of the University of California at San Diego have shown that HDL can bind to cells and keep the LDL from binding to their receptors on the cell surface, a necessary first step for accumulation of LDL cholesterol. The cells take up some cholesterol from the HDL, says Carew, but not nearly as much as they would from the LDL.

Thus, there are several indications that HDL can prevent cholesterol accumulation by cells or remove it if it has already been deposited there. But there are a number of uncertainties about the role postulated for HDL.

For one, most of the work has been done in the test tube. There is much less evidence to suggest that the same things can happen in the living animal. For another, no one has convincingly demonstrated that cholesterol picked up by the HDL is actually carried to the liver and excreted—the last step of the hypothetical cholesterol-lowering pathway.

In addition, there is evidence that cholesterol picked up by HDL can be transferred first to VLDL and from there to LDL. This would seem to increase concentrations of the lipoproteins associated with an increased risk of heart disease. Glomset points out, "We can not just think of HDL as an independent particle preventing heart disease. We have to consider its interactions with the other lipoproteins."

As a final example of lipoprotein complexity, investigators have now shown that there are several types of HDL particles. In the human, the most abundant are the two designated HDL_2 and HDL_3. Researchers are still trying to sort out the functions of these HDL subfractions. There is some evidence that HDL_2 is the form that protects against heart disease. For example, the higher HDL concentrations of women compared to men are accounted for by increased amounts of HDL_2. Also, the HDL_2, and not the HDL_3, are elevated in runners.

Because of the many unresolved issues concerning the role of the HDL, many heart researchers are reluctant to endorse efforts to prevent heart attacks by adopting measures aimed at increasing HDL concentrations, even if these should prove feasible. They point out, however, that most of the steps already recommended as a means of reducing the risk of coronary heart disease are precisely those being linked to high HDL concentrations in the current research.

But the question that still must be answered is whether the elevated HDL levels directly prevent cholesterol buildup in the arteries, as is now being postulated. Charles Day of the Upjohn Company was talking about drug development when he said, "You can raise the HDL but it does not mean a thing if it does not affect atherosclerosis." The same thing can also be said about other efforts to increase HDL levels.—JEAN L. MARX