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The “Good Cholesterol” High-Density Lipoprotein

Peter P. Toth, MD, PhD



Atherosclerosis is an insidious and dangerous disease: a progressive chemical and structural injury to the blood vessels in such critical organs as the heart, brain, and kidney. The hallmark feature of atherosclerosis is the buildup of cholesterol into lesions called plaques that can reduce the flow of blood. When the delivery of blood to heart muscle drops enough, this can result in the development of chest pain or angina. Angina indicates that the heart muscle is not receiving enough oxygen to carry out its pumping functions. Atherosclerotic plaques can also suddenly rupture, develop a blood clot on their surface, and completely choke off a portion of heart muscle. This chain of events frequently results in heart attack or sudden death without warning. Atherosclerotic disease also predisposes people to stroke, peripheral vascular disease, lower-extremity amputation, and loss of kidney function, among other devastating outcomes.

Despite all that we have learned in the past 50 years, atherosclerosis remains the No. 1 killer of men and women and the chief reason for loss of quality of life in Western countries. We are, however, gaining ground. Considerable research has revealed the importance of factors that increase an

individual’s risk for developing this disease. Among the most important of these risk factors are elevated blood pressure, diabetes mellitus, obesity, inactivity, smoking, and cholesterol levels.

When your physician measures your cholesterol level, he or she is looking at your lipid profile, which comprises low-density lipoprotein cholesterol (LDL-C, or the “bad” cholesterol), triglycerides (blood fats), and high-density lipoprotein cholesterol (HDL-C, or the “good” cholesterol). In a general way, when it comes to measurement of your LDL-C and triglyceride values, a lower value is better because these lipids drive the development and progression of atherosclerosis. In sharp contrast, when it comes to HDL-C, with few exceptions, a higher value is better because HDL-C is beneficial and protects patients from the development and progression of atherosclerotic disease.

HDL and Cardiovascular Disease Risk

Studies of both men and women worldwide have demonstrated that the risk for atherosclerotic disease is inversely related to blood levels of HDL-C; that is, the higher your HDL, the lower your risk. On the other hand, the lower your HDL-C (1 milligram

HDL-C per 1 deciliter of blood), the higher your risk. As shown in the Framingham Heart Study, this relationship holds across a broad range of LDL-C levels. Even in patients whose LDL-C is 100 mg/dL (considered by many experts to be an optimal level of “bad” cholesterol), as HDL-C drops, the risk of developing atherosclerosis increases continuously. Consequently, you are at increased risk for heart disease or stroke if your HDL-C is low, even if your LDL-C or total cholesterol is well controlled. Studies have shown that for every 1-mg/dL rise in HDL-C (1 milligram HDL-C per 1 deciliter of blood), the risk for developing cardiovascular disease decreases by 2% to 3%.

How is a low HDL-C defined? According to the National Cholesterol Education Program, a group comprising the foremost authorities on cholesterol in the United States, a low HDL-C is defined as a level less than 40 mg/dL.¹ An expert panel convened by the American Heart Association has recently concluded that in women, HDL is low when it is below 50 mg/dL.² Among patients with diabetes, the American Diabetes Association recommends that HDL-C be above 40 and 50 mg/dL for men and women, respectively.³

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TABLE 1. DEFINITION OF LOW HDL-C

| | |
|-------|-----------|
| Men | <40 mg/dL |
| Women | <50 mg/dL |

Low levels of HDL-C (see Table 1) are present in millions of men and women in the United States. Because of the rising epidemic of obesity and diabetes, the number of individuals whose HDL-C is low is increasing every year. On the basis of the results of your lipid profile, your doctor may recommend the initiation of lifestyle modification and, if necessary, may couple these measures with medications to help raise your HDL-C (discussed below).

Beneficial Effects of HDL

HDL-C is beneficial for a number of reasons. The most important is its ability to drive a process called “reverse cholesterol transport.”⁴ HDL is some-

thing of a mop in that it helps to extract excess cholesterol deposited in blood vessel walls and deliver it back to the liver for elimination through the gastrointestinal tract (see the Figure). In general, the higher your HDL-C, the greater your capacity to remove cholesterol and prevent dangerous blockages from developing in your blood vessels. HDL-C helps to keep your blood vessels widened (dilated), thereby promoting better blood flow. HDL-C also reduces blood vessel injury through its antioxidant and antiinflammatory functions, among other effects.

Lifestyle Modification and HDL-C

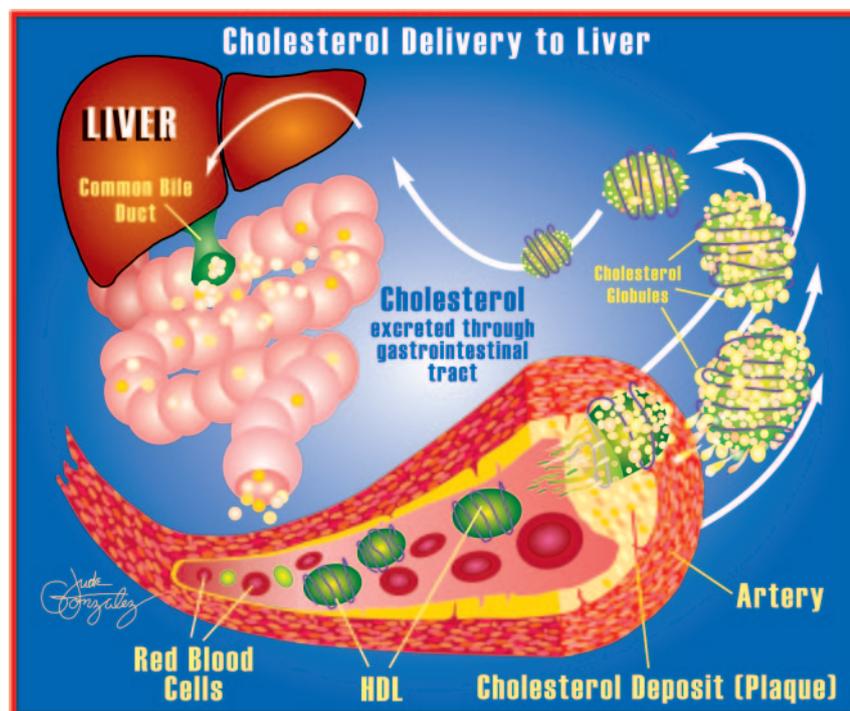
Lifestyle modification is always front-line therapy for men and women with low HDL-C. Obesity, cigarette smoking, and a sedentary lifestyle all reduce blood levels of HDL-C.^{5,6} In contrast, weight loss, smoking cessation, and exercise all promote raising HDL-C. If you are obese and then lose weight, the greater your weight loss and reduction

in the circumference of your waist, the greater will be the elevation in your HDL-C level. The more you exercise, the more your HDL-C will increase. If you quit smoking, then your HDL-C can increase up to 15% to 20%, an elevation on par with some of the best drugs available for raising HDL-C. Increased fish⁷ and reduced carbohydrate consumption both are associated with higher HDL-C. The so-called Mediterranean diet (a diet enriched with fruits, vegetables, whole grains, olive oil, and legumes) is associated with increased HDL-C.⁸ Alcohol consumption can raise HDL-C significantly,⁶ but this benefit must be counterbalanced with knowledge of the risks of alcohol consumption. In general, the average patient could responsibly consume 2 to 6 ounces of wine with each evening’s meal.⁹

Medications That Raise HDL-C

For many patients, lifestyle modification may not be enough to achieve adequate elevations in HDL-C. Your heredity plays an important role in regulating the level of your HDL-C. Mutations in one or more genes can give some people a very high level of HDL-C and predispose others to very low levels of HDL-C. Many patients will require the combination of medication with lifestyle modification.

A number of medications can have an impact on blood levels of HDL-C.¹⁰ The statins have been shown to reduce the risk of heart attack and death in patients with high LDL-C and low HDL-C. Fibrates (gemfibrozil, fenofibrate) are an effective therapy for patients with high triglycerides and low HDL-C. Niacin is the most potent drug currently available for raising HDL-C and has been shown to reduce the risk of heart attack and stroke in patients with heart disease. Several forms of niacin are available, but dietary-supplement niacin must not be substituted for the niacin that your doctor prescribes because the supplement can cause significant liver injury. When taking a statin and niacin in combination, patients with low HDL-C should



Schematic depiction of reverse cholesterol transport. As HDL-C in blood penetrates atherosclerotic plaque in the vessel wall, it mobilizes and binds cholesterol and transports it back to the liver for elimination through the gastrointestinal tract.

TABLE 2. MEASURES TO RAISE HDL-C

| | |
|-------------------|---|
| Lifestyle Changes | Weight Loss Aerobic exercise Smoking cessation Mediterranean diet, increased fish/reduced carbohydrate consumption Wine (2–6 oz) with evening meals |
| Medications | Statins Fibrates Niacin Fish oils enriched with omega-3 fatty acids Thiazolidinediones |

not take vitamin E, vitamin C, or beta-carotene supplements because these agents appear to impair the ability of statins and niacin to raise HDL-C. If you are asked to stop taking your antioxidant vitamins, you will not be missing out on much. In several studies, antioxidant vitamins had no effect on risk for cardiovascular disease.

Fish oil supplements enriched with omega-3 fatty acids can raise HDL-C.¹¹ If you are diabetic, the thiazolidinedione class of drugs has also been shown to increase blood levels of HDL-C. Your doctor may prescribe one or more drugs simultaneously to treat your low HDL-C, depending on your overall clinical picture and the results of other components of your lipid profile (see Table 2).

Conclusion

HDL-C is the "good" cholesterol because it exerts multiple beneficial functions within the cardiovascular system. Higher levels are more beneficial, and your physician should not undertake any therapeutic measures to reduce your HDL-C. Raising HDL-C can be challenging, but if you persist in the implementation of lifestyle modification and take your medications as prescribed, you can significantly alter

your risk of cardiovascular disease. After beginning medication, you must continue with lifestyle modification to achieve long-term success in raising HDL-C. Given the wide prevalence of low HDL-C and its importance as a risk factor, a number of therapies are being developed in an effort to raise HDL-C even more effectively. The introduction of these drugs will constitute a major advance in heart disease prevention.

Additional Web Resources on HDL-C

1. Heart Center Online web site. Available at: <http://www.heartcenteronline.com/myheartdr/common/articles.cfm?ARTID=505>.
2. American Heart Association web site. Available at: <http://www.americanheart.org/presenter.jhtml?identifier=183>.
3. MedicineNet.com web site. Available at: <http://www.medicinenet.com/cholesterol/article.htm>.
4. American Association for Clinical Chemistry web site. Available at: <http://www.medicinenet.com/cholesterol/article.htm>.

Disclosure

Dr Toth is a consultant to AstraZeneca, Merck, and GlaxoSmithKline, and a member of the speakers' bureaus of AstraZen-

eca, Merck, Kos Pharmaceuticals, Novartis, and Pfizer.

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