The two faces of the ‘good’ cholesterol

ABSTRACT

Although a low level of high-density lipoprotein (HDL) cholesterol is a useful clinical predictor of coronary heart disease, raising the HDL cholesterol level does not necessarily lower this risk. Part of the explanation for this paradox may be that, under certain conditions, HDL either can be less functional as an antioxidant or can even enhance the oxidation and inflammation associated with atherosclerotic plaque. Thus, the functional properties of HDL—not simply the level—may need to be considered and optimized.

KEY POINTS

HDL from healthy people is most often anti-inflammatory, but a systemic inflammatory stimulus or acute phase response, such as in infection, surgery, autoimmune disease, diabetes mellitus, and even atherosclerosis itself, can cause HDL to become proinflammatory, as can foods high in saturated fat.

Several tests (not yet commercially available) hold promise that we may be able to characterize the nature of HDL in addition to simply measuring the HDL cholesterol level.

Exercise, a low-fat, high-fiber diet, statin drugs, and certain experimental drugs appear to enhance HDL’s anti-inflammatory properties.

Until these tests and interventions are validated, clinicians should follow established guidelines for reducing cardiovascular risk.

HIGH-DENSITY LIPOPROTEIN (HDL) has a more complex relationship with coronary artery disease than was once thought. Although low levels of HDL cholesterol (HDL-C) predict coronary disease, raising these levels does not necessarily lower this risk.

Part of the reason seems to be that the quality of the HDL counts at least as much as the quantity. Ordinarily anti-inflammatory and protective, HDL sometimes becomes proinflammatory, enhancing the oxidation and inflammation associated with atherosclerotic plaque. In other words, the “good” cholesterol has two faces.

In this article, I examine the other face of HDL and how a better understanding of its complex functional properties could lead to better therapies.

LOW HDL-C IS BAD, BUT HARD TO RAISE

The inverse relationship between HDL-C levels and the risk of coronary heart disease is well documented, with each decrease of 1 mg/dL in HDL-C corresponding to a 2% to 3% increase in risk. Furthermore, clinical trials such as the Helsinki Heart Study, the Veterans Affairs HDL Intervention Trial, and the HDL and Atherosclerosis Treatment Study have shown that lipid-modifying drugs are beneficial in patients with low HDL-C levels.

Analyses of these trials raised the tantalizing prospect that some of the reduction in risk was explained by increases in HDL-C, and
consensus panels of lipid experts have recommended raising HDL-C above specified targets in patients at high risk of coronary heart disease once low-density lipoprotein cholesterol (LDL-C) targets are met.\textsuperscript{6,7} But enthusiasm for raising HDL-C levels has been tempered by practical barriers to doing so: it is harder to raise levels of HDL-C than it is to lower levels of LDL-C.

At high doses, niacin can raise HDL-C levels by 25\% to 30\%, but often with treatment-limiting side effects, such as flushing, pruritis, and worsening of glycemic control. Fibrates and statins are tolerated better but offer a much more modest 5\% to 10\% potential to raise HDL-C levels.

\section*{RAISING HDL-C LEVELS MAY NOT DECREASE RISK}

The approach to HDL-C is proving to be more complex than with LDL-C. Lowering the LDL-C level lowers coronary risk, but raising the HDL-C level (by some methods at least) may not always be protective.

Torcetrapib, an inhibitor of the enzyme cholesteryl ester transfer protein (CETP), was greeted with cautious optimism after it increased HDL-C levels by more than 100\% in early trials in humans.\textsuperscript{8} However, a large-scale trial designed to assess the rates of cardiovascular disease and death was recently halted early when the rate of death from any cause was found to be 61\% higher in the group receiving combination therapy with torcetrapib and atorvastatin (Lipitor) than in the group receiving atorvastatin monotherapy.\textsuperscript{9}

Torcetrapib has been reported to have a mildly hypertensive effect, and this or another non-HDL effect could have contributed to the excess deaths. Another possibility is that CETP inhibition could have adversely affected the HDL particles themselves, rendering them either ineffective at slowing atherosclerosis or, worse, contributory to vascular inflammation.

\section*{NEW TESTS ASSESS HDL FUNCTION}

It is becoming clear that the functional characteristics of HDL are as important as or more important than the HDL-C level. Under normal circumstances, HDL promotes reverse cholesterol transport from arterial walls to the liver, slows vascular inflammation, and limits oxidation of LDL particles—all of which help keep plaque formation in check (\textbf{FIGURE 1}). However, in the setting of systemic inflammation, HDL can become dysfunctional in these same capacities. Moreover, evidence is mounting that HDL can sometimes paradoxically enhance the oxidation and inflammation associated with atherosclerotic plaque.

Several ex vivo and in vitro assays have been developed to assess HDL's various functions. These tests are not yet commercially available but hold promise that we may be able to go beyond measuring the HDL-C level and determine the functional characteristics of the patient's HDL.

A monocyte chemotaxis assay for assessing HDL was described by Navab et al\textsuperscript{10} in 2000. This test measures how strongly serum monocytes are attracted to cultured human arterial wall cells in response to LDL before and after HDL is added. In the body, the arterial wall increases its production of monocyte chemoattractant protein-1 (MCP-1) in response to exposure to LDL, so that monocytes are more strongly attracted to it—which promotes inflammation in the arterial wall.

Under normal circumstances, HDL markedly decreases MCP-1 production and therefore decreases monocyte chemotaxis,\textsuperscript{11} and thus is considered anti-inflammatory. If the patient's HDL actually increases the amount of MCP-1 produced, it is considered proinflammatory. The effect of HDL on monocyte chemotaxis is inversely correlated with HDL's ability to promote efflux of cholesterol from lipid-containing macrophage cells.\textsuperscript{12}

\textbf{Adhesion molecules.}\ The effect of HDL on the expression of adhesion molecules on the surface of endothelial cells lining the interior of blood vessels can also be measured. Recently, Nicholls et al\textsuperscript{13} reported that levels of endothelial cell intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) could be used to assess the effect of HDL on these inflammatory cell receptors.\textsuperscript{13} A low adhesion molecule level suggests that the patient's HDL is anti-inflammatory, while a high level would indicate a proinflammatory effect.
The two faces of high-density lipoprotein (HDL)

Normal, anti-inflammatory HDL.
The function of HDL is as important as the level. Normally, HDL has an anti-inflammatory role, promoting reverse cholesterol transport from arterial walls to the liver, slowing vascular inflammation, and limiting the oxidation of low-density lipoprotein (LDL) particles—all of which help keep plaque formation in check.

- Responsible for reverse cholesterol transport
- Keeps levels of monocyte chemotactic protein-1 (MCP-1) in check
- Apolipoprotein A-1 (apo A-1) helps HDL with reverse cholesterol transport and antioxidative and anti-inflammatory roles
- Limits the production of oxidized lipids (eg, LDL)

Impaired, proinflammatory HDL.
Systemic infection, stress related to surgery, coronary artery disease, diabetes mellitus, autoimmune disease, and a diet high in saturated fat impair HDL's ability to perform its key roles and even cause it to enhance the oxidative and inflammatory processes that lead to plaque formation.

- Less able to perform reverse cholesterol transport
- Lower apo A-1 levels in HDL impair reverse cholesterol transport and antioxidative and anti-inflammatory roles
- Increased production of MCP-1 and cellular adhesion molecules (ICAM-1, VCAM-1) attracts inflammatory cells to the vascular wall
- Myeloperoxidase (MPO), an oxidative enzyme from white cells in plasma, damages HDL
A cell-free assay developed by Navab and colleagues evaluates the effect of multiple antioxidant enzymes within HDL on oxidation of phospholipids, which are major components of both LDL and HDL. Copper stimulation. Hasselwander and colleagues reported a different technique to assess HDL's effect on the production of oxidized lipids in response to copper stimulation, which may differ from in vivo sources of oxidative stress.

**WHAT CONDITIONS MAKE HDL GO BAD?**

HDL from healthy people is most often anti-inflammatory. However, when systemic inflammation is present, HDL can become proinflammatory as part of an acute phase response. Elective surgery is a good example of this effect. Van Lenten et al. showed that HDL obtained several days after elective surgery was less able to suppress chemotaxis (as assessed by the monocyte chemotaxis assay) than was HDL obtained before surgery. This dysfunctional HDL reverted to a normal anti-inflammatory role once the patients had recovered from surgery.

Influenza also appears to make HDL proinflammatory.

Sepsis has been reported to have dramatic effects on the composition of HDL, including a marked reduction in levels of the major apolipoprotein within HDL, apolipoprotein A-I (apo A-I). Chronic systemic inflammation drives a more protracted state of impaired HDL function in some patients. This has been observed in patients with coronary heart disease, in people with coronary risk equivalents, and in patients on hemodialysis. In one relatively unusual cohort of patients who developed symptomatic coronary disease despite very high HDL-C levels (≥ 84 mg/dL), HDL uniformly increased monocyte chemotaxis (as assessed by the monocyte chemotaxis assay) and phospholipid oxidation (as assessed by the cell-free assay), while HDL from healthy matched controls had opposite effects. HDL from a second cohort of patients with known coronary disease or coronary risk equivalents who had more typical HDL-C levels (mean 57 mg/dL) also showed proinflammatory tendencies on the same tests.

Recent research has also produced evidence of dysfunctional HDL in patients with chronic nonvascular inflammation, such as in rheumatologic diseases. McMahon and colleagues reported that 44% of patients with systemic lupus erythematosus and 20% of those with rheumatoid arthritis had proinflammatory HDL as assessed by the cell-free assay, compared with only 4.1% of controls. These observations may help explain why women with lupus have a risk of myocardial infarction 50 times higher than normal, and why rheumatoid arthritis doubles the risk of coronary disease, even when conventional risk factors have been controlled for.

**HOW DOES HDL BECOME PROINFLAMMATORY?**

Systemic inflammation can promote specific changes within HDL particles that can hinder their antiatherosclerotic effects.

One such target within HDL is apo A-I, a protein critical to HDL's reverse cholesterol transport, antioxidant, and anti-inflammatory roles. Apo A-I levels can fall in response to inflammation and can be displaced from HDL particles by acute phase reactants such as serum amyloid A. Apo A-I can also be chemically damaged by the white blood cell enzyme myeloperoxidase.

Inflammation and associated oxidative stress can also lead to a reduction in levels of protective antioxidant enzymes such as paraoxonase, as well as to a buildup of oxidized phospholipid molecules within HDL. These changes lead to an increase in oxidized LDL particles, which in turn promote a variety of inflammatory processes within the blood vessel wall.

**MODIFYING HDL’S FUNCTIONAL PROPERTIES**

The proinflammatory and anti-inflammatory effects of HDL can be altered by several different treatment approaches (Table 1).

Saturated fat raises ICAM-1 and VCAM-1; unsaturated fat decreases them

In one study, the fat composition of a diet markedly affected HDL's impact on ICAM-1...
and VCAM-1 expression on endothelial cells. Nicholls et al.\textsuperscript{13} found that HDL collected from patients 6 hours after eating a meal high in saturated fat increased the levels of these adhesion molecules 50\% to 80\% from baseline. In contrast, HDL from patients who ate a meal high in unsaturated fat inhibited ICAM-1 and VCAM-1 expression by 50\% to 70\%. These changes occurred without significant changes in HDL-C levels. In this study, then, saturated fat promoted qualitative changes in HDL that could potentially increase monocyte adhesion to the arterial wall.

**Healthy diet and exercise inhibit monocyte chemotaxis**

Roberts and colleagues\textsuperscript{24} studied the effects of a 3-week intervention consisting of a high-fiber, low-fat diet and exercise (45–60 minutes of walking fast on a treadmill) in obese men with metabolic syndrome. The lifestyle changes significantly improved the ability of the men’s HDL to inhibit monocyte chemotaxis compared with baseline. Before the intervention the men’s HDL was proinflammatory as assessed by the monocyte chemotaxis assay, with a mean inflammatory index of 1.14 plus or minus 0.11 (1.0 is neutral); afterward, their HDL was anti-inflammatory, with a mean index of 0.94 plus or minus 0.09 ($P < .05$). This study suggests that therapeutic lifestyle changes may affect HDL function, in addition to exercise’s well-recognized effect of raising HDL-C levels.

**Statins can modify HDL’s properties**

Statins have also shown the ability to modify HDL’s proinflammatory and anti-inflammatory properties. My colleagues and I conducted a study\textsuperscript{12} in which patients with coronary heart disease or risk equivalents were treated with simvastatin (Zocor) 40 mg for 6 weeks. Over the treatment period, their HDL changed from mostly proinflammatory to mostly anti-inflammatory, as assessed by both the monocyte chemotaxis assay and the cell-free assay.

More recently, Charles-Schoeman et al.\textsuperscript{25} showed that HDL from patients with active rheumatoid arthritis became more anti-inflammatory after the patients were treated with atorvastatin 80 mg daily for 12 weeks.

**Experimental modulators of HDL function**

A new class of drugs known as apo A-I mimetics shows promise as a way to modulate HDL function, as tested in animal models.

These drugs are relatively small peptides. An example is D-4F, which is 18 amino acids long and has a helical structure similar to the active sites of apo A-I and a dextro orientation that makes it resistant to gastrointestinal enzymatic degradation and therefore active when taken orally. Mice and monkeys who were fed D-4F produced more anti-inflammatory HDL as assessed by the monocyte chemotaxis assay.\textsuperscript{26} Interestingly, statins and D-4F appear to work synergistically in promoting aortic lesion regression in monkeys when they are given together compared with the effects of low doses of the two agents alone.\textsuperscript{27} In preliminary studies in humans,\textsuperscript{28} D-4F was well absorbed when taken orally, and the subjects’ HDL showed subsequent improvement in anti-inflammatory and antioxidant effects.

It is clear, then, that HDL is a dynamic...
molecule, and that whether it is anti-inflammatory or proinflammatory depends on circumstances such as inflammatory stimuli and on therapeutic interventions.

■ WHAT SHOULD CLINICIANS DO?

Low levels of HDL-C can be a useful clinical predictor of coronary heart disease risk, but the complex functional properties of HDL mean that raising HDL-C levels does not necessarily lower this risk. Systemic inflammation due to infection, autoimmune disease, diabetes mellitus, and even atherosclerosis itself seems to promote the proinflammatory nature of HDL. On the other hand, some therapeutic interventions that have been shown to be antiatherogenic also enhance HDL's anti-inflammatory potential.

In development are HDL functional assays and also drugs that more specifically improve HDL's anti-inflammatory effects. Research is ongoing to characterize how lipid-modifying therapies and lifestyle practices can promote or inhibit HDL function. Studies are also under way to relate HDL's proinflammatory properties to the results of currently available HDL subfractionation testing. In the future, when clinical tests of HDL's anti-inflammatory capacity become available, they may provide a way to identify patients who should receive treatment directed toward the quality of HDL. Discovery and evaluation of potential drug therapies may be aided by assessing their impact on HDL function.

Until such tools become clinically available, clinicians are advised to:

- Consider patients with low HDL-C levels to be at substantially increased risk of coronary heart disease
- Consider chronic systemic inflammation to be a potential driver of dysfunctional (ie, proinflammatory) HDL and, therefore, of increased coronary risk, regardless of the HDL-C level
- Use a lipid-lowering drug (a statin in most cases, with niacin or possibly a fibrate) and other treatments that have been proven to reduce cardiovascular events in those patients at risk of coronary heart disease.

■ REFERENCES

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