HDL and Cardiovascular-Disease Risk — Time for a New Approach?
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Clinical and epidemiologic studies have consistently shown that low levels of high-density lipoprotein (HDL) cholesterol are strongly associated with an increase in the risk of coronary artery disease. Moreover, hypercholesterolemic mice with genetic defects in HDL metabolism are markedly atherosclerotic, providing compelling evidence that HDL is a key modulator of the disease in animal models. These observations, together with the large residual disease risk among patients with coronary disease who are treated with statins, have triggered intense interest in therapies that raise levels of HDL cholesterol.

Despite the abundant evidence for the inverse association between HDL cholesterol and the risk of coronary disease, certain drugs, such as fibric acid derivatives, that elevate HDL cholesterol levels show inconsistent clinical benefit. Moreover, it is unclear how HDL in humans interacts with the artery wall to influence the progression or regression of atherosclerosis. A central hypothesis — based on cell culture and studies in animals — is that HDL promotes cholesterol efflux from macrophage foam cells in atheromatous vessels, decreasing the cholesterol burden and macrophage-driven inflammation (Fig. 1).

In this issue of the Journal, Khera et al. measured the ability of human serum HDL to promote cholesterol efflux from cultured macrophage foam cells. In two large, independent groups of subjects, this capacity was strongly associated with coronary disease status. It is important to note that the association was inverse, which is consistent with studies in animals that show that HDL is atheroprotective because it promotes cholesterol efflux from macrophages. These observations provide important evidence that the ability of HDL to promote cholesterol efflux from macrophage foam cells is a key property that explains in part the inverse relationship between HDL and the risk of atherosclerotic coronary artery disease in humans.

It has been suggested that inflammation and other disorders that increase the risk of coronary disease involve the conversion of HDL to a dysfunctional form that is no longer cardioprotective. However, the underlying mechanisms are unclear, and no widely accepted methods for determining HDL function in humans have been described. Khera et al. found that the ability of serum HDL to promote cholesterol efflux from macrophages was not determined simply by measuring HDL cholesterol levels and that the association between efflux capacity and the risk of coronary disease remained significant after adjustments for levels of HDL cholesterol and apolipoprotein A-I, the major protein component of HDL. These observations suggest that HDL efflux capacity is a measure of HDL function that is relevant to the pathogenesis of atherosclerosis. These observations also support the proposal that dysfunctional HDL contributes to the risk of coronary disease.

An understanding of the deleterious effects of dysfunctional HDL may lead to new diagnostic and therapeutic approaches to atherosclerosis. However, the underlying factors that render HDL dysfunctional remain poorly understood. One important pathway may involve oxidative damage to HDL. Oxidation of apolipoprotein A-I by myeloperoxidase and other reactive intermediates impairs the ability of this apolipoprotein to remove cellular cholesterol from macrophages, which suggests that HDL apolipoproteins might be targets for oxidation reactions that contribute to atherogenesis.

Remarkably little is known about the function of proteins other than apolipoprotein A-I that are carried in normal and dysfunctional HDL. Proteomic studies suggest that HDL carries a unique cargo of proteins in patients with coronary disease and that these proteins might make contributions to the proinflammatory and antiinflammatory properties of HDL. Oxidative and compositional changes could affect the ability of HDL particles to remove cholesterol from macrophages. In future studies, it will be important to identify the proteins and other factors that alter the function of HDL in humans and that are selectively enriched or depleted in subjects who...
are at risk for coronary artery disease. The ability to measure the efflux capacity of HDL, as shown by Khera et al., may thus be a useful tool in the further investigation of HDL function.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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7. de la Llera-Moya M, Drazul-Schrader D, Asztalos BF, Cuchel M, Rader DJ, Rothblat GH. The ability to promote efflux via ABCA1 determines the capacity of serum specimens with similar high-density lipoprotein cholesterol to remove cholesterol from macrophage foam cells by means of the ATP-binding cassette transporter A1 and G1 (ABCA1 and ABCG1) pathways.

Figure 1. HDL Promotes Cholesterol Efflux from Macrophages.

Macrophages become inflammatory foam cells when they accept lipids from cholesterol-rich low-density lipoprotein (LDL). Foam cells play critical roles in atherosclerosis by promoting inflammation. In mouse models of atherosclerosis, high-density lipoprotein (HDL) is atheroprotective in part because it removes excess cholesterol from macrophage foam cells by means of the ATP-binding cassette transporter A1 and G1 (ABCA1 and ABCG1) pathways.