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HIGH-DENSITY LIPOPROTEIN PROCESSING AND PREMATURE CARDIOVASCULAR DISEASE

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Abstract

High plasma concentrations of low-density lipoprotein-cholesterol (LDL-C) are a well-accepted risk factor for cardiovascular disease (CVD), and the statin class of hypolipidemic drugs has emerged as an effective means of lowering LDL-C and reducing CVD risk. In contrast, the role of plasma high-density lipoproteins (HDL) in protection against atherosclerotic vascular disease is the subject of considerable controversy. Although the inverse correlation between plasma HDL-C and CVD is widely acknowledged, reduction of CVD risk by interventions that increase HDL-C have not been uniformly successful. Several studies of large populations have shown that the first step in reverse cholesterol transport (RCT), the transfer of cholesterol from the subendothelial space of the arterial wall via the plasma compartment to the liver for disposal, is impaired in patients with CVD. Here we review HDL function, the mechanisms by which HDL supports RCT, and the role of RCT in preventing CVD.

Introduction

Cardiovascular disease (CVD) remains an important and growing disease in developed and developing countries. Hypertriglyceridemia, a low plasma high-density lipoprotein cholesterol (HDL-C) concentration, hyperglycemia, hypertension, and a large waist circumference are all CVD risk factors. Patients with at least three of these risk factors satisfy the criteria for the diagnosis of metabolic syndrome (MetS). Recent studies in humans and in mouse models suggest that raising plasma HDL-C concentrations is not a valid therapeutic strategy and that enhancing the disposal of HDL-C is more likely to reduce CVD events. This might include a recently described bacterial protein which diverts HDL-C to the low-density lipoprotein (LDL) receptor and profoundly lowers plasma cholesterol concentrations in mice. The following provides a review of plasma lipoproteins as CVD risk factors and discusses the role of reverse cholesterol transport in the prevention of CVD.

Plasma Lipoproteins

The plasma lipoproteins comprise three major classes defined by the densities at which they are isolated: high (HDL), low (LDL), and very low-density lipoproteins (VLDL). Intermediate-density lipoproteins (IDL), which are transient in normolipidemic persons, form during the conversion of VLDL to LDL. Chylomicrons, which are formed from dietary fat, are produced and secreted by the intestine into the lymph as triglyceride (TG) -rich particles. An elevated plasma LDL-C concentration, a risk factor for CVD, is usually managed by changes in diet and lifestyle; failure of this first approach leads to statin therapy as the next option. In contrast, a low plasma HDL-C concentration is a CVD risk factor for which current therapies are not adequate.

Higher Plasma HDL-C Concentrations Are Associated with Lower CVD Risk

Human HDL occurs as distinct subclasses of large and small particles, HDL_2 and HDL_3, respectively. Numerous observational and prospective studies provoked the hypothesis that raising HDL-C is a rational therapeutic goal for reducing CVD. On the basis of a 10-year prospective study of male employees at the Livermore Radiation Laboratory, Gofman et al. first reported that men who developed ischemic heart disease had lower HDL_2 and HDL_3 and higher LDL, IDL, and small VLDL.[1] A 29-year follow-up to the Livermore study[2] showed that total incident coronary heart disease (CHD) varied inversely with HDL_2 and HDL_3 mass, and concordantly related to LDL-mass, IDL-mass, and small and large VLDL mass concentrations. The protective effects of HDL, expressed as a hazard reduction per mg/dL, was greater for HDL_2, which are larger particles and more lipid-rich than HDL_3. Premature CHD risk was greater in men within the lowest HDL_2 and HDL_3 quartiles. Other observational and interventional trials also supported the higher-HDL-is-better hypothesis and suggested that raising HDL-C might provide a cardioprotective effect. The Framingham Heart Study identified many CVD risk factors, including low HDL-C levels, that were associated with a higher death rate.[3]

In some studies, interventions that increased HDL-C reduced CHD events. In both the Helsinki Heart Study[4,5] and the Veterans Administration HDL Intervention Trial,[6] increasing HDL-C with fibrate therapy was associated with reduced CVD events. Finally, regular modest alcohol consumption is associated with reduced CVD death,[7] an effect once attributed to the attendant increases in HDL-C;[8] however, this has never been tested, nor likely will be, in a prospective placebo-controlled study.

The higher-HDL-is-better hypothesis was incorporated into a model for RCT (Figure 1) that connected elevated plasma HDL with atheroprotection. Briefly, all nucleated cells produce cholesterol that is used for membrane biogenesis and steroid hormone production. However, only the liver has a high capacity for cholesterol disposal via its conversion to bile salts, which, along with cholesterol, are secreted into the intestine and excreted. Excess cholesterol can accumulate in the subendothelial space of

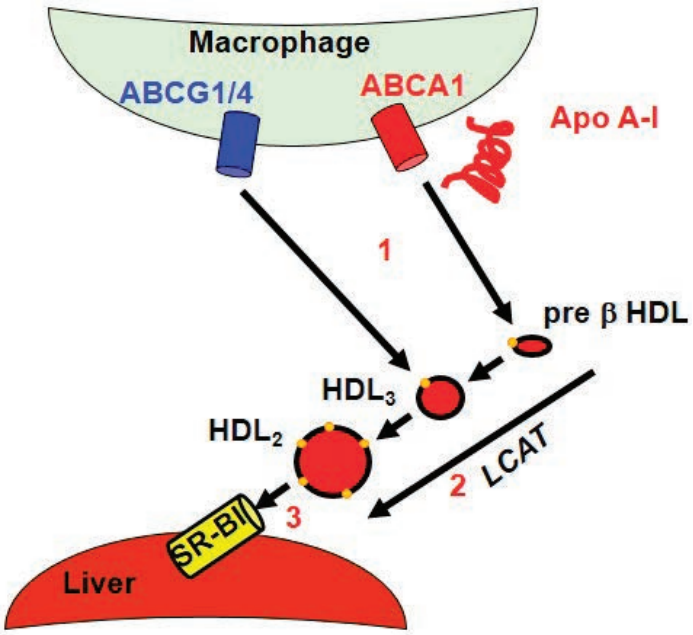

Figure 1. Schematic representation of reverse cholesterol transport comprising (1) cholesterol efflux from macrophages, (2) its esterification by lecithin:cholesterol acyltransferase (LCAT), and (3) uptake of high-density lipoprotein-cholesteryl ester (HDL-CE) by hepatic scavenger receptor class B type I (SR-BI).

the arterial wall to initiate atherogenesis. The cholesterol burden of the arterial wall can be reduced by RCT, wherein subendothelial macrophage-foam cells transfer cholesterol to HDL and its major protein, apolipoprotein (apo) AI, to form larger HDL and nascent HDL, respectively. These HDL particles diffuse into the plasma compartment, where the free cholesterol is esterified by the plasma protein, lecithin:cholesterol acyltransferase (LCAT). The resulting cholesteryl ester (CE) in the resultant particle is internalized by liver hepatocytes via the HDL receptor, scavenger receptor class B type I (SR-BI). Thus, RCT comprises three major steps: transfer of cholesterol from macrophages to HDL or apo AI, esterification by LCAT, and hepatic removal by SR-BI.

Evidence that Raising Plasma HDL Does Not Necessarily Prevent CVD

There is no hard and fast rule that high plasma levels of HDL-C translate to low CVD event rates; many patients with low HDL-C do not develop symptomatic CVD, and vice versa. Mouse models in which hepatic SR-BI has been deleted exhibit higher HDL-C levels but increased atherosclerosis.[9] Cholesteryl ester transfer protein (CETP) is a plasma protein that exchanges the cholesteryl esters (CE) of HDL for the TGs of VLDL and chylomicrons, thereby reducing the cholesterol content of HDL and overall plasma HDL-C concentrations; this effect is dose-dependent with respect to plasma VLDL concentrations.[10] Consequently, the HDL CE content is reduced without changing the HDL particle number. Patients with CETP deficiency have high plasma HDL-C levels but lower cardioprotection than CETP-competent patients with the same HDL-C levels.[9,11,12] HDL-C was profoundly increased (+72%) among patients receiving a CETP inhibitor, but they experienced an increased number of cardiovascular events.[13] Daily treatment with 120 mg of torcetrapib, one of the early CETP inhibitors, increased plasma HDL-C concentrations by 46% in control patients and 61% in patients receiving atorvastatin cotherapy.[14] Nevertheless, the phase III trial of torcetrapib was terminated because of "an imbalance of mortality and cardiovascular events" due to off-target effects—thereby sparking an insightful analysis of the failed drug.[15]

On the basis of the model of RCT (Figure 1), one might expect that enhancing each of the steps would be atheroprotective, yet the results of such studies have been mixed. The earliest study showed that the apo B-depleted plasma of patients with similar HDL-C levels, whether high or low, can have very different capacities for cellular cholesterol efflux, the initial step in RCT.[16] A later study found a paradoxical association of enhanced cholesterol efflux with increased prospective risk of myocardial infarction/stroke and major adverse cardiovascular events.[17] Another large study observed a strong inverse association of macrophage cholesterol efflux with both carotid intima-media thickness and the likelihood of angiographically confirmed coronary artery disease, independently of the HDL-C level.[18]

Based on the cholesterol efflux studies, it would seem that enhancement of this RCT step would have a salutary effect; however, there are some caveats. One is the use of fluorescent or radiolabeled cholesterol analogs, which give only the efflux rate but not the balance between efflux and influx. Indeed, a different picture emerges when the cholesterol mass of the cell is measured directly. As the cholesterol content of reassembled HDL is increased, the balance of cellular cholesterol shifts from efflux to influx above 15 mol% in the HDL, so the net flux of cholesterol between the cell and HDL shifts from efflux to influx. Concurrent with increased cholesterol influx, intracellular cholesterol biosynthesis is down-regulated while that of cholesterol esterification increases.[19] Another caveat is the use of apo B-depleted serum that provides a measure of cholesterol efflux to HDL and to the lipoprotein-deficient fraction but lacks the full physiological setting of whole plasma, which contains the apo B-containing proteins that bind a large fraction of effluxed cholesterol.

Cholesterol efflux is altered in patients with MetS. A recent study compared efflux to the plasma of control subjects versus obese MetS patients before and after weight loss.[20] Surprisingly, efflux to MetS patient plasma was higher than that to control plasma, but weight loss among the MetS patients "normalized" efflux by reducing it to control values. Also surprising was that the magnitude of efflux correlated with plasma apo B levels and non-HDL-C but not with plasma levels of HDL or apo AI. Kinetic studies showed that macrophage cholesterol initially (~10 minutes) associates with HDL but transfers to apo B-containing lipoproteins at later times. This would seem to be important because apo B-containing lipoproteins are cleared much faster than HDL (Figure 2). The affinity of LDL for cholesterol is greater than that of HDL, so that the rate of cholesterol desorption from HDL is much faster than that from LDL, having half times of 3 and 45 minutes, respectively.[21] However, the number of HDL particles in human plasma is nearly ten times greater than that of all other lipoproteins combined. Therefore, based on chemical kinetics, the most-likely first encounter of a cholesterol molecule desorbing from a cell membrane will be HDL. Yet within minutes, cholesterol transfers from HDL to LDL where over time most of it accumulates due to cholesterol's higher affinity for LDL.

These data compel reconsideration of the atheroprotective value of cholesterol efflux from a different perspective. Maximizing cholesterol efflux is not necessarily the optimal therapeutic endpoint. Reducing traditional CVD risk factors—hypertension, total cholesterol, LDL-C, non-HDL-C, apo B, and HOMA-IR—is

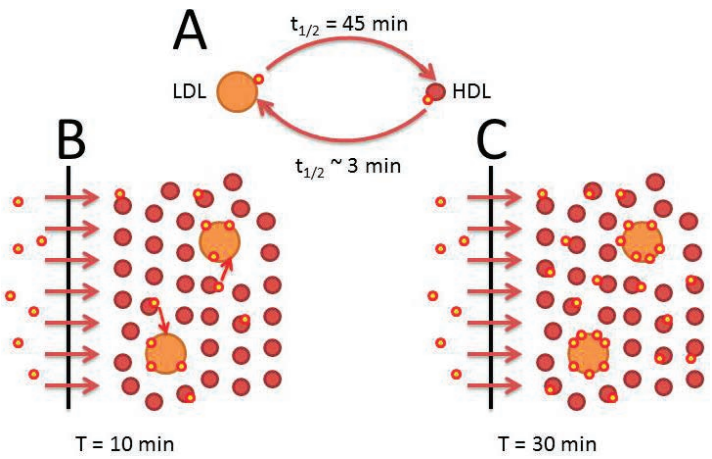

Figure 2. Model for cellular cholesterol efflux. (A) Transfer of cholesterol (yellow circles) from high-density lipoprotein (HDL, red circles) is ~15 times faster than that from low-density lipoprotein (LDL, beige circles). (B) Early in efflux, cholesterol associates with HDL, the most abundant lipoprotein. (C) Later, after cholesterol transfer from HDL to LDL, it accumulates in LDL.

atheroprotective, and reducing these risk factors by weight-loss must also be considered a sensible therapeutic strategy despite the attendant decrease in macrophage cholesterol efflux. The higher CVD risk in diabetic and MetS patients compared to control nondiabetic subjects suggests that the reduction in cholesterol efflux to that of control plasma is not as important as reducing traditional CVD risk factors, especially the number of apo B-containing lipoproteins. Thus, putative detrimental effects of weight loss-associated decreases in efflux to total lipoproteins are outweighed by reduction of other risk factors. In the MetS population, other RCT steps beyond efflux, such as selective hepatic cholesterol uptake, may be more important.

Other evidence against the higher-HDL-is-better hypothesis has emerged from studies of large populations. Patients in the Copenhagen City Heart Study with genetically elevated levels of apo A-I and HDL-C, both of which are acceptors of macrophage cholesterol, did not have a reduced risk for ischemic heart disease or myocardial infarction.[22] Low plasma HDL-C levels due to heterozygous loss-of-function ABCA1 mutations were not associated with an increased risk of CHD.[22] According to a Mendelian randomization study, an HDL-C-raising gene (LIPG Asn396Ser) is not associated with reduced myocardial infarction.[23] Therapies such as nicotinic acid and fibrates increase HDL-C levels, but the link between these drugs and clinical risk reduction has been elusive.[24,25]

In the Copenhagen City Heart Study and the Copenhagen General Population Study, a common variant of LCAT, which catalyzes the second step in RCT (Figure 1), was found in individuals with the lowest 2% HDL-C who had a 13% decrease in HDL-C but no increased risk of myocardial infarction or other ischemic end points.[26] Comparison of LCAT activity in CVD cases and controls revealed that high plasma LCAT activity did not predict reduced CVD risk.[27] In the EPIC-Norfolk and the IMPROVE studies,[28] plasma LCAT levels showed weak or no association with future cardiovascular events. These findings in CVD patients do not support the hypothesis that increasing levels of LCAT is antiatherogenic; a definitive correlation between loss-of-function LCAT mutations and CVD has been elusive.[29]

A positive correlation between alcohol consumption and reduced overall death, especially CVD death, has been affirmed in numerous studies.[7] However, a 2011 study of the Cohort of Norway Population showed that controlling for HDL-C does not affect the magnitude of the relationship between alcohol intake and CVD death.[30] In summary, many mechanisms that increase HDL are not atheroprotective, and enhancing RCT via improved cholesterol efflux or esterification is not clearly atheroprotective. Only the final RCT step, cholesterol disposal to liver via SR-BI, seems to be atheroprotective by reducing plasma HDL-C concentrations.[9]

Dysfunctional HDL

Given the role of HDL in RCT, there are several steps that, if impaired, could produce an atherogenic state. The studies of macrophage cholesterol efflux to plasma showed that not all HDL are created equal, and that plasma with similar HDL concentrations could have very different capacities to accept cholesterol from cells. Additional potential mechanisms for HDL dysfunction can arise from other pathological conditions such as MetS, which is frequently associated with obesity. The onset of MetS is usually but not always a gradual process. One notable exception is the MetS that is associated with HIV-positive patients receiving antiretroviral therapy. In less than 1 year after starting therapy, these patients can develop many of the symptoms of MetS, including low HDL-C levels, hypertriglyceridemia, hyperglycemia, and ectopic fat usually presenting as abdominal or central obesity. The underlying cause has been attributed to increased lipolysis in adipose tissue, particularly the femoral-gluteal depots.[31] The fatty acids liberated from this depot are transferred to skeletal muscle, where they impair glucose disposal, to the liver, where some are converted to VLDL-triglyceride that produces hypertriglyceridemia when hypersecreted, and to other depots such as the waist line, which gives rise to central obesity.

HIV patients on antiretroviral therapy (HIV/ART) exhibit a unique atherogenic-dyslipidemic profile that emulates MetS. In the Heart Positive Study of HIV/ART patients, a combination hypolipidemic therapy—fenofibrate, niacin, diet, and exercise—reduced hypertriglyceridemia and plasma non-HDL-C concentrations and raised plasma HDL-C.[32] Tests revealed that HDL in HIV/ART patients have abnormal structures and properties and are dysfunctional.[33] Hypolipidemic therapy reduced the TG contents of LDL and HDL. At baseline, LDL in HIV/ART patients were more TG-rich, and HDL were more TG- and CE-rich than the corresponding lipoproteins from normolipidemic (NL) subjects. VLDL, LDL, and HDL were larger than the corresponding lipoproteins from NL subjects; HDL in HIV/ART patients were less stable than HDL in NL patients. Hepatic uptake of HIV/ART HDL-CE is impaired when compared with normolipidemic plasma HDL. The larger size of all lipoproteins supports a model of impaired hepatic extraction of HDL-CE, with dysregulated lipoprotein lipolytic processing in plasma by hepatic and lipoprotein lipases (Figure 3).

Enhancing Hepatic Extraction of HDL-CE

In a shift from thinking about HDL as the "good" cholesterol, recent data support a new hypothesis that all lipoprotein cholesterol, even HDL-C, is not uniformly salutary. Thus, one might begin to look for ways to enhance HDL-C disposal. One possibility is a reaction catalyzed by the streptococcal protein, serum opacity factor (SOF). The SOF spontaneously transfers all of the CE from 400,000 HDL particles into one new particle, a CE-rich microemulsion (CERM) that contains apo E as its major protein.[34] The occurrence of so much cholesterol in a particle containing apo E, a ligand for multiple hepatic receptors, provoked the hypothesis that SOF could reduce plasma cholesterol. Testing this hypothesis

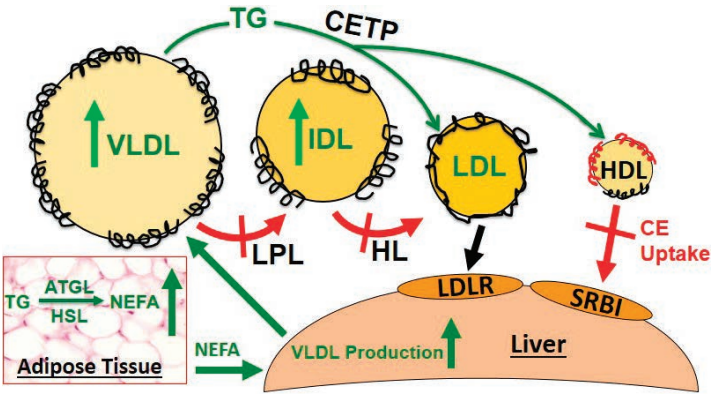

Figure 3. Metabolic model of dysfunctional lipoprotein metabolism in HIV patients on antiretroviral therapy (HIV/ART). Dyslipidemia in HIV/ART patients begins with hyperlipolytic activity in adipose tissue, which releases free fatty acids that are hepatically extracted for increased very-low-density lipoprotein (VLDL) production, thereby producing a hypertriglyceridemic state; Cholesteryl ester transfer protein (CETP) exchanges the VLDL-triglyceride for high-density lipoprotein-cholesteryl ester (HDL-CE) and low-density lipoprotein-cholesteryl ester (LDL-CE), yielding triglyceride (TG)-rich HDL and LDL. TG hydrolysis by hepatic lipase (HL) is inhibited, resulting in larger TG-rich lipoprotein species. The high HDL triglyceride content makes the HDL less stable, so that apo A-I is more labile. In HIV/ART patients, the CE of HIV/ART HDL are hepatically extracted at a lower rate than those of NL HDL because of their intrinsically lower uptake and the lower plasma HDL-C levels. NEFA: nonesterified fatty acid; ATGL: adipose triglyceride lipase; HSL: hormone-sensitive lipase; IDL: intermediate density lipase; LPL: lipoprotein lipase.

in mice showed that low-dose SOF reduced plasma cholesterol approximately 45% in 3 hours, with the reduction lasting for nearly a day.[35] Subsequent tests on mice that underwent ablation of the genes for apo E or the low-density lipoprotein receptor (LDLR) supported a model wherein SOF diverts HDL-C to the LDLR, a process in which apo E is the lipoprotein ligand. These studies support a pharmacological strategy to identify small molecules that form a CERM from HDL.

Conclusion

Clearly there is much to be learned about RCT and its role in the prevention of CVD. The differences in macrophage cholesterol efflux in patients with CVD compared to control plasma seem well supported, but additional tests are needed. If increasing efflux is a desirable end point, new ways of doing this pharmacologically need to be identified. Similarly, if hepatic HDL-C disposal is a desirable end point, new strategies to achieve this are needed. Lastly, more research is needed on those interventions—exercise and alcohol consumption—that raise plasma HDL-C in a cardioprotective way.

Conflict of Interest Disclosure: Dr. Gotto is an advisor at Yellowstone Capital Inc. and has consulting relationships with Arisaph Pharmaceuticals, Inc., Aegerion Pharmaceuticals, Inc., Esperion Therapeutics, Inc., and Medtronic MiniMed, Inc.

Keywords: reverse cholesterol transport, metabolic syndrome, cardiovascular disease, HDL-C, LDL-C, macrophage cholesterol efflux

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