

Therapeutic interventions targeted at the augmentation of reverse cholesterol transport

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Purpose of review

Serum high-density lipoproteins (HDLs) and reverse cholesterol transport (RCT) are important therapeutic targets in the management of atherosclerotic disease. This review summarizes the pathway of RCT and the currently available means by which investigators are attempting to modulate HDL levels and increase rates of RCT.

Recent findings

Low levels of HDL are commonly encountered in patients with atherosclerotic disease. HDLs mediate a substantial number of antiatherogenic effects along blood vessel walls. One of the most important of these antiatherogenic mechanisms is RCT, a series of reactions by which HDL is able to facilitate the net translocation of cholesterol from peripheral cells to the liver for excretion. There is scientific evidence supporting the concept of RCT in both animals and humans. To facilitate RCT, it is important that therapeutic effort be made to raise serum levels of HDL. Statins, fibrates, niacin, thiazolidinediones, and various combinations of these drugs all raise HDL levels. However, in many high-risk patients with established atherosclerotic disease, the elevations in HDL achieved with these medications are frequently inadequate. Newer agents designed to raise HDL and promote RCT are currently being developed, including infusible bioengineered HDL, edible HDL composed of D-amino acids, and agents capable of inhibiting cholesterol ester transfer protein, among others.

Summary

Established therapies for raising HDL can be effective either as monotherapy or when used in combination. Newer strategies are being developed to exploit more specifically the capacity of HDL to drive RCT and either prevent or reverse the course of atherosclerotic disease.

Keywords

HDL, atherosclerosis, CETP inhibitors, apoA-I mimetics

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Abbreviations

ABCA1 ATP-binding membrane cassette transporter A1
apo apoprotein

CETP cholesterol ester transfer protein
HDL high-density lipoprotein
LCAT lecithin:cholesterol acyltransferase
LDL low-density lipoprotein
ndHDL nascent discoidal high-density lipoprotein
PLTP phospholipid transfer protein
PPAR peroxisomal proliferator-activated receptor
RCT reverse cholesterol transport

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Introduction

There is a strong inverse relation between risk for acute cardiovascular events and serum levels of high-density lipoproteins (HDLs) [1,2]. On the basis of the findings of a large number of prospective cohort studies [3–5], drug-based intervention trials [6,7], and a growing body of mechanistic data [8], HDL is widely recognized as a lipoprotein that protects against the development of atherosclerotic disease and its clinical sequelae. The National Cholesterol Education Program has defined an HDL lower than 40 mg/dL as a categorical risk factor for the development of coronary and other vascular disease [9]. HDLs exert a variety of vasculoprotective effects. HDL stimulates nitric oxide production by upregulating the expression of nitric oxide synthase [10], stimulates prostacyclin production [11], inhibits endothelial cell adhesion molecule expression by inhibiting activation of the nuclear factor κ B pathway [12], inhibits low-density lipoprotein oxidation via its constituent paraoxonase activity and the methionine residues of apoprotein (apo) A-I [13,14], prevents endothelial cell apoptosis [15], is antithrombotic by virtue of its ability to block platelet aggregation [16] and potentiate the activities of protein C and S [17], and can activate a variety of intracellular signaling systems [18]. Among the most important of its functions is its ability to drive reverse cholesterol transport (RCT), the process by which HDL is able to extract excess peripheral cholesterol and translocate it to the liver or steroidogenic organs for elimination as bile acids or for steroid hormone biosynthesis, respectively, thereby helping to prevent the net accumulation of atherogenic lipid in the vasculature [19,20].

There is experimental support for the concept of RCT in both humans [21] and animal models [22]. Raising serum HDL levels is an important therapeutic target in the prevention and management of atherosclerotic disease. However, currently available antilipidemic medications

phages in the subendothelial space. HDL can also directly deliver cholesteryl ester to hepatocytes by interacting with a variety of cell surface receptors, including scavenger receptor BI [24], the β -chain of F1-ATP synthetase [25], or glycosylphosphatidylinositol-anchored HDL-binding protein 1 [26]. The cholesteryl esters delivered back to the liver can either be converted to bile salts and eliminated through the gastrointestinal tract or be repackaged into lipoproteins and resecreted into the circulation. RCT thus constitutes an efficient, albeit complex, means by which excess peripheral cholesterol can be extracted and delivered back to the liver for elimination.

Lipoprotein lipase

Lipoprotein lipase is inhibited in patients with insulin resistance and hyperinsulinemia. Fibrates are peroxisomal proliferator-activated receptor (PPAR)- α agonists that increase lipoprotein lipase activity by decreasing the expression of apoCIII, an inhibitor of this enzyme. Fibrates can raise HDL substantially, particularly when baseline HDLs are lower than 40 mg/dL [27]. The thiazolidinediones pioglitazone [28] and rosiglitazone [29] are also able to relieve lipoprotein lipase inhibition to some extent by reducing insulin resistance. In patients with insulin resistance and diabetes mellitus, the thiazolidinediones raise serum levels of HDL [30] and provide elevations in HDL that are additive to those obtained with statin therapy [31].

Apoprotein A-I

The intravenous infusion of apoA-I and transgenic expression of human apoA-I in animal models are antiatherogenic and can stimulate atheromatous plaque resorption [32,33]. The statins and fibrates both stimulate the hepatic expression of apoA-I via PPAR- α agonism. Of considerable interest is the recent development of an edible form of apoA-I mimetic peptides composed of D-amino acids that decreased atheromatous lesions by 79% and reduced LDL-stimulated monocyte chemotaxis in LDL receptor-null mice fed a Western diet [34]. It will be of great interest to determine whether such an edible form of apoA-I mimetic peptides will be efficacious in preventing atherosclerotic disease in humans.

ApoA-I_{Milano} is a mutant form of apoA-I and arises from the amino acid substitution Arg173 \rightarrow Cys [35]. Patients with the apoA-I_{Milano} genotype typically have low serum levels of HDL but remarkable resistance to the development of atherosclerotic disease. ApoA-I_{Milano} appears to be atheroprotective because it is antithrombotic and it has augmented capacity for promoting cellular cholesterol efflux [36]. The introduction of liposomes containing recombinant ApoA-I_{Milano} into rabbits [37] and apoE-deficient mice [38] is associated with reduced atheromatous plaque lipid content. The weekly intravenous infusion of apoA-I_{Milano} liposomes into humans with established

CAD reduced plaque volume after only 5 weeks of therapy as determined by intravenous ultrasound measurements [39••]. Clearly, the use of apoA-I mimetic peptides and apoA-I_{Milano}-enriched liposomes offers considerable potential therapeutic application in patients with CAD, and the results of trials using these agents will be eagerly awaited.

ATP-binding membrane cassette transporter A1

The capacity for cellular cholesterol efflux via ABCA1 affects serum levels of HDL and risk for CAD significantly. The overexpression of human ABCA1 in transgenic mice increases serum HDL and biliary cholesterol (a measure of RCT) and decreases risk for atherosclerotic disease [40]. Human subjects heterozygous for mutations in ABCA1 that decrease capacity for cholesterol efflux experience increased risk for CAD [41]. Fibrates may increase rates of RCT by both upregulating the expression of ABCA1 [42] and decreasing the esterification of cholesterol in macrophages by inhibiting acyl-CoA: cholesterol acyltransferase-1 [43]. When acyl-CoA: cholesterol acyltransferase-1 is inhibited, more cholesterol is available for ABCA1-driven cholesterol export. Novel agonists of the retinoid X receptor and liver X receptor have demonstrated capacity for upregulating the expression of ABCA1 in rodents [44]. The PPAR- γ agonist rosiglitazone activates liver X receptor expression, which in turn increases ABCA1 activity and apoA-I-induced cholesterol translocation into the extracellular space in both human macrophages and macrophage-derived foam cells [45]. An interesting set of findings is obtained when New Zealand white rabbits are infused with phosphatidylinositol, a phospholipid that becomes concentrated in the HDL of these animals [46]. The infusion of phosphatidylinositol resulted in a substantial rise in RCT, as indicated by the increased delivery of plasma-derived cholesterol to the liver and a 21-fold elevation in the biliary excretion of cholesterol. The exposure of cholesterol-loaded macrophages to phosphatidylinositol stimulates the transfer of intracellular cholesterol to ndHDL, possibly by an ABCA1-dependent pathway.

Lecithin:cholesterol acyltransferase

In rabbits, the increased expression of LCAT has been shown to be antiatherogenic. There are no known human mutations that lead to the overexpression of LCAT, and no trials manipulating the activity of LCAT are currently underway.

Phospholipid transfer protein

In addition to its functions in mediating the transfer of phospholipid between lipoproteins and catalyzing HDL conversion reactions, PLTP appears to interact with ABCA1 and mediate the net transfer of lipid from cells to apoA-I and ndHDL particles [47]. PLTP may therefore

participate in RCT by helping to (1) regenerate ndHDL during HDL conversion and (2) facilitate the lipidation of ndHDL in the subendothelial space. Despite these observations, when transgenic mice overexpressing human PLTP were fed a high-cholesterol diet, serum HDL decreased and aortic atherosclerosis increased significantly [48]. There are no characterized human mutations in PLTP that lead to the overexpression of this enzyme.

Hepatic lipase

The overall impact of hepatic lipase activity on risk for CAD is complex and can be either proatherogenic or antiatherogenic depending on differences in overall genetic and metabolic backgrounds [49]. Increased hepatic lipase activity can produce significant reductions in serum levels of HDL. The thiazolidinediones can decrease the magnitude of hepatic lipase activation induced by hyperinsulinemia [50]. Consistent with this, the treatment of diabetic patients with rosiglitazone can increase HDL and HDL₂ by 18% and 13%, respectively, and also decrease the percentage of LDL that is small and dense [51]. In the Familial Atherosclerosis Treatment Study, combinations of antilipidemic medications (lovastatin/colestipol and niacin/colestipol) were able to induce variable reductions in hepatic lipase activity in patients with CAD [52]. The magnitude of hepatic lipase inhibition correlated with the degree of plaque resorption as measured by coronary angiography. Atorvastatin induces dose-dependent reductions in hepatic lipase activity in patients with diabetes mellitus with as much as a 20% inhibition at 80 mg [53]. The effects of hepatic lipase inhibition on risk for CAD and rates of RCT are areas of ongoing investigation.

Cholesterol ester transfer protein

A number of genetic polymorphisms resulting in CETP deficiency have been identified and are particularly prevalent in people of Asian ancestry [54]. Two of the more common mutations that give rise to significant CETP deficiency include a G→A substitution in the 5' splice donor site of intron 14 and a D442→G missense mutation in exon 15. Although CETP deficiency is associated with hyperalphalipoproteinemia, this is not consistently associated with reduced risk for atherosclerotic disease and may even increase risk, as shown in the Omagari region of Japan [55]. The reduced capacity for transferring cholesteryl ester into apoB100-containing lipoproteins leaves the HDL of these patients particularly enriched with cholesterol. In cell culture systems, the HDL of these patients has decreased ability to extract cholesterol from cholesterol-loaded macrophages [56]. However, interest in therapeutic CETP inhibition is mounting because some patient groups appear to derive atheroprotective benefit. In both the Honolulu Heart Study [57] and studies performed in the Kochi Prefecture of Japan [58], elevations in HDL induced by the D442→G mutation were associated with reduced risk for

CAD-related events. In the Veterans Administration HDL Intervention Trial, men with the TaqI B2B2 genotype for CETP had reduced CETP activity, higher baseline serum HDL levels, and a 48% lower risk for acute coronary events compared with subjects homozygous for the B1 allele [59].

There are currently two principal strategies used to inhibit CETP. The first involves the development of autoantibodies to CETP by injecting subjects with anti-CETP sera. Rabbits vaccinated with such sera experience a reduction in serum CETP activity, an elevation in serum HDL, and decreased risk for aortic atherosclerosis even when fed an atherogenic diet [60]. The feasibility of using anti-CETP sera in humans was recently demonstrated [61•]. The vaccination was well tolerated, and 53% of patients developed autoantibodies after two injections. Additional investigation is needed to determine the effects of vaccination on lipoprotein metabolism and whether a booster vaccination schedule must be developed. The second therapeutic approach to modulating CETP activity is to use a direct inhibitor of the enzyme. One such inhibitor is the compound JTT-705. JTT-705 has been shown to inhibit CETP, raise serum HDL, and decrease aortic atherosclerosis by 70% in rabbits [62]. In the short term, JTT-705 has demonstrated safety in humans and can raise HDL as much as 37% in a dose-dependent fashion after 1 month of therapy [63]. Additional studies must be performed with each of these therapies to determine whether their long-term use will result in sustained elevations in serum HDL, augmented RCT, and reductions in coronary morbidity and mortality. It is postulated that even if these therapies do not result in significant potentiation of RCT, the elevations in HDL they produce will likely be antiatherogenic because of the many other protective functions HDL performs within the vasculature.

Conclusion

A large body of clinical and scientific investigation supports the importance of raising HDL in patients with hypoalphalipoproteinemia. One of the most important reasons to raise HDL is to potentiate RCT, a process that has been shown to be antiatherogenic in a number of animal models. A variety of new therapies targeting specific enzymes or components of the RCT pathway are being developed to (1) augment the ability of HDL to extract cholesterol from the cellular constituents of blood vessel walls and (2) increase HDL formation and decrease its catabolism. Whether and to what degree these agents increase RCT and decrease cardiovascular morbidity and mortality will require prospective testing in clinical trials. In the mean time, established agents such as statins, fibrates, niacin, and the thiazolidinediones can be used either individually or in combination in appropriate clinical settings to increase serum levels of HDL.

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