Brief Review

Cholesteryl Ester Transfer Protein
A Novel Target for Raising HDL and Inhibiting Atherosclerosis


Abstract—Cholesteryl ester transfer protein (CETP) promotes the transfer of cholesteryl esters from antiatherogenic HDLs to proatherogenic apolipoprotein B (apoB)—containing lipoproteins, including VLDLs, VLDL remnants, IDLs, and LDLs. A deficiency of CETP is associated with increased HDL levels and decreased LDL levels, a profile that is typically antiatherogenic. Studies in rabbits, a species with naturally high levels of CETP, support the therapeutic potential of CETP inhibition as an approach to retarding atherogenesis. Studies in mice, a species that lacks CETP activity, have provided mixed results. Human subjects with heterozygous CETP deficiency and an HDL cholesterol level >60 mg/dL have a reduced risk of coronary heart disease. Evidence that atherosclerosis may be increased in CETP-deficient subjects whose HDL levels are not increased is difficult to interpret and may reflect confounding or bias. Small-molecule inhibitors of CETP have now been tested in human subjects and shown to increase the concentration of HDL cholesterol while decreasing that of LDL cholesterol and apoB. Thus, it seems important and timely to test the hypothesis in randomized trials of humans that pharmacological inhibition of CETP retards the development of atherosclerosis. (Arterioscler Thromb Vasc Biol. 2003;23:160-167.)

Key Words: HDL ■ LDL ■ reverse cholesterol transport ■ genetic CETP deficiency

The possibility that cholesteryl ester transfer protein (CETP) might be proatherogenic and that inhibition of its activity might be antiatherogenic was first raised >10 years ago.1 The potential atherogenicity of CETP relates to its ability to transfer cholesteryl esters from the antiatherogenic HDLs to the proatherogenic VLDL and LDL fractions. However, there is also evidence that CETP may be involved in reverse cholesterol transport (RCT). Thus, theoretically, CETP may be either proatherogenic or antiatherogenic. Most experimental evidence in animals favors a proatherogenic role for CETP and supports a view that inhibition of CETP is antiatherogenic.

It has also been suggested that CETP has the potential to inhibit atherogenesis by enhancing the rate of RCT, the pathway by which cholesterol in peripheral tissues is transported to the liver for elimination in the bile. This pathway involves an initial uptake of cell cholesterol by HDL, where it is esterified by lecithin:cholesterol acyltransferase (LCAT). A proportion of the HDL cholesteryl esters is delivered directly to the liver, whereas another proportion is transferred by CETP to LDL and VLDL. The cholesteryl esters in the VLDL/LDL pool are subsequently delivered to the liver via the LDL receptor pathway.

The available clinical data in humans are incomplete and do not permit a definite conclusion about the relation of CETP deficiency to the risk of coronary heart disease (CHD). In this article, we review the totality of evidence on CETP and suggest further research.

What Is CETP and What Does It Do?
CETP is a hydrophobic glycoprotein that is secreted mainly from the liver and that circulates in plasma, bound mainly to HDL.2 It promotes the redistribution of cholesteryl esters, triglycerides, and, to a lesser extent, phospholipids between plasma lipoproteins. CETP transfers lipids from 1 lipoprotein particle to another in a process that results in equilibration of lipids between lipoprotein fractions.3 Most of the cholesteryl esters in plasma originate in HDL in the reaction catalyzed by LCAT, and the majority of the triglycerides enter the plasma as a component of chylomicrons and VLDLs (triglyceriderich lipoproteins [TRLs]). The overall effect of CETP is a net mass transfer of cholesteryl esters from HDLs to TRLs and LDLs and of triglycerides from TRLs to LDLs and HDLs (Figure 1). Thus, CETP-mediated transfers from HDL to VLDL and LDL provide a potential indirect pathway by...
which HDL cholesteryl esters can be delivered to the liver. In a high-CETP species such as the rabbit, this indirect pathway may account for as much as 70% of the cholesteryl esters that originate in HDL.4

Under usual conditions, the rate of CETP-mediated cholesteryl ester transfer is rapid relative to the rate of HDL and LDL catabolism.3 As a consequence, the pools of cholesteryl esters in HDLs and LDLs approach equilibrium in vivo. Thus, whereas an increase in the activity of CETP beyond physiological levels would further increase the rate of bidirectional transfers between HDLs and LDLs, the effect on the distribution of cholesteryl esters between the 2 lipoprotein fractions would be relatively small. In contrast, if CETP were inhibited, then there would be a point beyond which its activity was rate limiting. Under these circumstances, the level of CETP activity may have an important role in determining the distribution of cholesteryl esters between LDLs and HDLs. In the case of transfers between HDLs and the much more rapidly catabolized VLDLs, the amount of CETP in plasma is almost certainly rate limiting under most conditions. Indeed, when the concentration of VLDLs is increased, the quantity of CETP is demonstrably the limiting factor in the rate at which cholesteryl esters are transferred from HDLs.5

When the level of VLDLs is normal, CETP-mediated transfers of HDL cholesteryl esters are directed preferentially to LDLs6 (Figure 2). In contrast, when the concentration of VLDLs is increased, as in patients with type 2 diabetes, HDL cholesteryl esters are preferentially transferred by CETP to larger VLDL particles that become cholesterol rich and thus, potentially more atherogenic.6 Transfers of cholesteryl esters to TRLs are enhanced in the postprandial state.7,8 The rate of cholesteryl ester transfer to TRLs and LDLs and the mass of CETP are increased in patients with a range of atherogenic dyslipidemias.9 CETP contributes to an atherogenic lipid phenotype in several ways. It increases the cholesteryl ester content and thus, the atherogenicity of VLDLs. It also interacts with triglyceride lipases to generate small, dense LDLs10 and HDLs11 (Figure 2). The CETP-mediated reduction in HDL particle size is accompanied by the dissociation of lipid-poor apolipoprotein A-I (apoA-I) from the particle.12-14 When the number of circulating acceptor VLDL and LDL particles is reduced in vivo by treatment with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, there is retention of cholesteryl esters in the HDL fraction and an increase in the proportion of larger HDL2 particles.15

**Figure 1.** Role of CETP in plasma lipid transport. CETP promotes bidirectional transfers of cholesteryl esters (CE) and triglyceride (TG) between plasma lipoproteins. Because most of the CE in plasma originate in HDL in the reaction catalyzed by LCAT and the majority of the TG enters plasma as a component of TRLs secreted either from the liver (VLDL) or intestine (chylomicrons), the overall effect of CETP is to promote a net mass transfer of CE from HDL to TRL and LDL and of TG from TRL to HDL and LDL. Pathways of RCT that deliver plasma CE to the liver include the hepatic uptake from HDL via the scavenger receptor B-1 (SRB-1) or the hepatic uptake of LDL via the LDL receptor (LDL-R).

**Figure 2.** Effects of CETP in normotriglyceridemia (Normo TG) and hypertriglyceridemia (Hyper TG). The magnitude of the net flux of cholesteryl esters (CE) and TGs between lipoproteins is dependent, in large part, on the relative sizes of the TRL, LDL, and HDL pools. In Normo TG, net CE flux to LDLs from HDLs predominates, with minor transfer to TRLs. In contrast, in Hyper TG, increased particle numbers of large VLDLs exhibit elevated acceptor activity for CETP. Under these conditions, there are high net transfer rates of CE from HDLs to TRLs and of TGs from TRLs to both HDLs and LDLs. TG-enriched LDLs and HDLs are substrates for hepatic lipase (HL) that hydrolyzes phospholipid (PL) and TGs to form small, dense LDL and small, dense HDL, respectively.
Natural Inhibitors of CETP in Human Plasma

The presence of natural inhibitors of CETP has been reported in human plasma. One such protein, initially referred to as lipid transfer inhibitor protein, has recently been identified as apoF.16 This protein preferentially suppresses transfers involving LDLS but has less effect on transfers involving HDLS. CETP inhibitory activity within the HDL fraction has been identified as apoC-I.17

Role of CETP in the Development of Atherosclerosis in Animals

Expression of CETP in Transgenic Mice

Several species, including mice and rats, are naturally deficient in CETP. Introduction of the human CETP gene into mice results in a dose-related reduction in HDL levels and a small increase in VLDL and LDL cholesterol and apoB levels.18,19 Mice are relatively resistant to the development of diet-induced atherosclerosis and must clearly accomplish RCT by pathways that do not involve CETP activity. In fact, in studies of bile salt and cholesterol-fed, C57-B16 mice, the introduction and expression of the simian CETP gene resulted in enhanced formation of fatty streak lesions compared with nonexpressing controls.20 It was concluded that the enhancement of lesion development by CETP was secondary to a redistribution of cholesterol from HDLs to the VLDL/LDL fraction.

In another study,21 the human CETP gene was introduced into chow-fed, apoE-knockout mice and also into Western diet–fed, LDL receptor–knockout mice, both of which develop spontaneous atherosclerosis. CETP expression in these animal models redistributed cholesterol from HDLs to the VLDL/LDL pool and also increased the development of atherosclerosis. These results again support a view that CETP is proatherogenic, possibly by virtue of reducing the concentration of HDLs and redistributing cholesteryl esters from HDLs to the VLDL/LDL pool. However, when the CETP gene was overexpressed in apoE-knockout mice that also overexpressed human apoA-I, the effect of CETP on the development of atherosclerosis was nonsignificant, despite being associated with a major reduction in the concentration of HDL cholesterol.21

There are some circumstances in which the expression of CETP in mice has been reported to be antiatherogenic rather than proatherogenic. An antiatherogenic effect of CETP has been observed in mice that have been engineered to overexpress human apoC-III.22 These animals have high levels of triglyceride-rich remnant lipoproteins and develop small fatty-streak lesions. Introduction and expression of the CETP gene into these animals appeared to reduce the extent of the lesions.23 In this and a more recent study in a hypertriglyceridemic mouse model (produced by streptozotocin-induced diabetes and lipoprotein lipase deficiency), CETP was antiatherogenic, probably by decreasing the concentration of cholesterol in small VLDL remnants.23 Whether a comparable situation ever prevails in humans is uncertain. Another example of an antiatherogenic effect of CETP is seen in transgenic mice expressing human LCAT.24 These LCAT-transgenic mice have an increased concentration of HDL cholesterol but paradoxically, also an increased susceptibility to atherosclerosis. Expression of simian cett in these animals reduces the atherosclerosis.25 It has been speculated, though not tested, that the cholesteryl ester–enriched HDLs that circulate in LCAT-transgenic mice may be less able to accept cholesterol from cells. If this were proved to be so, then the introduction of CETP would provide a means for transferring cholesteryl esters from the HDLs, possibly restoring their efficiency as acceptors of cell cholesterol and thus, as inhibitors of the development of atherosclerosis. This speculation is consistent with studies of rabbits, a species with a naturally high level of CETP. Transgenic expression of the human LCAT gene in rabbits increases the level of HDL cholesterol, reduces the concentration of LDL cholesterol, and, in contrast to mice, reduces diet-induced atherosclerosis.26

Inhibition of CETP in Rabbits

Rabbits are highly susceptible to the development of diet-induced atherosclerosis. Rabbits also have a naturally high level of CETP. Furthermore, it has been demonstrated in several rabbit models of atherosclerosis that inhibiting CETP results in a marked reduction in atherosclerosis.

In cholesterol-fed rabbits, the inhibition of CETP by injection of antisense oligodeoxynucleotides (ODNs) against CETP resulted in a reduction in CETP mRNA and mass in the liver, a reduction in plasma total cholesterol, and an increased concentration of HDL cholesterol.27 There was also an increase in LDL receptor mRNA associated with the anti-sense ODNs. These changes were accompanied by a marked reduction in aortic cholesterol content as a marker of the extent of atherosclerosis.

It is also possible to inhibit CETP in vivo by infusing anti-CETP antibodies into rabbits.28 This study showed an effect of CETP on the distribution of cholesteryl esters between HDLs and VLDLs/LDLs but did not investigate the effects of inhibition on the development of atherosclerosis. In a more recent report,29 a vaccine approach has been used to generate auto-antibodies against CETP in vivo in rabbits. In a study of cholesterol-fed rabbits, animals that were immunized against CETP had a reduced plasma activity of CETP and a substantial increase in the concentration of HDL cholesterol. They also had a modest decrease in LDL cholesterol concentration and a significant reduction in aortic atherosclerotic lesions. This study demonstrates that long-term inhibition of CETP is not only possible but also, at least in rabbits, reduces the susceptibility to atherosclerosis.

A newly developed chemical inhibitor of CETP has been used in another recent study of cholesterol-fed rabbits.30 This inhibitor reduced CETP activity in rabbits by >90%, almost doubled the level of HDL cholesterol, and decreased the non-HDL cholesterol by ∼50%. There was an accompanying 70% reduction in atherosclerotic lesions in the aortas of these animals. It was not possible to determine the relative importance of the increased HDL versus the decreased LDL in the reduction of atherosclerosis observed in these rabbit studies. It was speculated that short-term treatment of humans with the same CETP inhibitor would result in a 40% to 45% increase in HDL cholesterol and a 15% to 20% decrease in LDL cholesterol.
CETP, Lipoprotein Metabolism, and Atherosclerosis in Humans

Genetic CETP Deficiency in Humans and Effects on Lipoprotein Metabolism

Several mutations of the CETP gene have been identified as a cause of CETP deficiency and elevated levels of HDL cholesterol. These include a G-to-A mutation at the +1 position of exon 14,1,31 a mutation that is present in up to 2% of the overall Japanese population12,33 and in as many as 27% of people in the Omagari area of Japan.34 Individuals homozygous for this mutation have no measurable CETP mass or activity in their plasma but do have elevated concentrations of both HDL lipids (cholesterol and phospholipid; 3- to 4-fold) and apoA-I (1.7-fold).33 A second common functional mutation of the CETP gene, present in up to 7% of the Japanese population, involves a D-to-G substitution at the 442 position of exon 1533 that also results in increased HDL levels. However, subjects homozygous for this D442G mutation have only a partial rather than a complete CETP deficiency, and HDL levels are elevated 1- to 2-fold.33

Subjects with a homozygous CETP deficiency have elevated concentrations of HDL cholesterol, apoA-I, apoA-II, and apoE. The HDL fraction is especially enriched in larger, less dense, cholesteryl ester and apoE-enriched HDL2 particles.35 The increased HDL concentration is due to a reduction in the rate of catabolism, with a markedly delayed catabolism of both apoA-I and apoA-II.36 In contrast, the synthesis of both apoA-I and apoA-II is similar to that in control subjects.36 Despite the delayed catabolism of apoA-I and apoA-II, it has not been established whether the net flux of cholesterol to the liver is decreased in patients with CETP deficiency. In fact, there are no data to suggest that the rate of HDL apolipoprotein turnover is directly correlated with the net flux of cholesterol to the liver.

The ability of HDLs from homozygous CETP-deficient individuals to promote the efflux of cholesterol from macrophages has been investigated.37 The large, apoE-rich HDLs were poor acceptors of macrophage cholesterol, but the apoE-free HDL2 and the HDL1 from these subjects functioned normally as acceptors of macrophage cholesterol.

In addition to the elevation of HDL that accompanies CETP deficiency, in homozygotes there is a substantial reduction (~40%) in the concentration of LDL cholesterol and apoB.31 These individuals have a polydisperse LDL fraction extending across the whole LDL density range.38,39 Human CETP deficiency is associated with both a decreased rate of production of apoB and an increase in its rate of catabolism, consistent with an upregulation of the LDL receptor in these subjects.40 When preparations of LDL isolated from CETP-deficient patients and from control subjects were injected into control subjects, the CETP-deficient LDL had a delayed catabolism.40 This result is consistent with the observation of decreased affinity of the CETP-deficient LDLs for the LDL receptor.41 One plausible explanation consistent with both the LDL kinetic studies and the LDL receptor-binding studies is that the LDLs from CETP-deficient patients are altered. However, these results are difficult to interpret in terms of atherogenic potential, because any rapidly cleared particles would be underrepresented. Furthermore, it is not known whether the net mass of cholesteryl esters cleared is altered when the particle number is reduced.

Atherosclerosis in CETP-Deficient Human Subjects

The relation between mutations of the CETP gene and susceptibility to premature atherosclerosis is complex. In the Honolulu Heart Study, many of the participants of Japanese origin were heterozygous for the D442G mutation in the CETP gene and had reduced levels of CETP.42 Those in whom the CETP deficiency coincided with HDL cholesterol concentrations of 41 to 60 mg/dL (1.0 to 1.5 mmol/L) had an apparent 50% increase in CHD, although the total number of events in this group was too low to enable firm conclusions to be drawn. When the CETP deficiency was associated with higher HDL cholesterol levels (>60 mg/dL; >1.5 mmol/L), there was no evidence of an increase in CHD. Rather, in this subgroup, there was a low rate of CHD, comparable to that observed in the subjects in whom an elevated HDL cholesterol level was not associated with a deficiency of CETP.

A recent analysis of the 7-year prospective data from the Honolulu Heart Study revealed no statistically significant relation between heterozygous mutations of CETP and CHD or stroke, a finding at variance with the previous suggestion from prevalence data of increased risks (A.R Tall et al, in preparation). In fact, prospective analysis of the data has revealed a nonsignificant trend toward a lower incidence of cardiovascular events in subjects with CETP mutations.

Results similar to those from the Honolulu Heart Study were found in another study of Japanese subjects.43 Individuals with HDL cholesterol levels >80 mg/dL were genotyped for intron 14 and D442G mutations. Subjects with and without CETP gene mutations (homozygous or heterozygous) who had HDL cholesterol levels >80 mg/dL had a very low risk of CHD. Given that the plasma level of CETP is, if anything, lower in deficient subjects with the highest HDL cholesterol levels,42 it is difficult to implicate CETP deficiency per se as a cause of increased CHD. It is possible that a deficiency of CETP is protective, so long as it induces a substantial increase in HDL cholesterol.

HDLs may inhibit the development of atherosclerosis by mechanisms independent of their involvement in RCT. These include antioxidant44 and anti-inflammatory45,46 properties of HDL, both of which have an antiatherogenic potential that may be enhanced when the concentration of HDL is increased in CETP-deficient states.

CETP Polymorphisms and Susceptibility to Atherosclerosis in Humans

There are several reported restriction fragment length polymorphisms (RFLPs) in the human CETP gene (Table 1). Although many of these studies have demonstrated associations between CETP single-nucleotide polymorphisms and small changes in plasma CETP and HDL levels, the relation between these polymorphisms and susceptibility to atherosclerosis is variable (Table 2). Indeed, no consistent picture has emerged from numerous studies examining the relation
TABLE 1. Mutations or Polymorphisms of the Human CETP Gene

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<th>Variation</th>
<th>Location</th>
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<tr>
<td>+524 G→T</td>
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</table>

Mutations or polymorphisms in bold are those that directly affect CETP function or expression. Sources: Bruce et al.59 and Corbex et al.57

between polymorphisms and atherosclerotic cardiovascular disease.

The best-studied RFLP is Taq1B in intron 1. In 1 study, the Taq1B polymorphism accounted for 5.8% of the variance in HDL cholesterol.47 Subjects homozygous for the B1 allele in the Framingham Offspring Study48 had higher levels of CETP and lower levels of HDL cholesterol when compared with either B1B2 or B2B2 subjects. Men with the B2 allele appeared to have a reduced risk of CHD, although there was no significant association in women. A similar result was obtained in the VA-HIT study in men with CHD and low HDL.49 The Taq1B genotype is associated with some of the variation in response to statin therapy, as measured by the progression of coronary atherosclerosis by angiography.50

Some of the reasons for these apparently conflicting observations remain unclear but may be related, at least in part, to uncontrolled confounding by other genes or environmental factors.

Another possibly functional polymorphism has recently been reported in the promoter region of the CETP gene (−629/AC).59 The mass of CETP was higher and the concentration of HDL cholesterol lower in individuals with the A allele than in those with the C allele, although the HDL cholesterol concentration was not correlated significantly with CETP mass. In studies of possible mechanisms whereby the polymorphism influenced CETP mass, it was found that repressor transcription factors that bound to the A allele did not bind to the C allele. An interaction between CETP polymorphisms and lifestyle factors is suggested by 2 recent reports that alcohol consumption greatly influences the apparent effects of several of the CETP polymorphisms.56,57

Inhibition of CETP in Humans: Effects on Plasma Lipoproteins

A newly developed chemical inhibitor of CETP, JTT-705, has been tested in humans.58 In a 4-week, phase II, dose-response study, 198 healthy individuals with mild hyperlipidemia were randomly assigned to 300, 600, or 900 mg/d of JTT-705 or to placebo.58 Treatment with the highest dose was associated with a highly significant 37% decrease in CETP activity, a 34% increase in HDLs, and a 7% decrease in LDLs. Levels of triglycerides, phospholipid transfer protein, and LCAT were unchanged. Doses up to 900 mg/d were safe and well tolerated but were significantly more likely than placebo to cause mild gastrointestinal side effects.

Conclusions

Expression of CETP in transgenic mice, a species that is naturally deficient in this protein, has yielded inconsistent results, with reports of both an increased susceptibility and protection against atherosclerosis in different models. In contrast, the effects in rabbits have been remarkably consistent and strongly support the therapeutic potential of CETP
inhibition for blunting or even halting the development and progression of atherosclerosis.

The available human data, though sparse, generally support the hypothesis that CETP deficiency, especially when associated with a high HDL level, is antiatherogenic. Those studies suggesting that atherosclerosis is increased in some individuals with a heterozygous CETP deficiency may reflect chance owing to small sample sizes, confounding by other risk factors, or biases inherent in the study design. There are no reliable data indicating that CETP inhibition in humans...
would be unsafe. Indeed, CETP inhibitors may provide a powerful therapeutic approach to raising HDL levels, lowering LDL levels, and reducing the development of atherosclerosis in humans. However, such a proposition is based on circumstantial evidence and will remain hypothetical until subjected to direct testing. The recent negative trials with postmenopausal estrogens (that also increase HDL and lower LDL levels) highlight the pitfalls of drawing therapeutic conclusions from circumstantial evidence.

Thus, the hypothesis that pharmacological inhibition of CETP reduces the risk of atherosclerosis should be directly tested in randomized trials with either surrogate or clinical end points. Such trials should be of sufficient size, dose, and duration to reliably test the hypothesis. Further multidisciplinary research efforts into the metabolism of HDL, the precise roles played by CETP, and its interactions with other components of lipid transport and metabolism are also necessary to complete the totality of evidence.

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CETP as a Target for Inhibiting Atherosclerosis


Cholesteryl Ester Transfer Protein: A Novel Target for Raising HDL and Inhibiting Atherosclerosis
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