

Targeting Low HDL – Recent Developments

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The inverse relationship between the plasma high-density lipoprotein cholesterol (HDL-C) and risk of coronary heart disease (CHD) is well-recognized in the general population. However, the development of effective therapeutics that target HDL continues to be challenging due, in part, to the heterogeneity of its structure and the composition and complexity of its metabolism. This issue of *Endocrinology Rounds* reviews a number of recent advances in our understanding of HDL metabolism and its role in atherogenesis. This issue also discusses the HDL-C raising effect of a number of lifestyle measures, as well as several currently available lipid-modifying drugs and novel HDL-targeted therapeutic strategies under development.

Over the past decade, great progress has been made in the development of effective lipid-lowering therapies for the treatment of CHD, with the main treatment target being plasma levels of low-density lipoprotein cholesterol (LDL-C). In large-scale clinical trials, aggressive lowering of LDL-C has generally resulted in about a one-third reduction in the relative risk for major cardiovascular events.¹ Therefore, much remains to be explored to fill in the remaining treatment gaps.

HDL as therapeutic target

Numerous large-scale epidemiological studies have persistently demonstrated an inverse relationship between plasma HDL-C levels and the risk of CHD. An aggregate analysis of 4 of the largest US studies, including the Framingham Heart Study,² Lipid Research Clinic Prevalence Mortality Follow-up Study, Lipid Research Clinic Primary Prevention Trial, and Multiple Risk Factor Intervention Trial,³ estimated that each 1 mg/dL (0.02 mmol/L) elevation in HDL-C is associated with a 2%-3% reduction in CHD risk, a magnitude comparable to that for LDL-lowering. Over the last decade, there have been numerous experimental studies, both in vitro and in vivo, to support the notion that HDL confers direct anti-atherosclerotic actions. However, in spite of such remarkable epidemiological and experimental data on the HDL/CHD relationship, targeting low HDL to prevent CHD is considerably more challenging than lowering LDL. This is primarily because of the complexity of the pathways involved in HDL metabolism and the interactions of various HDL fractions with the vessel wall in atherogenesis. This complexity is exemplified by observations of the paradoxical lack of accelerated CHD risk despite severe HDL deficiency caused by certain monogenic disorders, including apoA-I Milano,⁴ apoA-I Paris,⁵ other apoA-I mutations, and lecithin cholesterol acyltransferase (LCAT) deficiency syndromes.⁶ The following sections review our evolving understanding of various forms of low HDL and ongoing clinical strategies that target at-risk, low-HDL subjects.

Metabolism of HDL

Circulating HDLs are highly heterogeneous in terms of their size, structural protein and lipid compositions, and associated lipid- and oxidation-modulating enzymes (Figure 1).

Apolipoprotein A-I : the main structural protein. The liver synthesizes and secretes the major structural apolipoprotein (apo) A-I and acquires phospholipids (PL) and cholesterol from cell membranes to generate small, cholesterol-poor, nascent HDL. This nascent particle may acquire more cholesterol from peripheral cells (eg, lipid-laden macrophages in atherosclerotic plaques).⁷ Likewise, HDL may also form during lipolysis of triglyceride-rich lipoproteins (ie, very-low-density lipoprotein [VLDL]) by transferring excess surface PLs and cholesterol to existing HDL or apoA-I. ApoA-I is a major determinant of plasma levels of HDL-C. Naturally-occurring mutations of the gene for apoA-I have been shown to be associated with extremely low HDL-C, either through impairment of apoA-I synthesis or increased clearance from the circulation on the basis of protein structure-related instability. Among the reported



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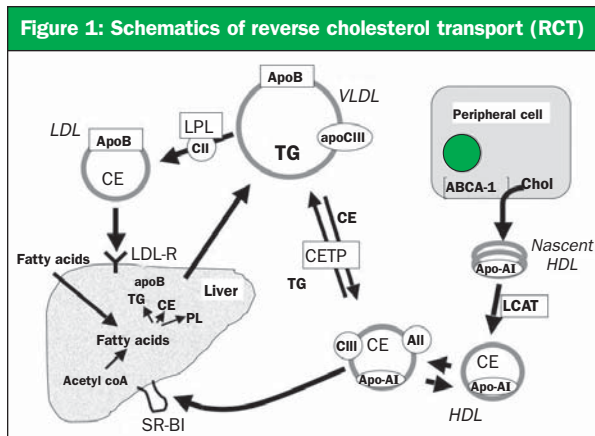
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cases of low HDL because of apoA-I mutations, those related to the impaired apoA-I synthesis defect appear to be more consistently associated with accelerated atherosclerosis. Intriguingly, several cases of severe HDL-C deficiency caused by mutations in apoA-I were not linked to premature CHD.⁸ Induction of apoA-I synthesis has been shown to raise plasma apoA-I and HDL-C levels, both in experimental animal models (eg, apoA-I transgenic mice⁹) and in humans with pharmacological agents (eg, fibrates through activation of PPAR γ in the liver). Transgenic mice overexpressing apoA-I have been shown to attenuate diet-induced atherosclerosis.⁹

ABCA1: the key mediator of cholesterol efflux: Cholesterol efflux describes the transfer and incorporation of cell-derived cholesterol into nascent HDL. Recently, this process was shown to be mediated mainly by the transporter, ABCA1. This transporter was discovered during the study of patients with Tangier disease, who share common features of extremely low HDL-C, enlarged yellow tonsils, splenomegaly, foam cell infiltration in the marrow, and increased risk of premature CHD.¹⁰ Subjects heterozygous for the ABCA1 mutation harbour “half-normal” levels of HDL-C and have been shown to manifest impairment in endothelial function (as measured by flow-mediated dilatation [FMD]). This transporter is abundantly expressed in macrophages, the liver, and the brain, amongst other tissues.

The role of ABCA1 in mediating cholesterol efflux from atherosclerotic plaque macrophages and the subsequent protection from atherosclerosis has been elegantly demonstrated in studies on macrophage-specific ABCA1 knockout mice.¹¹ Selective depletion of macrophage ABCA1 is sufficient to promote accelerated atherosclerosis without any change in serum HDL-C. Similarly, macrophage-specific upregulation of ABCA1 is effective in attenuating atherosclerosis without significantly altering plasma HDL-C levels.¹² It recently became apparent that ABCA1-mediated cholesterol efflux of hepatic origin is the major modulator of plasma HDL-C levels, whereas macrophage ABCA1-mediated efflux, although antiatherogenic, is not.

Esterification of cholesterol by LCAT: Cell-derived cholesterol in HDL may combine with a fatty acid moiety released from hydrolysis of phospholipids to form a cholesterol ester (CE), as mediated by the enzyme, LCAT.⁸ The hydrophobic CE enters the interior of the HDL particle which, in turn, promotes more efflux of unesterified

cholesterol from cells. The more mature CE-enriched HDL particles may interact directly with the HDL receptor SR-BI (scavenger receptor class B type I) and the cholesterol content will be taken up by the liver, thus completing the transport of cell-derived cholesterol back to the liver. Alternatively, CE in HDL may be transferred to triglyceride (TG)-rich VLDL and IDL in exchange for TG as mediated by the enzyme cholesterol ester transfer protein (CETP). The CE then becomes part of LDL and returns to the liver by binding to LDL receptors.

LCAT is also a major modulator of plasma HDL-C. Complete LCAT deficiency has been reported and these patients all share the extremely low HDL-C phenotype. In addition, mild anemia, hypertriglyceridemia, and chronic glomeropathy are also common. Surprisingly, complete LCAT-deficient subjects are not particularly prone to accelerated atherosclerosis, despite their extremely low HDL-C.^{8,14} Animal models of complete LCAT deficiency reveal atypical changes in oxidative stress and unexpected improvements that may, at least in part, account for the apparent paradox.^{15,16} However, two recent studies on long-term follow-up of patients heterozygous for LCAT gene mutations with “half-normal” HDL-C suggest that partial LCAT deficiency may be proatherogenic on the basis of conventional risk markers and in vivo endothelial function study with FMD.^{17,18} Some subjects in these studies, however, developed features of central obesity that might confound the interpretation.¹⁷

The impact of LCAT deficiency on reverse cholesterol transport (RCT) in an in vivo setting has not yet been addressed. Partial LCAT deficiency is commonly observed in many proatherogenic conditions, including diabetes, cigarette smoking, and obstructive liver diseases, but its role in atherogenesis remains poorly understood. Data to date raise the possibility that LCAT and CHD risk may follow an inverted-J curve relationship.

Cholesterol transfer: CETP mediates the exchange of neutral lipids (ie, triglycerides and CE) between different lipoprotein fractions. Under most circumstances, the net effect is that CE is transferred from HDL to triglyceride-rich VLDL and IDL in exchange for TG. Excess CETP-mediated transfer causes TG enrichment of HDL leading to increased clearance, a mechanism that best explains HDL lowering in hypertriglyceridemia.

Low CETP activity also significantly impacts lipoprotein metabolism. As one would expect, subjects with genetically-determined CETP deficiency, due to mutations in the CETP gene, develop markedly increased levels of HDL-C. Although initial reports on a number of Japanese CETP-deficient kindreds suggested that the associated elevation in HDL-C might contribute to longevity, subsequent studies in other cohorts yielded inconsistent results.¹⁹ In the Honolulu Heart Program – a large cross-sectional study – subjects with 2 of the common mutations causing CETP deficiency were at reduced risk only if they developed very high levels of HDL-C.

Several animal models have been utilized to investigate the role of CETP in atherogenesis. Mice and rats are naturally deficient in CETP. Transgenic overexpression of CETP in diet-induced atherosclerosis^{20,21} or in spontaneous atherosclerosis models²¹ all resulted in enhanced atherosclerosis. This proatherogenic effect is attributable to a redistribution

of CE from HDL to VLDL and LDL. However, in genetically-defined metabolic backgrounds, concomitant over-expression of CETP in these models significantly attenuated atherosclerotic lesion sizes.²² Collectively, animal model data to date suggest that CETP inhibition may be either pro- or antiatherogenic, depending highly on the metabolic background. In humans, a number of proatherogenic conditions, including type 2 diabetes mellitus and mixed hyperlipidemia, are associated with elevated CETP levels.²³ In a recent, 6-year, prospective, epidemiological study in apparently healthy men and women, plasma CETP levels were found to correlate with clinical CHD events, but only at the extreme quintile of CETP and in patients with significant hypertriglyceridemia.²⁴

Etiology of low HDL-C

Low HDL-C in insulin-resistant states and diabetes: Low HDL-C is highly prevalent in the general population. Based on a sample of 8,608 participants aged >20 years in the National Health and Nutrition Examination Survey (NHANES) III, low HDL-C (according to the National Cholesterol Education Program [NCEP] definition of metabolic syndrome, which is HDL <1.03 mM in men and <1.3 mM in women) was a component of the metabolic syndrome in 35.1% of adult men and 39.1% of adult women.²⁵ In the same cohort, the prevalence of the metabolic syndrome by NCEP criteria was 24.2% in men and 23.5% in women. Insulin resistance and metabolic syndrome may, therefore, represent the major causes of low HDL.^{26,27} In vivo lipoprotein-turnover studies suggest that low HDL-C in insulin resistance and the metabolic syndrome is attributable to increased clearance of HDL, whereas hypertriglyceridemia is largely a result of hepatic overproduction of VLDL, in conjunction with a partial impairment in lipoprotein lipase (LPL) activities. Elevated CETP activities are commonly seen in insulin-resistant states and have been hypothesized to account for the hypertriglyceridemic (HTG)-associated increase in HDL catabolism, resulting in low HDL.²⁸

Monogenic forms of low HDL-C: Molecular defects causing rare genetic forms of HDL deficiency have been identified in the genes encoding apoA-I, ABCA1, and LCAT. Homozygotes for mutations in these genes have virtually absent plasma HDL-C, whereas heterozygotes have approximately half the normal plasma levels of HDL-C. Intriguingly, the complete absence of HDL-C in homozygotes for these mutations is not universally associated with premature CHD. Both the prevalence and the CHD risk for subjects heterozygous for mutations in these 3 genes are not well-established.⁸

In a recent study of 2 population-based cohorts – the Dallas Heart Study and a cohort from Canada – up to 16% of subjects with HDL-C below the 5th percentile were shown to have sequence variations in the ABCA1, LCAT, and apoA-I genes. About 72% of these variations have been predicted to be functionally important, suggesting that rare alleles with major phenotypic effects contribute significantly to low plasma HDL-C in the general population.²⁹ Cardiovascular (CV) risks for subjects with low HDL-C in association with various heterozygous mutations of these individual genes have not been fully elucidated. Studies with small numbers of subjects heterozygous for ABCA1 and LCAT suggest that low HDL-C from the partial loss of

these 2 components of RCT may be pro-atherogenic.^{17,18} There remains a significant proportion of subjects with low HDL-C due to no known underlying cause and their CV risk is unknown.

Therapeutic strategies in treating low HDL

Effect of exercise: Aerobic exercise may lead to a 3% -9% increase in HDL-C and the greatest increases are found in those involving frequent, low-intensity exercises.³⁰ On the other hand, the effect of walking has yielded conflicting results; a recent meta-analysis pooling 33 studies revealed no significant change in HDL-C levels.³¹ In a substudy of the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) family study, 200 sedentary men were evaluated to examine the effect of a 20-week endurance exercise program on lipoprotein profiles. These authors reported that HDL-C in men with combined elevated TG/low HDL-C and central obesity increased significantly in response to exercise, whereas those with “isolated low HDL” did not achieve improvement in HDL-C.³²

Effect of weight loss: According to NHANES II, obesity is associated with reduced HDL-C and elevated TG levels in both men and women.^{33,34} Weight reduction, through dieting, has also been shown to raise HDL-C and lower LDL-C and TG levels in a meta-analysis.³⁵ For every kilogram decrease in body weight, a 0.009-mmol/L increase in HDL-C occurred for subjects at a stabilized, reduced weight and, for subjects actively losing weight, there was a 0.007 mmol/L decrease.

Orlistat, an inhibitor of pancreatic, gastric, and carboxylester lipase, with the net effects of inhibiting fat absorption and emission of unabsorbed TG and cholesterol, has been approved as a weight-control agent. Meta-analysis of 28 randomized trials demonstrated that orlistat at 120 mg 3-times daily is effective for improving both weight loss and reducing serum TG and LDL-C, but the effects on HDL-C are neutral.³⁶

The Rimonabant in Obesity (RIO)-Lipids study is a 12-month randomized, double-blind, placebo-controlled, trial comparing rimonabant, a selective cannabinoid-1 receptor, versus placebo in either overweight or obese individuals. Rimonabant, at a daily dose of 5 mg and 20 mg, resulted in an additional 4.2 kg and 8.6 kg weight reduction after initial weight loss during run-in. In association with the weight loss, the authors also reported a 15.6% ± 15.3 % and a 23.4% ± 21.8% increase in HDL-C from baseline for the 5 mg and 12 mg groups, respectively.³⁷

Lipid-lowering drugs

Of the lipid-lowering agents currently available, niacin, fibrates, and statins have been shown to confer significant HDL-C raising effects in large-scale outcome clinical trials, as well as in smaller efficacy studies.

Niacin: Niacin is by far the most efficacious agent for raising HDL-C. Although the mechanism by which niacin raises HDL-C is not fully understood, recent studies suggest that it selectively reduces the clearance rate of the apoA-I-only subfraction of HDL, a fraction putatively considered to be more efficient in mediating RCT.³⁸ In the HDL-Atherosclerosis Treatment Study (HATS) Trial, 160 high-risk men and women with the combination of elevated LDL-C and low HDL-C, were randomized to

simvastatin alone versus simvastatin plus niacin; each group was further subdivided into an antioxidant-treated arm and a placebo arm. The addition of niacin to simvastatin resulted in a markedly significant reduction in angiographic evidence of coronary plaque progression and clinical events, attesting to the utility of niacin in reversing the excess risk associated with low HDL-C.³⁹ However, the tolerability of this drug and its modest effect in LDL-C lowering, limit its role primarily to an attractive adjunct therapy.⁴⁰ A much larger, randomized, secondary prevention trial (AIM-HIGH), comparing simvastatin alone versus simvastatin plus extended-release niacin (a more tolerable formulation of niacin), on high-risk subjects with low HDL-C is currently underway. In this study, ezetimibe may also be added to secure on-trial LDL-C levels to below 2.5 mM in both arms. This 5-year study will likely provide better definitive evidence on whether adding extended-release niacin to low HDL-C patients in the context of secondary prevention will augment the clinical benefit beyond the LDL-lowering strategy; the results are expected in 2010.

Statins: Post hoc and subgroup analyses have been performed for the recent, large, prospective, controlled, statin trials to determine whether raising HDL-C levels with statins translates into a reduced risk of CHD. Generally, in these trials, statins result in a modest, but highly variable increase in HDL-C levels, up to a 15% increase.⁴¹ Each individual statin has a unique dose-response relationship with HDL-C levels, suggesting the possibility of differences in the metabolic effects of different statins. On the other hand, based on results from the 5 landmark prospective statin trials, pretreatment HDL-C level remains a powerful predictor of CHD risk in the placebo-treated groups. Another common feature in these trials is that if subjects are divided into “high” and “low” HDL-C groups, statin treatment results in a greater risk reduction in the low HDL-C subgroup than in the higher HDL-C group. CHD risk in the statin-treated low HDL-C subjects is comparable to the risk in the placebo-treated high HDL-C.⁴² These studies, collectively, suggest that while statins are able to raise HDL-C and statin treatment improves CHD risk, the relative contribution of HDL-C to the overall clinical benefit remains to be firmly established.

Fibrates: Fibrates are known to be highly effective in lowering plasma TG and raising HDL-C, while their LDL-C-lowering effects are modest. Through acting as a ligand for peroxisome proliferator-activated receptor α (PPAR α), fibrates raise HDL-C by coordinately up-regulating a number of lipid modifying genes (eg, LPL, apoA-I, apoA-II) and down-regulating apoC-III. The combined effects of fibrates on LPL and apoC-III synergistically lowers plasma TG by facilitating the hydrolysis of VLDL-TG. Meanwhile, up-regulation of apoA-I results in elevation of plasma apoA-I and HDL-C levels. In the Veteran Administration HDL intervention (VA-HIT) trial, 1200 mg of gemfibrozil given daily for an average of 5 years to patients with a previous history of CHD and “isolated”

low HDL was found to result in a significant reduction in CHD risk compared to placebo.⁴³ Originally, the trial was designed to address the question of whether high-risk patients with an “isolated low HDL” phenotype would benefit from taking a drug known to raise HDL. Post hoc analysis revealed that, in this trial, although on-treatment HDL-C predicts future coronary events, a mere 6% increase in post-treatment HDL-C cannot account for the variability in the outcome risk.⁴⁴

In addition to their effects on lipoprotein metabolism, fibrates have been shown to have direct anti-atherogenic effects on arterial walls. This analysis is consistent with the notion that gemfibrozil may confer additional risk reduction beyond raising HDL. The results of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial were recently released. Ten thousand type 2 diabetic subjects with and without a prior history of CHD, but not on statins, were randomized to fenofibrate versus placebo. The overall outcome was a nonsignificant 11% reduction in the primary endpoint of CHD events, but a significant 11% reduction in total CVD events, the latter being one of the secondary endpoints. The interpretation of the results is confounded by the unequal initiation of statins in the two arms during the trial. This trial was not designed to address the clinical benefit of fibrates on low-HDL patients (baseline HDL-C was 1.10 ± 0.26 mM in both the placebo- and active-treatment groups).⁴⁵ It is of interest to note that subgroup analyses revealed a modest, but statistically significant outcome benefit in the low HDL-C subgroup. However, this benefit was not shared with the metabolic syndrome subgroup⁴⁵ and the benefit was significantly less than that seen in the VA-HIT trial.

Emerging strategies

Targeting the reverse cholesterol transport pathway

Infusion of reconstituted HDL: In line with the experimental evidence of direct vascular effects with HDL, a number of laboratories have investigated the therapeutic potential of infusions of HDL, either endogenous or reconstituted. Infusions of homologous plasma HDL in cholesterol-fed rabbits not only reduced the progression of aortic atherosclerotic lesions, they also caused regression of preexisting lesions.⁴⁶ Infusion of recombinant HDL made of apoA-I and phosphatidylcholine into healthy volunteers, led to changes suggestive of increased RCT, namely, increased plasma pre- β -HDL production, LCAT activities, and CETP-mediated transfer of lipoproteins.⁴⁷ Infusion of recombinant pro-apoA-I/phospholipid complexes to hypercholesterolemic subjects led to increased bile acid and neutral sterol excretion, findings also consistent with increased RCT.⁴⁸

More recently, the therapeutic potential of recombinant HDL made from an apoA-I variant, apoA-I Milano has been of great interest. ApoA-I Milano is the naturally-occurring mutation of the apoA-I gene, initially identified in an Italian kindred in the town of Limone sul Garda by a group of investigators from

Milano. It was observed that, despite very low plasma HDL-C levels caused by the mutation, the carriers were not at risk of accelerated premature CHD compared to subjects with comparable HDL-C. A direct single-dose infusion of recombinant apoA-I Milano into a rabbit carotid artery resulted in rapid reductions in plaque lipid content, consistent with the notion of rapid lipid removal from the plaques.⁴⁹ In humans, short-term intermittent infusions of recombinant apoA-I Milano/phospholipid complex in patients who presented with acute coronary syndrome resulted in a significant 4.2% reduction in coronary plaque volume by intravenous ultrasound evaluation.⁵⁰ Although the endpoint of plaque volume size change may still be considered as a surrogate marker for coronary events, this study provides the best human data to date on the efficacy of a recombinant HDL strategy in the reversal of atherosclerotic burden. The mechanism by which recombinant HDL infusion reverses atherosclerotic plaque remains to be fully elucidated. While results from a number of studies are consistent with the notion of increased RCT, other direct vascular effects of HDL should also be considered.

Inhibition of CETP as a novel therapy: In spite of the complex relationship between CETP and HDL metabolism, pharmacological inhibition of CETP as means of raising HDL-C constitutes a promising approach to target low HDL. Recently, a phase II study using a chemical CETP inhibitor, JTT-705, was reported. At the highest dose tested, the compound was well-tolerated and achieved a 37% reduction in CETP activity and a 34% increase in HDL-C as compared to placebo control.⁵¹ A phase I, multidose study on torcetrapib, a novel CETP inhibitor, revealed impressive HDL-raising effects. At a maximum dose of 120 mg twice daily, up to a 90% increase in HDL-C was achieved.⁵² In a more recent single-blind, placebo-controlled study, torcetrapib was tested in a small group of subjects with low HDL-C, with and without co-administration of atorvastatin. Treatment with 120 mg of torcetrapib daily significantly increased HDL-C levels by 61% and 46% in atorvastatin and non-atorvastatin cohorts, respectively. Treatment with 120 mg twice daily increased HDL-C by 106%.⁵² Several trials examining various clinical outcomes, including CVD endpoints, and comparing a torcetrapib/atorvastatin combination versus atorvastatin over 5-years, are currently underway.

Summary

Based on epidemiologic data, it is well-established that HDL-C is inversely associated with elevated CHD risk. This relationship applies to both patients with and without pre-existing CHD. However, at the individual level, for any given level of HDL-C, circulating HDLs vary greatly in their composition, size, distribution, effectiveness in promoting RCT, direct vascular protective effects and, as a result, their composite CHD risk. In many instances (eg, in the insulin resistance syndrome), low HDL-C may be both a risk

marker and, at the same time, reflect a loss of the cardioprotective lipoprotein fractions. A number of existing therapeutics are effective in reversing the low HDL state, either by improving CVD outcome or increasing HDL-C levels. Likewise, a number of novel and exciting therapeutic measures are under intense investigation. Appropriate therapies should eventually be guided by clinical outcome trials.

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