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HDL metabolism, composition, function and deficiency

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Abstract

Purpose of review—Our purpose was to examine recent advances in our knowledge of high density lipoprotein (HDL) metabolism, composition, function, and coronary heart disease (CHD), as well as marked HDL deficiency states due to mutations at the apolipoprotein (apo) A-I, ATP binding cassette transfer protein A1 (ABCA1), and lecithin cholesterol acyltransferase (LCAT) gene loci.

Recent findings—It has been documented that apoA-I, myeloperoxidase (MPO), and paraoxonase 1 (PON1) form a complex in HDL that is critical for HDL binding and function. MPO has a negative impact on HDL function, while PON1 has a beneficial effect. Patients that lack apoA-I develop markedly premature CHD. Patients that lack ABCA1 transporter function have only very small discoidal preβ-1 HDL, and develop hepatosplenomegaly, intermittent neuropathy and premature CHD, although significant heterogeneity for these disorders has been reported. Patients with LCAT deficiency have abnormal small discoidal low density lipoproteins and HDL particles, and develop kidney failure. Enzyme replacement therapy is being developed for the latter disorder.

Summary—Recent data indicates that proteins other than apoA-I and apoA-II such as MPO and PON1 have important effects on HDL function. There has been considerable recent progress made in our understanding of HDL protein content and function.

Keywords

ABCA1; apoA-I; HDL; LCAT; MPO

INTRODUCTION

There is considerable controversy with regard to the role of HDL and CHD risk. Some authorities suggest that HDL plays little or no role in protection from CHD. However in my view such scientists are missing the concept that plasma lipoproteins are not individual

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Conflicts of interest

Drs. Asztalos and Schaefer are employees of Tufts University, Boston, MA and Boston Heart Diagnostics, Framingham, MA. Dr. Anthanont receives fellowship support from Thammasat University, Bangkok, Thailand. Dr. Schaefer serves as a consultant for Amarin, Amgen, Arisaph, AstraZeneca, Mediimmune, and Merck, and serves on the speaker's bureau for Merck, Sharpe, and Dohme, Rahway, NJ.

compartments, but interact significantly with one another, and must be considered as part of an entire system. While low density lipoproteins clearly play a major role in the pathogenesis of atherosclerosis, chylomicron remnants, very low density lipoproteins, lipoprotein(a), and HDL all can clearly modulate CHD risk. This review focuses on recent developments in the field of HDL metabolism, composition, and function, and marked HDL deficiency states.

HDL METABOLISM

A method has been developed using mass spectrometry for the simultaneous measurement of HDL-C and apoA-I kinetics in mice following a single deuterated H_2O tracer (given in drinking water) [1*]. ApoE(-/-) mice displayed increased fractional catabolic rates ($P<0.01$) and reduced production rates of both HDL-C and apoA-I ($P<0.05$) compared with controls. Human apoA-I transgenic mice had levels and production rates of HDL-C and human apoA-I that were strikingly higher than in wild-type mice. In these latter studies HDL-C had a fractional catabolic rate of about 2.5 hours, while for HDL apoA-I it was about 11 hours, consistent with the concept that cholesterol and apoA-I within HDL are not catabolized as a unit. Myriocin, an inhibitor of sphingolipid synthesis, significantly increased both HDL flux and macrophage-to-feces reverse cholesterol transport, indicating that this HDL turnover method can be used to study macrophage-specific reverse cholesterol transport [1*].

While the liver may serve as the major site of HDL cholesterol clearance, the kidney appears to be a major site of HDL apoA-I catabolism. Cubilin is a receptor expressed in renal proximal tubules, where it mediates uptake of filtered forms of apoA-I/HDL and albumin. In mice heterozygous for a cubilin gene deletion it was documented that cubilin deficiency leads to reduced renal proximal tubular uptake of apoA-I and albumin, and significantly increased urinary excretion of apoA-I and albumin. Moreover, cubilin human transgenic mice displayed significantly increased blood levels of apoA-I and HDL cholesterol, associated with decreased plasma clearance of small HDL_3 particles (density > 1.13 g/ml), but not large HDL_2 particles, indicating that cubilin in the kidney regulates the catabolism of very small HDL particles [2*].

HDL COMPOSITION, FUNCTION, AND CHD RISK

HDL particles are not only important for reverse cholesterol transport, but also have anti-inflammatory and anti-oxidative properties. Proteomic studies have revealed more than 100 proteins on HDL particles in addition to apoA-I and apoA-II [3]. Certain populations of HDL particles have distinct functions suggesting that HDL may serve as a platform for assembly of protein complexes with very specific biological roles [3]. We have previously reviewed the effects of cholesteryl ester transfer protein (CETP) inhibitors on lipoprotein metabolism and CVD risk [4]. In our view the reason these drugs have failed to reduce CHD risk is because they form complexes with HDL and CETP, which probably interfere with the multiple biologic functions of HDL [4].

Investigators have examined characteristics of HDL particles and HDL function using samples obtained from controls and either cases with either kidney disease or heart disease. Using HDL from children and adults with chronic kidney disease (HDL-CKD) who are at

high CHD risk, it has been shown that HDL-CKD in contrast to control HDL promotes endothelial superoxide production, reducing nitric oxide (NO) bioavailability, and increasing blood pressure [5].. Symmetric dimethylarginine in HDL-CKD was found to be the cause of the endothelial dysfunction, due to reduced nitric oxide availability and increased cellular inflammation. Therefore dimethylarginine appears to modify HDL particles and cause endothelial dysfunction and hypertension [5]. HDL from patients with stable CHD (HDL-sCHD), acute CHD (HDL-aCHD), and healthy subjects were isolated [6]. Normal HDL induced expression of the endothelial antiapoptotic Bcl-2 protein and reduced endothelial cell apoptosis in vitro and in apoE-deficient mice in vivo, while HDL-sCHD and HDL-aCHD did not have these effects. HDL proteomics analyses indicated further that these differences were due to reduced clusterin and increased apoC-III content in HDL-sCHD and HDL-aCHD. Endothelial antiapoptotic effects of normal HDL were observed after inhibition of endothelial NO synthase and after delipidation, but were not observed with apoA-I or reconstituted HDL, suggesting an important role of the HDL proteome [6].

Both PON1 and myeloperoxidase (MPO) are found on HDL and are linked to inflammation, oxidant stress, and atherosclerosis. Decreased serum arylesterase activity, catalyzed by HDL-associated PON1, has been associated with increased oxidant stress and CHD risk. Serum arylesterase and PON1 activities were measured in 630 subjects with CKD and matched controls, with both groups being followed for CHD events for 3 years [7]. Serum arylesterase and PON1 activities were lower in CKD subjects than in controls. Lower serum arylesterase was a predictor of increased CVD risk, even after adjustment for risk factors and medication use (hazard ratio 1.55, $P<0.05$). The data indicate that decreased serum arylesterase activity (a measure of low antioxidant properties of PON1) in patients with CKD predicts higher risk of future CHD events [7].

MPO is a source of reactive oxygen species during inflammation and can oxidize apoA-I on HDL, impairing its atheroprotective functions, while PON1 fosters antioxidant effects and promotes some of the atheroprotective properties attributed to HDL. It has recently been shown that MPO, PON1, and HDL bind to one another, forming a complex, wherein PON1 partially inhibits MPO activity, while MPO inactivates PON1. MPO oxidizes PON1 on tyrosine 71 (Tyr71), a modified residue found in human atheroma that is critical for HDL binding and PON1 function [8**]. Acute inflammation model studies with transgenic and knockout mice for either PON1 or MPO confirmed that MPO and PON1 reciprocally modulate each other's function in vivo. Important contact sites between ApoA-I, PON1, and MPO within HDL were identified. Proteomics studies of HDL recovered from acute coronary syndrome subjects revealed enhanced chlorotyrosine content, site-specific PON1 methionine oxidation, and reduced PON1 activity. HDL thus serves as a scaffold upon which MPO and PON1 interact during inflammation, with PON1 binding partially inhibiting MPO activity, and MPO promoting site-specific oxidative modification and impairment of PON1 and ApoA-I function [8**].

Studies have shown beneficial effects of infusions of apoA-I on atherosclerosis. ApoA-I is a target for MPO-mediated oxidation, leading in vitro to a loss of its ability to promote ABCA1-dependent macrophage cholesterol efflux. ApoA-I$^{-/-}$ or apoE$^{-/-}$ mice were subcutaneously injected with native human apoA-I, oxidized human apoA-I treated with

MPO/hydrogen peroxide/chloride, or carrier [9*]. At 8 hours post-injection levels of plasma apoA-I were similar for native versus oxidized human apoA-I, with native apoA-I being primarily in HDL, while most of the oxidized human apoA-I was highly cross-linked and not on HDL, consistent with impaired ABCA1 interaction. In apoA-I$^{-/-}$mice, apoA-I oxidation significantly impaired reverse cholesterol transport in vivo. In advanced aortic root atherosclerotic plaques of apoE$^{-/-}$ mice, native apoA-I injections led to significant decreases in lipid content, macrophage number, and an increase in collagen content, while oxidized human apoA-I failed to cause these changes. These studies indicate that MPO-mediated oxidation renders apoA-I dysfunctional and unable to promote reverse cholesterol transport, or mediate beneficial changes in atherosclerotic plaques, or decrease inflammation in plaque macrophages [9*].

Studies have shown that apoA-I recovered from human atherosclerotic lesions is highly oxidized. Ex vivo oxidation of apoA-I or HDL cross-links apoA-I and impairs lipid binding, cholesterol efflux, and LCAT activities of HDL. A monoclonal antibody was developed that equally recognizes lipid-free and HDL-associated apoA-I in both native and oxidized forms. Examination of homogenates of atherosclerotic plaque-laden aorta showed >100-fold enrichment of apoA-I compared with normal aorta ($P<0.001$) [10*]. Only a minority (< 3% of total) of apoA-I recovered from either lesions or normal aorta was found within HDL particles (density 1.063 - 1.21 g/mL). More than 90% of the apoA-I within aortic tissue (normal and lesions) was found in the lipoprotein free fraction (density >1.21 g/mL). ApoA-I in both lesion and normal artery tissue was highly cross-linked (50% to 70% of total), and isolation of this apoA-I showed about 80% lower cholesterol efflux activity and about 90% lower LCAT activity relative to circulating apoA-I. These data indicate that the function and distribution of apoA-I in human aorta are quite distinct from those found in plasma [10*].

Using a monoclonal antibody that recognizes MPO modified apoA-I and HDL, specifically at an oxindolyl alanine (2-OH-Trp) moiety at Trp72 of apoA-I, investigators have confirmed a critical role for apoA-I Trp72 in MPO-mediated inhibition of the ABCA1 transporter-dependent cholesterol acceptor activity of apoA-I in vitro and in vivo [11**]. ApoA-I containing a 2-OH-Trp72 group (oxTrp72-apoA1) is in low abundance in plasma, but accounts for 20% of the apoA-I in atherosclerosis-laden arteries. OxTrp72-apoA-I recovered from human atheroma or plasma is lipid poor, with no cholesterol acceptor activity, potent proinflammatory activity on endothelial cells, and impaired HDL biogenesis activity in vivo. Elevated oxTrp72-apoA-I levels in subjects presenting to a cardiology clinic (n = 627) were associated with increased CVD risk. Therefore circulating oxTrp72-apoA-I levels may serve as a way to monitor atherosclerosis in the artery wall [11**].

The relationship between MPO and disease progression in diabetic patients was examined in 881 patients with angiographic coronary artery disease who underwent serial coronary intravascular ultrasound studies [12*]. Of these subjects 199 were diabetic, and 682 were not. MPO levels were similar in patients with or without diabetes. No relationship was observed between increasing quartiles of MPO and either baseline or serial changes in levels of percent atheroma volume (PAV) in non-diabetic patients. In contrast, increasing MPO quartiles were associated with accelerated PAV progression in diabetic patients ($p = 0.03$). While optimal control of lipids and the use of high-dose statin treatment was associated with

less disease progression, a greater benefit was observed in diabetic patients that had lower MPO levels at baseline. Therefore increased MPO levels are associated with greater progression of atherosclerosis in diabetic patients. This finding indicates the potential importance of MPO pathways in diabetic cardiovascular disease [12*].

Decreased cholesterol efflux activity of apoB-depleted serum has been associated with prevalent coronary artery disease in case control studies [13]. Cholesterol efflux activity from free cholesterol-enriched macrophages was measured in 2 case-control cohorts: an angiographic cohort (n=1150) comprising stable subjects undergoing elective diagnostic coronary angiography and an outpatient cohort (n=577) [14**]. Analysis of media from cholesterol efflux assays revealed that the HDL fraction (density 1.063 -1.21 g/mL) contained only about 40% of the labeled cholesterol released, with the majority found within the lipoprotein particle-depleted fraction (density > 1.21 g/mL). From this latter fraction about 60% was recovered after apoA-I immunoprecipitation, and about 30% after albumin immunoprecipitation. Enhanced cholesterol efflux activity from ABCA1 stimulated macrophages was associated with reduced risk of prevalent coronary artery disease in unadjusted models within both cohorts; however, the inverse risk relationship remained significant after adjustment for traditional coronary artery disease risk factors only within the outpatient cohort. Surprisingly, higher cholesterol efflux activity was associated with an increase in prospective (3 year) risk of myocardial infarction/stroke (adjusted hazard ratio, 2.19, $p<0.05$), and major adverse cardiovascular events (adjusted hazard ratio, 1.85; $p<0.05$). The data indicate increased ABCA1 mediated cellular cholesterol efflux to apoB-depleted serum being associated with increased prospective risk for myocardial infarction, stroke, and death, with a majority of the released radiolabeled cholesterol from macrophages in cholesterol efflux activity assays residing in the lipoprotein free fraction [14**].

Our group has recently reported that niacin therapy upregulates ABCA1 liver gene expression in vivo in hamsters, consistent with prior cell studies [15,16]. Recent studies using apoB-depleted serum have reported that niacin treatment in humans had no significant effect on cellular cholesterol efflux, despite significant HDL-C increases [17].

MARKED HDL DEFICIENCY STATES

Disorders associated with marked HDL deficiency include apoA-I deficiency, Tangier disease, and LCAT deficiency [18].

ApoA-I deficiency—Patients with apoA-I deficiency have undetectable plasma apoA-I levels due to lack of apoA-I production [18]. A patient with significant coronary heart disease since age 42 years and marked HDL deficiency (HDL cholesterol 1 mg/dL and apoA-I 23 mg/dL) was reported with significant triglyceride elevation at 417 mg/dL, despite maximal therapy with statin, ezetimibe, fenofibrate, and niacin [19]. APOA-I gene sequencing revealed a novel heterozygous in-frame insertion mutation with duplication of nucleotides 1535 through 1552 inserted at position 1553, causing a new amino acid glycine at codon 157 and a duplication of amino acids alanine, arginine, alanine, histidine, and leucine at codons 158-162. This novel apoA-I mutation results in the formation of apoA-I

(apoA-I_{Nashua}) that appears to have abnormal lipid binding properties, resulting in impaired reverse cholesterol transport and premature CHD [19].

Tangier Disease—Tangier disease (TD) is caused by mutations in the ABCA1 transporter, resulting in lack of cellular cholesterol efflux, excess cellular cholesterol, and only very small preβ-1 HDL in plasma, which is rapidly catabolized via the kidney [18]. A female patient was described with a unique phenotype of TD from a novel homozygous splice site mutation in the ABCA1 gene that was associated with marked HDL deficiency, a central nervous system presentation resembling multiple sclerosis, and the presence of premature atherosclerosis [20]. In another study ABCA1 gene mutations were characterized in 10 patients with extremely low HDL-cholesterol [21]. Five patients (aged 6 months to 76 years) presented with splenomegaly and thrombocytopenia, three of whom were homozygous for novel mutations either in intron (c.4465-34A>G) or in exons (c.4376delT and c.5449C>T), predicted to encode truncated proteins. One patient was compound heterozygous for a nucleotide insertion (c.1758_1759insG), resulting in a truncated protein and for a nucleotide substitution c.4799A>G, resulting in a missense mutation (p.H1600R). The last TD patient, found to be heterozygous for a known mutation (p.D1009Y), had a complete defect in ABCA1-mediated cholesterol efflux in fibroblasts, suggesting the presence of a second undetected mutant allele. Among the other patients, four were asymptomatic, but one, with multiple risk factors, had severe peripheral artery disease. Three of these patients were heterozygous for known mutations (p.R130K+p.N1800H, p.R1068C, p.N1800H), while two were carriers of novel mutations (c.1195-27G>A and c.396_397insA), predicted to encode truncated proteins. Moreover the pathogenic effect of the two intronic mutations (c. 1195-27G>A and c.4465-34A>G) was demonstrated by the analysis of the transcripts of splicing reporter mutant minigenes expressed in COS-1 cells. Both mutations activated an intronic acceptor splice site which resulted in a partial intron retention in mature mRNA with the production of truncated proteins. This study confirms the heterogeneity of TD, and indicates that the diagnosis of TD must be considered in patients with an unexplained splenomegaly, associated with thrombocytopenia and marked HDL deficiency [21].

ABCA1 is involved in the production of amyloid-β protein. However when plasma from 5 TD patients and 5 controls were analyzed, no differences in amyloid-β levels were noted. Therefore loss of ABCA1 function may not have any profound effect on amyloid-β metabolism in humans [22]. In another study a 45-year-old female was reported with a history of early CHD, marked HDL deficiency, and a history of idiopathic thrombocytopenia purpura and prior tonsillectomy. She had no evidence of hepatosplenomegaly, corneal opacities, or neuropathy. She was found to have three mutations in the ABCA1 gene, A1046D (c.3137C>A) in exon 22; Y1532C (c.4595A>G) in exon 34, and W1699C (c. 5097G>T) in exon 37. All three have been reported to affect cholesterol efflux [23].

Investigators compared the effects of an ABCA1 mutation that produced an apparent lack of atherosclerosis (TD family 1, N935S) with an ABCA1 mutation with a functional ABCA1 knockout that was associated with severe atherosclerosis (TD family 2, Leu(548):Leu(575)-End), using primary and telomerase-immortalized fibroblasts [24]. Telomerase-immortalized TD fibroblasts of family 1 (TT1) showed 30% residual cholesterol efflux capacity in response to apoA-I, whereas telomerase-immortalized TD fibroblasts of family 2 (TT2)

showed only 20%. The total cellular cholesterol content increase was 2-3-fold and 3-5-fold increased in TT1 and TT2 cells, respectively, relative to control cells. The corresponding increase in esterified cholesterol concentration was 10- and 40-fold, respectively. Moreoever the 24-, 25-, and 27-hydroxycholesterol concentrations were only moderately increased in TT1 cells, but were 200 fold increased in TT2 cells. In addition cholesterol biosynthesis was moderately decreased in TT1 cells, but was markedly decreased in TT2 cells. Finally atheroprotective LXR-dependent SREBP1c signaling was normal in TT1, but was suppressed in TT2 cells. These and prior results may help to understand the differential susceptibility to CHD in TD [24].

LCAT deficiency—Familial LCAT deficiency (FLD) is associated with an inability to esterify free cholesterol, marked corneal opacification, and the formation of only small discoidal pre-1 and α-4 HDL, with hypercatabolism of these particles by the kidney [18]. Enzyme replacement is being developed for FLD [25]. Recombinant human LCAT was tested for its ability to correct the lipoprotein profile in LCAT deficient plasma [26]. The results showed that LCAT efficiently reduced the amount of unesterified cholesterol (-30%) and promoted the production of plasma cholesteryl esters (+210%) in LCAT deficient plasma. LCAT induced a marked increase in HDL-C levels (+89%) and induced the maturation of small preβ-HDL into α HDL particles. Moreover, the abnormal phospholipid-rich particles migrating in the LDL region were converted to normally sized LDL [26]. We have confirmed these findings in vivo in an LCAT deficient patient of ours treated with LCAT enzyme (prepared by Alpha Core, Ann Arbor, MI) at the National Institutes of Health by Drs. Robert Shamburek and Alan Remaley (EJ Schaefer, BF Asztalos, unpublished observations).

CONCLUSION

MPO can modify an oxindolyl alanine (2-OH-Trp) moiety at Trp72 of apoA-I, resulting in the loss of its ability to accept lipids. Elevated plasma oxTrp72-apoA-I levels have been associated with increased CHD risk. PON1 and clusterin on HDL protect apoA-I from being modified, whereas apoC-III, in addition to MPO, has deleterious effects on HDL function. Patients with marked HDL deficiency have a great deal of variability in clinical presentation, but often present with premature CHD except for patients with LCAT deficiency. LCAT deficiency often leads to kidney failure, and enzyme replacement therapy is being developed for this disease.

Acknowledgements

None

Abbreviations

Apo	apolipoprotein
CHD	coronary heart disease
CKD	chronic kidney disease

ABCA1	ATP binding cassette protein transporter A1
LCAT	lecithin:cholesteryl acyltransferase
HDL	high density lipoprotein
MPO	myeloperoxidase
PON1	paraoxonase 1

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■ of special interest

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KEY POINTS

- ApoA-I, myeloperoxidase (MPO), and paraoxonase 1 (PON1) form a complex in HDL that is critical for HDL binding and function.
- Patients that lack apoA-I develop markedly premature CHD.
- Patients that lack ABCA1 transporter function develop hepatosplenomegaly, intermittent neuropathy and premature CHD, although significant heterogeneity for this disorder has been reported.
- Patients with LCAT deficiency develop anemia and kidney, and enzyme replacement therapy is being developed.