Improving cardiovascular disease prevention: from risk assessment to novel therapy
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Inherited disorders of HDL metabolism and atherosclerosis

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ABSTRACT

Purpose of review – Genetic disorders of HDL metabolism are rare and, as a result, the assessment of atherosclerosis risk in individuals suffering from these disorders has been difficult. Ultrasound imaging of carotid arteries has provided a tool to assess the risk in hereditary hypo- and hyperalphalipoproteinemia. This review gives a comprehensive summary.

Recent findings – Epidemiological studies have unequivocally shown that HDL cholesterol levels are inversely related to coronary artery disease risk, but the literature concerning genetic disorders of HDL metabolism provides less convincing information. Fortuitously, we were able to directly compare carotid intima media thickness data of substantial numbers of individuals with mutations in either apolipoprotein A-I, ATP binding cassette A1 (ABCA1), lecithin:cholesterol acyltransferase (LCAT) or cholesteryl ester transfer protein (CETP). These data show that carriers of an apolipoprotein A-I mutation exhibit the most pronounced accelerated atherosclerosis compared with those carrying mutations in ABCA1 and LCAT. Heterozygosity for a non-sense mutation in CETP did, by contrast, not distinguish carriers from controls in terms of intima media thickness progression. We will discuss these results in the context of the current literature.

Summary – Intima media thickness studies have provided evidence that hypoalphalipoproteinemia due to mutations in apolipoprotein A-I, ABCA1, and LCAT is associated with increased progression of atherosclerosis. In contrast, hyperalphalipoproteinemia as a result of loss of CETP function is associated with unaltered atherosclerosis progression compared with family controls. This insight is of interest, since it can assist in the prioritizing of anti-atherogenic therapy by increasing HDL cholesterol levels.

Abbreviations – ABCA1, ATP-binding cassette transporter A1; CAD, coronary artery disease; CETP, cholesteryl ester transfer protein; FED, fish-eye disease; FHA, familial hypoalphalipoproteinemia; FLD, familial lecithin:cholesterol acyltransferase deficiency; HDL, high-density lipoprotein; IMT, intima media thickness; LCAT, lecithin:cholesterol acyltransferase; LDL, low-density lipoprotein; RCT, reverse cholesterol transport
Inherited disorders of HDL metabolism

REVIEW

Introduction
Coronary artery disease (CAD) is the major cause of morbidity and mortality in developed countries and is becoming increasingly important in less developed regions (1). Numerous clinical trials have consistently shown that lowering low-density lipoprotein (LDL) cholesterol levels reduces the risk for atherosclerosis and is thus considered the cornerstone in the prevention of sequelae. Nevertheless, in all ‘landmark’ statin trials at least half of all events in patients on active treatment could not be prevented (2, 3). This has led to a more aggressive approach to lowering LDL cholesterol (4), as well as to a quest for novel pharmacological targets. High-density lipoprotein (HDL) is widely accepted as such a target (5). Of the various atheroprotective properties that have been ascribed to this lipoprotein (6), its role in reverse cholesterol transport (RCT), the transport of cholesterol from peripheral cells to the liver, has been emphasized most strongly (7). A large number of proteins, enzymes and receptors are involved in HDL metabolism, and mutations in the genes encoding these factors are associated with marked alterations in plasma HDL cholesterol levels. Mutations in apolipoprotein A-I, ATP binding cassette A1 (ABCA1) and lecithin:cholesterol acyltransferase (LCAT) have all been shown to underlie familial hypoalphalipoproteinemia (FHA), whereas cholesteryl ester transfer protein (CETP) gene defects underlie familial hyperalphalipoproteinemia. Studying these disorders has given crucial insight into the in-vivo relevance of these proteins in HDL metabolism, as recently reviewed by Miller and colleagues (8).

A number of recent studies in rodents as well as in man suggest that interventions that specifically raise apolipoprotein A-I concentration, or increase ABCA1 or LCAT activity may be atheroprotective but direct evidence is scarce. Infusions of apolipoprotein A-I phospholipid complexes in post-acute coronary syndrome patients was shown to reduce atheroma in the coronaries (9), but this needs confirmation in larger controlled trials. In addition, CETP inhibition was recently proven to effectively raise HDL cholesterol levels in man (10, 11), however data on the anticipated reduction of CAD risk has yet to be generated.

It has been suggested, in single case descriptions and small family studies, that some monogenetic disorders of HDL cholesterol metabolism result in ‘paradoxical phenotypes’; that is, low HDL cholesterol but unaltered CAD risk (12), as well as high HDL cholesterol associated with increased risk (13). Addressing this issue more methodologically, we have studied preclinical manifestations of atherosclerosis in a unique set of families of Dutch descent with various genetic disorders of HDL metabolism. We used the instrument of carotid intima media thickening (IMT), a validated surrogate marker for atherosclerosis. Specifically, this review discusses the main findings of a direct comparison of individuals with mutations in apolipoprotein A-I, ABCA1, LCAT and CETP, in the context of the existing IMT literature in this field.

Prior to discussing the IMT data, we will briefly summarize the functions of the aforementioned proteins in HDL metabolism (for a review, see Miller and colleagues (8)).
Apolipoprotein A-I is the major protein constituent of the HDL particle. The gene is exclusively expressed in the liver and small intestine, and upon secretion into plasma, apolipoprotein A-I is lipidated through ABCA1-mediated efflux of free cholesterol and phospholipids from peripheral cells. This lipidation results in the formation of nascent disc-shaped HDL particles (14). Through the esterification of free cholesterol into cholesteryl ester by LCAT, the nascent HDL particle can mature into larger and spherical HDL. The HDL-cholesteryl ester is transferred, in part, to apolipoprotein B containing lipoproteins in exchange for triglycerides by the action of CETP. Through this activity, tissue-derived cholesterol can find its way to the liver via receptor mediated uptake of LDL particles for secretion into bile.

Intima media thickness
The ability to noninvasively measure carotid IMT to study morphological changes of the arterial wall has been described in extenso elsewhere (15). In summary, IMT measurements acquired with B-mode ultrasound imaging depict the intima–media complex of carotid arterial walls as a continuous variable. As was shown in prospective epidemiological studies, a modest increase in IMT substantially increases the risk for myocardial infarction and stroke. IMT measurements have also shown the benefit of cholesterol-lowering and antihypertensive compounds. Taken together, IMT has now been accepted by regulatory authorities, such as the Food and Drug Administration of the USA, as a validated surrogate marker for atherosclerotic vascular disease. Noninvasive IMT studies have allowed a more refined view of the progression of atherosclerosis over age both in large epidemiological studies as well as in small study groups (16).

Apolipoprotein A-I
Apolipoprotein A-I has unambiguously been shown to protect against atherosclerosis in animal studies (17, 18). In humans, large prospective epidemiological studies have also established that apolipoprotein A-I levels are strong predictors of CAD risk (19). Surprisingly, susceptibility for CAD has been shown to differ markedly between carriers of apolipoprotein A-I defects. To our knowledge, approximately 25 patients with complete apolipoprotein A-I deficiency have been reported (20-22). Although almost all cases were characterized by the absence of HDL cholesterol, premature CAD was present in only 11 of these patients. Of note, however, is that the remaining 14 cases were below the age of 50, with the exception of one case (21). These patients may therefore have been too young for clinical manifestations of atherosclerosis to occur. Despite this notion, it remains remarkable that even at these ages, manifestations of atherosclerosis are absent in the context of nearly complete HDL deficiency. However, the relatively small number of carriers and the focus on clinical events may have resulted in an underestimation of the clinical consequences of such mutations.

To date, two IMT studies have been performed in carriers of apolipoprotein A-I defects. In the Limone sul Garda Study, IMT was measured in 21 carriers of the apolipoprotein A-I Milano defect, 41 age and sex-matched controls, and 42 FHA individuals without a known defect. Carriers of
apoprotein A-I Milano (23) and controls did not differ in terms of mean IMT. By contrast, FHA individuals were characterized by significantly increased arterial wall thickness (24). The second IMT study was performed in 33 carriers of the apoprotein A-I(L178P) mutation and 40 family controls (25). Heterozygous carriers of the apoprotein A-I(L178P) mutation showed a 50% reduction in apoprotein A-I and HDL cholesterol levels when compared with controls. Atherosclerosis was visualized in these carriers by plotting the cross-sectional IMT data against age. This showed that arterial wall thickness progression was significantly increased in carriers compared with controls. Remarkably, the rate of progression in carriers of the apoprotein A-I defect was not different from patients suffering from familial hypercholesterolemia. Thus, the results of this study show that a monogenetic disorder of HDL metabolism had a similar detrimental vascular effect as a pronounced defect in LDL metabolism. In line with the IMT data, we noted a severely increased risk for CAD (odds ratio 18.9; CI 2.3–158.9) in the affected individuals. The striking difference in atherosclerosis progression between carriers of the apoprotein A-I Milano and apoprotein A-I(L178P) mutation is likely due to the profoundly different effects of the gene mutations at the protein level. Apoprotein A-I(L178P) is not detected in plasma, and heterozygosity for the mutation can thus be regarded as a null allele. Apoprotein A-I Milano, by contrast, contains an additional cysteine bridge, is secreted into the circulation and renders an increased potential to promote cellular cholesterol efflux compared with wild-type apoprotein A-I (26).

ATP binding cassette A1

In 1997, Calabresi and Franceschini (27) described that CAD risk in Tangier disease, due to loss of ABCA1 function, varied widely from one kindred to another. Based on the extremely low levels of HDL cholesterol (typically around 0.1 mmol/L), Tangier disease patients would be expected to die from premature atherosclerosis. However, elderly Tangier disease patients without CAD have been described (28). Low levels of atherogenic LDL cholesterol in Tangier disease patients have been postulated as a possible explanation for this paradox (29). This idea was, however, recently disputed by high LDL cholesterol levels in a 52-year-old Tangier disease patient without clinical events and with a normal carotid IMT (30). Possibly, part of the confusion with regards to the CAD risk in ABCA1 mutation carriers has been caused by misclassification. In early reports, Tangier disease was classified by HDL cholesterol levels and clinical phenotype. A more accurate classification of carriers became possible after the finding that mutations in the ABCA1 gene underlie Tangier disease (31–33). This has enabled a more accurate CAD risk estimation (reviewed in (34)). Also, Clee et al. (35) addressed the risk for CAD in five Tangier disease patients, 77 heterozygotes for ABCA1 mutations (a total of 13 different mutations) and 156 unaffected family controls, originating from 11 unrelated families. The odds ratio for CAD was shown to be 3.47 (95% CI 1.08–11.09) and 5.85 (95% CI 0.55–62.4) in the heterozygous and homozygous Tangier disease patients, respectively.
Four of the above-mentioned families were also enrolled in a study in which the relationships between HDL cholesterol, cellular cholesterol efflux (from cholesterol-loaded patient’s fibroblasts), and arterial wall changes were investigated in detail (36). HDL cholesterol levels and cellular cholesterol efflux were closely related \( (r=0.90; P<0.001) \). Moreover, IMT increased with decreasing cellular cholesterol efflux capacity of the patient’s fibroblasts \( (r=-0.60; P=0.018) \). These data underscore that ABCA1 dysfunction is directly linked with vascular disease risk. In contrast, no effects on carotid IMT were observed in carriers of another ABCA1 mutation (W590L) (37). The discrepancy with the results of Clee et al. (35) could be explained by the fact that the latter investigators only studied five carriers and 10 family controls. Sample size as well as the effect of the mutation on cholesterol efflux may have been too small to draw conclusions. In addition, HDL cholesterol levels were below 1.0 mmol/L in three of the five ABCA1 mutation carriers and in two of the 10 noncarriers, indicating that the W590L mutation suffers from low penetrance. In conclusion, most of the available data in humans point to a pro-atherogenic effect of compromised ABCA1 function. This is also supported by the finding of endothelial dysfunction in ABCA1 mutation carriers compared with family controls (38), which is currently considered to precede morphological changes in the arterial wall.

**Lecithin : cholesterol acyltransferase**

Mutations in the LCAT gene cause either familial LCAT deficiency (FLD) or fish-eye disease (FED). Both conditions are characterized, in the homozygous state, by 5–10% of normal HDL cholesterol (39) and corneal opacifications (40, 41). In addition, FLD patients also present with proteinuria, anemia and renal disease. The differences in clinical phenotypes are likely related to the fact that in FLD plasma LCAT activity is virtually absent, whereas in FED patients LCAT is still partly active, but mainly on apolipoprotein B-containing lipoproteins. It is of note that these phenotypes cannot be predicted by the nature of mutation, nor by its position in the gene (39). Heterozygous carriers of LCAT defects lack clinical symptoms, although their HDL cholesterol levels are typically half the normal level.

Despite its commonly accepted role in RCT, the association between LCAT and atherosclerosis has remained elusive. Thus far, over 40 mutations in the LCAT gene have been described in reports that predominantly investigated single cases or small nuclear families. As a consequence, CAD risk prediction has been biased and incomplete. Also, it has been proposed that FED and FLD patients are protected against CAD because of a preferential clearance of HDL fractions that have less anti-atherogenic potential (42). Furthermore, some hypothesize that HDL cholesterol derived from FLD would be a superior acceptor for cholesterol efflux, although this has been refuted by Ohta and colleagues (43).

Following our studies in carriers of apolipoprotein A-I and ABCA1 mutations, we recently investigated 68 carriers of LCAT defects and 74 family controls to better understand the role of LCAT in human atherogenesis. For this study, we recruited the family members of three previously described probands (44-47) with FED and those of two novel FED index patients. Compared with
controls, heterozygotes and homozygotes presented with a 40 and 90% decrease in HDL cholesterol, respectively (P<0.001 for both), as well as with a 22% and 337% increase in triglyceride levels (P=0.017 and P<0.0001, respectively). Surprisingly, heterozygotes and homozygotes also displayed a significant approximate twofold increase in median high-sensitivity C-reactive protein (hs-CRP) levels compared with controls. The atherogenic lipid profile of the heterozygotes was accompanied by an IMT increase progression of 0.00538 mm/year (versus 0.00301 mm/year for controls). After correction for kinship interactions and baseline values, this difference in IMT progression was highly statistically significant (P<0.0001). The low number of homozygotes (n=9) combined with their relatively high age (compared with heterozygotes and controls) could, unfortunately, not provide the required information for solid conclusions.

This finding of increased progression of atherosclerosis in LCAT mutations carriers was substantiated by a markedly increased incidence of CAD (0% in family controls, 7% in heterozygotes and 33% in homozygotes; P<0.001). Thus, loss of LCAT function is associated with an atherogenic lipid profile, increased hs-CRP, increased IMT, and an increased incidence of CAD. These findings strongly suggest that LCAT protects against atherosclerosis as was recently supported by LCAT gene therapy studies in mice (43). Consequently, upregulation of LCAT in man would be expected to protect against CAD.

Cholesteryl ester transfer protein

Complete loss of CETP activity due to mutations in the CETP gene can result in up to five times normal HDL cholesterol levels (48). CETP deficiency is common in Japan, where it explains almost half of all hyperalphalipoproteinemia cases (49). In Caucasians, however, CETP deficiency has hardly been described (50). The relationship between CETP defects and CAD risk is confusing. Initially, CETP-deficient patients were thought to have a reduced CAD risk (48) but, in contrast, more recent studies revealed that hetero- and homozygosity for CETP gene mutations is associated with an increased CAD risk (13, 51, 52). This discrepancy was ascribed to the actual HDL cholesterol levels; in fact, only CETP-deficient patients with high HDL cholesterol levels (>1.6 mmol/L) were shown to be protected from CAD.

Recently, our group identified a novel CETP gene defect in a Caucasian family. This CETP mutation (IVS7+1), causing a null allele, underlay half normal CETP activity and concentration. We compared 25 heterozygotes for this splicing defect (IVS7+1) with 25 family controls. CETP IVS7+1 carriers differed from family controls with regards to HDL cholesterol levels (+36%, P=0.001), HDL size (+5%, P=0.008) and LDL size (+1.5%; P=0.045). However, IMT progression over age did not differ between carriers and controls (P=0.4). In agreement with data from the Honolulu Heart Program, in which CETP-deficient Japanese were exposed to the North American diet and lifestyle (53), these data indicate that in a Western environment, reduced CETP function is not associated with an altered risk for CAD.

Studies focusing on atherogenesis in CETP-deficient patients are of particular interest, since they can be considered as the model for life-long reduced CETP activity. It is tempting to use this
natural model of loss of CETP function to predict the vascular effects of CETP inhibitors (10, 11). It should, however, be kept in mind that pharmacological modulation of CETP activity and reduced CETP function due to genetic defects may not necessarily result in similar effects on vascular outcome.

*Intima media thickness progression in carriers of monogenetic disorders in HDL metabolism*

Taken together, we have consecutively measured carotid IMT in carriers of apolipoprotein A-I, ABCA1, LCAT and CETP mutations and in their family controls. All these Caucasian participants were of Dutch Caucasian descent and environmental factors were essentially similar amongst all cohorts (table 1). For all groups, age was plotted against IMT to illustrate the increase in carotid arterial wall thickening over time in the different groups as well as unaffected family controls. Standardized ultrasound imaging and image analysis procedures (15) allowed for a direct comparison of cross-sectional IMT data between the different monogenetic disorders. The box plot in figure 1 clearly shows the impact of HDL cholesterol levels on the arterial wall. From these data, also summarized in figure 2, it becomes clear that arterial wall thickness progression was fastest in apolipoprotein A-I mutation carriers, followed by carriers of ABCA1 and LCAT mutations (while all three exhibited a significant increase in IMT compared with the family controls). This implies that the underlying genetic defect in hypoalphalipoproteinemia may be of importance when it comes to the risk for vascular disease. In contrast to FHA, CETP mutation carriers showed similar carotid IMT compared with controls.

We noted that a 50% loss of apolipoprotein A-I concentration, and a concomitant decrease in HDL cholesterol levels, yields a more pronounced effect on atherosclerosis progression than similar reductions in HDL cholesterol due to loss of either ABCA1 or LCAT activity. This leads us to

<table>
<thead>
<tr>
<th>TABLE 1.</th>
<th>Demographic, biochemical and vascular characteristics by genetic defect and control status</th>
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<table>
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<tr>
<th></th>
<th>Controls</th>
<th>ApoA-I defect</th>
<th>ABCA1 defect</th>
<th>LCAT defect</th>
<th>CETP defect</th>
</tr>
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<tbody>
<tr>
<td>Total number, n</td>
<td>280</td>
<td>33</td>
<td>27</td>
<td>68</td>
<td>18</td>
</tr>
<tr>
<td>Homozygous/compound heterozygous carriers, n</td>
<td>-</td>
<td>0</td>
<td>2</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Heterozygous carriers, n</td>
<td>-</td>
<td>33</td>
<td>25</td>
<td>59</td>
<td>18</td>
</tr>
<tr>
<td>Age, years</td>
<td>40.1 ± 20.7</td>
<td>40.8 ± 19.9</td>
<td>46.4 ± 20.8</td>
<td>42.4 ± 21.3</td>
<td>41.1 ± 21.2</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.8 ± 4.6</td>
<td>24.8 ± 5.1</td>
<td>23.3 ± 4.2</td>
<td>25.8 ± 5.6</td>
<td>23.8 ± 5.0</td>
</tr>
<tr>
<td>Male/Female, n/n</td>
<td>137/143</td>
<td>21/12</td>
<td>12/15</td>
<td>41/27</td>
<td>7/11</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>53 (19%)</td>
<td>7 (21%)</td>
<td>5 (19%)</td>
<td>15 (22%)</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>28 (10%)</td>
<td>2 (6%)</td>
<td>3 (11%)</td>
<td>11 (16%)</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>2 (1%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>3 (1%)</td>
<td>5 (15%)</td>
<td>6 (22%)</td>
<td>7 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.59 ± 0.57</td>
<td>0.47 ± 0.25</td>
<td>0.76 ± 0.34</td>
<td>0.70 ± 0.32</td>
<td>2.17 ± 0.69</td>
</tr>
<tr>
<td>Apolipoprotein A-I, g/L</td>
<td>1.53 ± 0.26</td>
<td>0.71 ± 0.30</td>
<td>0.94 ± 0.46</td>
<td>1.06 ± 0.34</td>
<td>-</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.87</td>
<td>0.89</td>
<td>0.98</td>
<td>1.35</td>
<td>0.98</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.13 ± 1.22</td>
<td>4.31 ± 1.13</td>
<td>4.67 ± 1.35</td>
<td>4.63 ± 1.19</td>
<td>5.66 ± 1.12</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.06 ± 1.03</td>
<td>3.24 ± 0.95</td>
<td>3.17 ± 1.20</td>
<td>3.04 ± 0.87</td>
<td>2.85 ± 1.05</td>
</tr>
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IMT progression (mm/year) 0.0046 ± 0.00024, 0.0082 ± 0.0011, 0.0073 ± 0.0015, 0.0055 ± 0.0062, 0.0047 ± 0.0011. All values are given as mean ± standard deviation.
hypothesize that reduced HDL cholesterol due to defects in the initial steps of the RCT process result in more accelerated atherosclerosis compared with defects in subsequent steps in the RCT. It is, however, unknown whether these differences can be explained by differential effects on RCT, or by variation in other HDL-related anti-atherogenic properties amongst the studied cohorts. These findings may illustrate that HDL cholesterol levels per se do not necessarily reflect the atheroprotective potential of HDL. Improved insight into the progression of atherosclerotic vascular disease in individuals with genetic disorders of HDL metabolism is of interest since it can assist in the prioritizing of anti-atherogenic therapy by increasing HDL cholesterol levels. In fact, the use of apolipoprotein A-I Milano infusion as a therapeutic agent, the materialization of a number of CETP inhibitors, and the discovery of ABCA1 agonists such as liver X receptor activators could partly be considered as a successful exploitation of knowledge obtained from these ‘extreme genetics’ studies that have successfully investigated the relationship between HDL and atherogenesis.

**FIGURE 1.** Mean carotid intima media thickness (IMT) in carriers of genetic defects in HDL metabolism

**FIGURE 2.** Inherited disorders of human HDL metabolism and atherosclerosis assessed by intima media thickness
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Conclusion
Regardless of the genetic cause, this review shows that FHA is associated with varying but always increased carotid IMT progression, and as such with increased CAD risk. This was indeed confirmed by more cardiovascular events in carriers compared with controls. In contrast, half normal CETP function, linked with high HDL cholesterol, was associated with unaltered atherosclerosis progression. Although one may speculate that CETP inhibition may therefore not be effective, we would like to underline that elevated HDL cholesterol levels in otherwise healthy individuals are not representative of pharmaceutical CETP inhibition in patients with low HDL cholesterol levels who are at increased risk for CAD.

These current insights into human disorders further add to our knowledge of HDL metabolism and atherosclerosis risk. Since FHA and hyperalphalipoproteinemia often remain unexplained, the future will undoubtedly bring new factors that regulate HDL cholesterol, potentially providing novel targets for pharmaceutical compounds.

REFERENCES


