Possible Induction of Renal Dysfunction in Patients With Lecithin:Cholesterol Acyltransferase Deficiency by Oxidized Phosphatidylcholine in Glomeruli

Shiro Jimi, Noriko Uesugi, Keijiro Saku, Hiroyuki Itabe, Bo Zhang, Kikuo Arakawa, Shigeo Takebayashi

Abstract—To clarify the causes of renal dysfunction in familial lecithin:cholesterol acyltransferase (LCAT) deficiency, kidney samples from 4 patients with LCAT deficiency (3 homozygotes and 1 heterozygote) were examined immunohistochemically. All of the patients exhibited corneal opacities, anemia, renal dysfunction, deficiencies in plasma high density lipoprotein and LCAT activity and mass, and an increase in the ratio of plasma unesterified cholesterol to esterified cholesterol. Renal lesions began with the deposition of lipidlike structures in the glomerular basement membrane, and these structures accumulated in the mesangium and capillary subendothelium. By electron microscopy, 2 types of distinctive structure were found in glomerular lesions: vacuole structures and cross-striated, membranelike structures. The plasma oxidized phosphatidylcholine (oxPC)–modified low density lipoprotein (LDL) levels in LCAT-deficient subjects were significantly (P<0.01) higher than those in controls (1.30±0.82 versus 0.42±0.32 ng/5 μg LDL, respectively), and a significant (P<0.01) difference was observed even after adjustment for confounding factors by an analysis of covariance. The patient with the highest plasma oxPC-modified LDL had the most membranelike structures in the glomeruli and showed the greatest renal deterioration from a young age. In glomerular lesions, although there was an abundance of apoB and apoE, oil red O–positive lipids, macrophages, apoA1, and malondialdehyde were scarce. OxPC was found extracellularly in glomerular lesions, and although its distribution differed from that of apolipoproteins, it was quite similar to that of phospholipids. In conclusion, these results indicate that oxPC in plasma and glomeruli is distinctive for patients with familial LCAT deficiency. Therefore, oxPC may be a factor in the deterioration of kidneys in patients with familial LCAT deficiency. (Arterioscler Thromb Vasc Biol. 1999;19:794-801.)

Key Words: lecithin:cholesterol acyltransferase deficiency ■ oxidized phosphatidylcholine ■ modified LDL ■ kidney

Familial lecithin:cholesterol acyltransferase (LCAT) deficiency is a rare inherited disease. The amino acid sequence of the LCAT gene has been determined. Various mutations of the LCAT gene in patients with LCAT deficiency have been reported. Mutations in the LCAT gene are responsible for the enzyme activities and symptoms found in this disease, while the clinical manifestations of such patients vary, even among members of the same family with identical mutations. Therefore, factors other than gene mutation may be involved in the clinical manifestation of patients with LCAT deficiency.

LCAT binds to HDL to catalyze the conversion of unesterified cholesterol and phosphatidylcholine (PC) to esterified cholesterol and lysophosphatidylcholine. A lack of LCAT activity causes an increase in unesterified cholesterol and phospholipids and a decrease in esterified cholesterol, which results in abnormalities of all kinds of lipoprotein particles and structures. Such lipid abnormalities are found in some organs in patients with LCAT deficiency, such as the kidney, cornea, and erythrocytes, and these changes clinically correspond to renal insufficiency, corneal opacities, and hemolytic anemia, respectively.

LCAT affects the plasma level of HDL through its role in HDL maturation. HDL is involved in the mechanism of reverse cholesterol transport by which free cholesterol is removed from peripheral tissue. Recently, Subbaiah and Liu showed that LCAT can also remove oxidized lipids. In atherosclerosis, the accumulation of cholesterol derived from LDL is thought to be an important event in the progression of atherosclerotic lesions, in which oxidatively modified LDL (oxLDL) plays a central role. It has been shown that oxLDL in human atherosclerosis contains malondialdehyde

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(MDA) and oxidized PC (oxPC).

Case 1

Case 1 underwent his first renal Bx at the age of 28 years when he was hospitalized for treatment of proteinuria (2 to 2.5 g/d) and hematuria. Although the plasma level of creatinine and creatinine clearance were normal at the time, renal Bx showed mild mesangial proliferative glomerulonephritis with segmental sclerosis. At the age of 33 years, he underwent a second Bx because his plasma total protein had decreased from 7.3 to 4.6 g/dL over that period, and he also exhibited nephrotic syndrome. The renal Bx showed advanced mesangial proliferative glomerulonephritis with deposition of foamy materials in glomeruli. By electron microscopy, irregularly shaped vacuoles were found within the glomerular basement membrane (GBM) and mesangial areas. Some capillary loops were distended with lipidlike, foamy material. Plasma lipid analysis revealed LCAT deficiency, and his sister also had corneal opacities and renal dysfunction.

Methods

Patients

Five patients with familial LCAT deficiency from 4 different families, including a pair of brothers with the same gene mutation (case 4Y, younger brother and case 4E, elder brother), were investigated. An immunohistochemical study was conducted in 4 kidney Bx specimens from 4 of these patients with renal dysfunction, and plasma lipoproteins and oxPC were measured in all 5 patients. As shown in Table 1, all of the patients exhibited corneal opacities in childhood, and all but case 4E showed renal manifestations, including hypertension and proteinuria. Cases 2, 3, and 4Y underwent hemodialysis, and case 1 was treated with dialysis. Another LCAT-deficient subject with normal renal function did not undergo a renal Bx. Case 4Y, who is the younger brother, underwent a renal Bx at age 44 years owing to rapid deterioration of renal function and severe hypertension and nephrotic syndrome appeared. A third Bx was performed at age 20 years; LCAT deficiency was strongly suspected from the biopsied specimen, because lipidlike, foamy material appeared to have been deposited within an expanded mesangium. His plasma and blood cells were sent to our research laboratory at Fukuoka University. LCAT gene analysis revealed a single C-to-G mutation, which converted Pro 250 (CCC) to Arg (CGC) in exon 6. His renal function deteriorated rapidly thereafter, and hemodialysis was started at age 21.

Case 2

Proteinuria and hematuria were noted at age 7 years in a school health examination. He underwent 2 renal biopsies at ages 11 and 13 years, by which he was diagnosed with membranous glomerulonephritis. Prednisolone therapy was administered for several years but did not reduce proteinuria or hematuria. During this period, his renal function gradually deteriorated, and uncontrollable, severe hypertension and nephrotic syndrome appeared. A third Bx was performed at age 20 years; LCAT deficiency was strongly suspected from the biopsied specimen, because lipidlike, foamy material appeared to have been deposited within an expanded mesangium. His plasma and blood cells were sent to our research laboratory at Fukuoka University. LCAT gene analysis revealed a single C-to-G mutation, which converted Pro 250 (CCC) to Arg (CGC) in exon 6. His renal function deteriorated rapidly thereafter, and hemodialysis was started at age 21.

Cases 4Y and 4E

Owing to severe decreases in the plasma levels of HDL cholesterol (HDL-C), LCAT activity, and LCAT mass, cases 4Y and 4E were diagnosed with LCAT deficiency at the ages of 38 and 46 years, respectively. They have been previously reported as homozgyous cases based on their remarkable clinical features.

Tables:

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<tr>
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<tbody>
<tr>
<td>Corneal opacity, age, y</td>
<td>Child</td>
<td>Child</td>
<td>Child</td>
<td>Child</td>
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<tr>
<td>Proteinuria, age, y</td>
<td>27</td>
<td>7</td>
<td>35</td>
<td>35</td>
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<tr>
<td>Nephrotic syndrome, age, y</td>
<td>30</td>
<td>16</td>
<td>35</td>
<td>46</td>
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<tr>
<td>Hypertension, age, y</td>
<td>33</td>
<td>19</td>
<td>35</td>
<td>…</td>
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<tr>
<td>Induction to HD, age, y</td>
<td>…</td>
<td>21</td>
<td>48</td>
<td>48</td>
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<td>Age in 1998, y</td>
<td>39</td>
<td>23</td>
<td>50</td>
<td>49</td>
</tr>
<tr>
<td>Clinical condition in 1998</td>
<td>CRF</td>
<td>HD</td>
<td>HD</td>
<td>HD</td>
</tr>
<tr>
<td>Gene mutation</td>
<td>G 873</td>
<td>Pro 250</td>
<td>Gly 344</td>
<td>Met 293</td>
</tr>
<tr>
<td>Zygosity</td>
<td>Homo</td>
<td>Homo</td>
<td>Homo</td>
<td>Hetero</td>
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HD indicates hemodialysis; CRF, chronic renal failure; and NRD, no renal disease.
TABLE 2. Laboratory Findings in Patients With LCAT Deficiency

<table>
<thead>
<tr>
<th></th>
<th>Normal Values</th>
<th>Case 1(6)</th>
<th>Case 2(8)</th>
<th>Case 3(10,11)</th>
<th>Case 4Y(12,15,31)</th>
<th>Case 4E(12,15,31)</th>
</tr>
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<tbody>
<tr>
<td>Age, y</td>
<td>27</td>
<td>33</td>
<td>37</td>
<td>20</td>
<td>35</td>
<td>41</td>
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<tr>
<td>Bx</td>
<td>Bx1</td>
<td>Bx2</td>
<td>Bx3</td>
<td>Bx1</td>
<td>Bx2</td>
<td>Bx3</td>
</tr>
<tr>
<td>Proteinuria*</td>
<td>(-)</td>
<td>2+</td>
<td>2+</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
</tr>
<tr>
<td>Hematuria†</td>
<td>(-)</td>
<td>+</td>
<td>2+</td>
<td>2+</td>
<td>3+</td>
<td>2+</td>
</tr>
<tr>
<td>Plasma-total protein, g/dL</td>
<td>(67–83)</td>
<td>7.3</td>
<td>4.6</td>
<td>4.8</td>
<td>4.0</td>
<td>4.2</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>(39–52)</td>
<td>40.2</td>
<td>32.9</td>
<td>32.5</td>
<td>23.8</td>
<td>26.4</td>
</tr>
<tr>
<td>Plasma-urea nitrogen, mg/dL</td>
<td>(6–22)</td>
<td>17</td>
<td>18</td>
<td>28</td>
<td>37</td>
<td>18</td>
</tr>
<tr>
<td>Plasma-creatinine, mg/dL</td>
<td>(0.4–1.0)</td>
<td>1.2</td>
<td>1.2</td>
<td>1.4</td>
<td>2.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Creatinine-clearance, mL/min</td>
<td>(&gt;62)</td>
<td>80</td>
<td>80</td>
<td>47</td>
<td>63</td>
<td>52</td>
</tr>
</tbody>
</table>

Note: Chol indicates cholesterol; *: semiquantitative biuret method; †: Nagasaki-Akanuma method (LCAT activity); §using a proteoliposome as a substrate (LCAT activity); ¶Bx1 was performed at the age of 44; and ... indicates that data were not measured.

Our laboratory at Fukuoka University. We detected a heterozygous variant only at Met 294 Ile, without other defects or compound heterozygosity, which indicated that this case is heterozygous dominant.11

In the present study, we used several renal Bx specimens from each case for morphological examination in case 1, Bx1 and Bx2; case 2, Bx3; case 3, Bx3, and case 4Y, Bx1. For immunohistochemical analysis, we used the following: in case 1, Bx1 and Bx2; case 2, Bx3; case 3, Bx3 and case 4Y, Bx1.

Plasma Lipoprotein Levels and LCAT Activity and Mass

Blood samples were obtained intravenously after an overnight fast. Total cholesterol, free cholesterol, triglyceride, and phospholipid concentrations in plasma were measured by enzymatic methods.32,33 HDL-C was measured by the heparin-calcium precipitation method.34 Plasma LCAT activity was measured by using a proteoliposome as a substrate (cases 1 and 3) as previously described6 or by using dipalmitoyl PC (Nagasaki-Akanuma method; cases 2, 4Y, and 4E)35 as a substrate. LCAT mass (cases 1, 3, 4Y, and 4E) was measured by radioimmunooassay using a polyclonal antibody and 125I-labeled LCAT as previously described66 by Dr. J.J. Albers, Washington University, Seattle.

Immunohistochemical Staining

Serial sections of frozen and paraffin-embedded samples were used for immunohistochemical staining using an alkaline phosphatase and an anti–alkaline phosphatase (DAKO) method. We used commercial primary antibodies against human apoB (Chemicon), apo E (Chemicon), apoAI (Chemicon), collagen types I (Chemicon) and IV (Siseido Inc), plasma fibronectin (Chemicon), cellular fibronectin (Chemicon), and human macrophages (HAM56, DAKO). We also used monoclonal antibodies for human oxLDL, which primarily recognize MDA (DLH2)38 and oxPC (DLH3).29 These antibodies can react with copper-oxidized LDL but not with native human LDL.

Level of OxPC-Modified LDL in Plasma

Blood samples were obtained intravenously by using EDTA as an anticoagulant from controls and 5 patients with LCAT deficiency. We measured oxPC in the sex- and age-matched controls (males, n=31) who showed normal coronary arteries as determined by coronary angiography (controls). As for LCAT-deficient subjects, fresh plasma samples were airmailed to our laboratory from their respective physicians in charge, and then oxPC levels for the 5 patients were assayed at the same time in January 1997. For the measurement of oxPC, we used only fresh plasma samples (containing 0.25 mmol/L EDTA) and kept at 4°C, and measurement was completed within 1 week. EDTA was used as an antioxidant. The monoclonal anti-oxPC antibody (DLH3), which was originally developed to detect human oxLDL,29 was used to determine the level of oxPC-modified LDL in plasma. After the LDL fraction...
(1.019 < d < 1.063) had been isolated by sequential ultracentrifugation, the concentrations of oxPC-modified LDL in plasma were measured by a sandwich ELISA method and are expressed as the oxPC concentration in 5 μg LDL protein and using copper-oxidized LDL as the standard, as previously described. Measurements were performed in duplicate, and the interassay and intra-assay coefficients of variation ranged from 7% to 10%.

**Statistical Analysis**

Statistical analysis was performed using the SAS Software Package (version 6, Statistical Analysis System, SAS Institute Inc). Categorical variables (such as hypertension) were compared between cases and controls by a χ² analysis. The distribution of variables was examined by the Shapiro-Wilk test. Variables that were normally distributed were compared between groups by an ANOVA. Variables that were not normally distributed were compared between groups by the nonparametric Wilcoxon rank-sum test. Age, hypertension, and diabetes mellitus were adjusted for by an ANCOVA. All probability value are 2-tailed. The significance level was considered to be 5% unless indicated otherwise.

**Results**

**LCAT Gene Mutation and Clinical and Laboratory Findings in Patients With LCAT Deficiency**

The gene mutations and the clinical and laboratory findings in each patient during their follow-up periods are shown in Tables 1 and 2, respectively. Sequence analysis of the LCAT gene revealed different gene mutations in each case, except 4Y and 4E, who were brothers with an identical mutation. Cases 1, 2, and 3 showed homozygous, single-gene mutations. Cases 4E and 4Y had a heterozygous missense mutation; ie, a G-to-A transition at position 4660 that changed Met 293 (ATG) to Ile (ATA). All patients showed laboratory findings characteristic of classic LCAT deficiency, such as normocytic normochloremic anemia with the appearance of target red blood cells. An increased ratio of plasma free cholesterol to total cholesterol, a minimum level of plasma HDL-C, suppressed plasma LCAT activity, and decreased LCAT mass were observed (Table 2). Fragility of red blood cell membranes was detected in cases 1, 3, and 4Y but was not checked in case 2. Case 2, the youngest in this group, showed severe renal dysfunction with lipid abnormalities, all of which are typical of LCAT deficiency. During a 10-year follow-up, HDL-C levels were greatly decreased while the ratio of free to total cholesterol increased in cases 4Y and 4E. Although LCAT activity increased slightly in case 4Y at age 48 compared with that at age 38 [21 versus 3 (nmol/mL)/h at 37°C, respectively], LCAT mass was deficient in cases 1, 3, 4Y, and 4E.

**Morphological Alterations in Renal Bx Specimens From Patients With LCAT Deficiency**

**Light and Immunofluorescence Microscopy**

Although the extent of renal involvement by light microscopy varied between cases and the time of Bx, characteristic features of the glomerular lesions in the renal specimens used in this study were vacuolization of the GBM (Figure 1A); “ballooning” of loops filled with lipiddike, foamy material (Figure 1A); and mesangial expansion with pale staining, with a “fluffy” appearance on periodic acid–Schiff staining. These glomerular lesions were found in all patients except 4E, who never underwent a renal Bx. Renal lesions began with small deposits of lipiddike structures in the GBM. Figure 1A shows diffuse vacuolization, capillary ballooning, and tuft adhesion in moderately affected glomeruli. Mesangial expansion became more apparent in advanced glomerular lesions, in which foamy cells were scarcely found in the glomeruli. As glomerular involvement progressed, interstitial damage with chronic inflammatory cell infiltration, tubular atrophy, fibrosis, and hyaline arterioles was also apparent. In the immunofluorescence analysis, IgM and C3 were positive in cases 1
and 4Y, whereas IgG, IgA, and C1q and fibrinogen were negative in all cases.

**Electron Microscopy**

Two distinct structures were observed in glomerular lesions, ie, variously sized electron-lucent vacuoles with or without osmiophilic particle cores (Figure 1B and 1C) and cross-striated, membranelike structures (Figure 2). The deposition of membranelike structures was found in cases 2, 3, and 4Y, while the amounts of such structures found in each case followed the order case 2 > case 3 > case 4Y, and case 2 showed a particularly large accumulation in the GBM (Figure 2B) and mesangium (Figure 2C). On the other hand, lucent vacuoles were deposited in the subendothelium, the GBM (Figures 1B and 2B), and expanded mesangium (Figure 1C) in cases 1, 2, 3, and 4Y. Some capillary loops were expanded with vacuolar structures. Thinning of the GBM, detachment of endothelial cells, fusion of epithelial foot processes, and/or tuft adhesion were frequently observed near the regions where these structures had accumulated in large amounts. In such glomeruli, no foamy cells were found.

**Immunohistochemical Analysis of Accumulated Lipids in Glomerular Lesions**

Accumulated lipids in glomerular lesions of subjects with LCAT deficiency were analyzed by special staining for lipids and immunohistochemical techniques. The lesions contained minimum amounts of oil red O–positive (Figure 3A) and Nile blue–positive lipids, whereas glomeruli were positive throughout for acid-hematin staining for phospholipids (Figure 3C). As a result, no acid-hematin–positive materials were found in normal glomeruli. Tubular epithelial cells were sometimes positive for oil red O. Immunohistochemically, distended loops and subendothelium were strongly positive for apoB (Figure 3E) and apo E (Figure 3F), whereas the
mesangium was weakly positive for both of these apolipoproteins. The glomeruli and interstitium were negative for apoA1. Glomeruli were diffusely positive for DLH3 (Figure 3D), but no materials were positive for DLH2, which detects MDA (Figure 3B). Distended capillary loops and mesangium were negative for cellular fibronectin but weakly positive for plasma fibronectin. Collagen type IV was found in sclerosed mesangium and at sites of adhesion, whereas glomeruli were negative for collagen type I.

**Level of OxPC-Modified LDL in Plasma**

The levels of oxPC-modified LDL in plasma were measured by a sandwich ELISA method. The values in cases 1, 2, 3, 4Y, and 4E varied (Figure 4; 0.64, 2.72, 1.08, 1.23, and 0.84 ng/5 μg LDL protein, respectively). Because all of the cases were men, only male controls (n=31) who showed normal coronary arteries as determined by coronary angiography were used in this study. The oxLDL values in the cases (n=5) were significantly higher than those in the controls (1.30±0.82 versus 0.42±0.32 ng/5 μg LDL protein, mean±SD; P<0.01 by the Wilcoxon rank-sum test). Similar significant (P<0.01) results were obtained even after adjustment for age, hypertension, and diabetes mellitus (including impaired glucose tolerance) by an ANCOVA.

**Discussion**

We examined the renal Bx specimens from 4 patients with LCAT deficiency who have different LCAT gene mutations. This is the first report to indicate that increases in both oxPC-modified LDL in plasma and oxPC in glomeruli are associated with renal symptoms of LCAT deficiency. The levels of oxPC-modified LDL were measured by a sandwich ELISA method. All patients with LCAT deficiency (black bars) exhibited higher levels of oxPC-modified LDL than did healthy normal controls (open bar, mean±SD).

Figure 4. Levels of oxPC-modified LDL in patients with LCAT deficiency. The levels of oxPC-modified LDL were measured by a sandwich ELISA. All patients with LCAT deficiency (black bars) exhibited higher levels of oxPC-modified LDL than did healthy normal controls (open bar, mean±SD).

By electron microscopy, 2 types of distinctive structure were accumulated in glomerular lesions, ie, foamy structures and cross-striated, membranelike structures. On the basis of our experience, these 2 structures are not common in any other renal diseases. The abundant accumulation of both structures was found in glomeruli in all of the cases, and they were also found in the vessel wall and tubular basement membrane to some extent. Interestingly, 3 cases (cases 2, 3, and 4Y) with higher plasma levels of oxPC-modified LDL had membranelike structures in glomeruli, and the highest level of plasma oxPC-modified LDL was seen in case 2, who also showed the greatest renal deterioration. His glomerular lesions showed the greatest accumulation of membranelike structures (Figure 2B and 2C). These immunohistochemical and electron microscopic findings suggest that the cross-striated, membranelike structures may contain oxPC. However, the exact relationship between oxPC and these struc-
tures is still unclear. An increase in PC in several different organs, including plasma, has been shown in LCAT deficiency,16 whereas an elevated level of sphingomyelin in the affected cornea is a characteristic of fish-eye disease,23 which is analogous to LCAT deficiency except that the kidney is not affected.43,44 perhaps due to some remaining LCAT activity. Stokke et al46 reported that a patient with LCAT deficiency had received a transplanted normal kidney; however, when his renal function became worse, the transplanted kidney was removed and analyzed biochemically. The removed kidney, especially the glomeruli, showed a remarkably high level of PC, suggesting that this change may have been induced by the circulating blood in this patient. In LCAT-knockout mice, the development of glomerular lesions has been noted.45 It is unclear why the kidney is a main target organ in LCAT deficiency. We found that oxPC accumulated in glomeruli in a patient with LCAT deficiency.

Subbaiah and Liu24 postulated that LCAT may play a role in oxPC catabolism. Moreover, in a recent in vitro study, we found that LCAT can metabolize oxPC. After oxidized 1-palmitoyl-2-[14C]linoleoyl PC was incubated with human plasma, nonpolar reaction products were separated by thin-layer chromatography. Several radioactive bands in addition to those for cholesteryl ester were formed in a dose- and time-dependent manner. These products were not formed from native 1-palmitoyl-2-[14C]linoleoyl PC. Plasma from LCAT-deficient patients also failed to form additional products from oxPC. These data suggest that LCAT is capable of metabolizing a variety of oxidized products of PC and of preventing the modification of LDL (H.I., unpublished data, 1998). These findings suggest that oxPC preferentially accumulates in glomeruli by unknown mechanisms, and such oxPC cannot be removed by LCAT-deficient plasma, which may ultimately cause renal dysfunction.

Recent studies have indicated that HDL inhibits the oxidative modification of LDL17,44 and that oxLDL inhibits LCAT activity.49,50 Sevanian et al51 reported that oxidatively modified plasma LDL is found largely among the small, dense LDL fraction, which is atherogenic. LDL particle sizes were not determined in our LCAT-deficient subjects in relation to plasma oxPC levels. However, we recently measured LDL particle size as related to the fractional esterification rate of cholesterol in VLDL- and LDL-depleted plasma, which reflects the reactivity of HDL to LCAT, in patients with coronary heart disease,52 and found that this rate was positively correlated with plasma apoB levels and negatively correlated with plasma HDL-C and LDL particle size. Therefore, decreased plasma HDL in LCAT-deficient patients accelerates the oxidation of LDL via several complicated, and still theoretical, pathways.

In this study, higher levels of oxPC-containing oxLDL were noted in all of the patients. OxLDL could suppress the remaining LCAT activity in patients with LCAT deficiency, and this may also be involved in the progression of renal impairment in LCAT deficiency. Therefore, oxPC may play an important role in renal dysfunction in familial LCAT deficiency.

Acknowledgments

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References


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