Lipid Parameters Including Lp(a) in Hemodialysis Patients

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CLINICAL STUDY

Lipid Parameters Including Lp(a) in Hemodialysis Patients

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ABSTRACT

Chronic hemodialysis (CHD) patients have a high incidence and prevalence of atherosclerotic disease which may be related to numerous atherosclerotic risk factors. Among them dyslipidemia plays a significant role. Elevated Lp(a) levels, which are strongly associated with atherosclerosis, have been reported recently in uremic patients. The aim of our study was the determination of the levels of lipid parameters including Lp(a) in 151 CHD patients (76 male) aged 57 (12–81) years, who were on hemodialysis for a mean of 44.3 (range 1 to 189) months. Eighty-four normal individuals age and sex matched were used as controls. The median serum Lp(a) concentration in hemodialysis patients was 13 mg/dL compared with 6.5 mg/dL in healthy controls, p < 0.001 by distribution-free Mann–Whitney test. The prevalence of subjects with Lp(a) levels above 25 mg/dL was significantly higher in CHD patients compared to normal subjects (30% vs. 8%, p < 0.001). Even if CHD patients were matched for fasting lipid levels, they showed Lp(a) levels significantly higher than controls. No significant correlation was found between Lp(a) levels and either the age of the patients or the duration of hemodialysis. The etiology of primary renal disease did not influence the Lp(a) levels.

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INTRODUCTION

Chronic hemodialysis (CHD) patients are at increased risk for accelerated atherosclerosis (1–3). Among the incriminated risk factors, dyslipidemia seems to play a significant role in the high cardiovascular mortality observed in this population (1, 3–5). Although hypertriglyceridemia and decreased HDL cholesterol are the most common lipid abnormalities in these patients (4–8), quantitative and qualitative lipoprotein disturbances have also been described (5, 6, 9, 10). Recently, a few studies have shown an increased concentration of Lp(a) lipoprotein in CHD patients (11–22).

Lp(a) is a genetic variant of low-density lipoprotein (LDL) containing Apo B covalently linked to apolipoprotein (a) [Apo (a)], the specific marker of Lp(a). Apo (a) is a glycoprotein coded by a single gene locus on the long arm of chromosome 6 which has several alleles accounting for its remarkable size polymorphism (300 to 800 kDa). Apo (a) size polymorphism is related to plasma levels and density distribution of Lp(a) (23–25). Previous reports have established that a high Lp(a) concentration is an independent risk factor for cardiovascular disease, namely for stroke (26), myocardial infarction (27, 28), restenosis after percutaneous transluminal coronary angioplasty (29), and the obstruction of saphenous vein bypass grafts to the coronary arteries that occurs a few years after coronary bypass surgery (30). Moreover, very recently Lp(a) was found to be an independent risk factor for cardiovascular disease in patients receiving CHD treatment as well as a predictor of vascular access occlusion in White and Hispanic hemodialysis patients (16–21).

We undertook the present study to determine the serum Lp(a) levels as well as the levels of the other lipid parameters in a large number of CHD patients, and to compare these levels with those of age- and sex-matched controls.

MATERIAL AND METHODS

One hundred fifty-one CHD patients (76 men) with a mean age of 57 (range 12–81) years were studied. The clinical characteristics of the study population are shown in Table 1. Patients with diabetes mellitus, hypothyroidism, liver failure, alcoholism, or primary hyperlipidemia were excluded from the study. Moreover, no subject in the study was administered with drugs known to affect lipid metabolism such as diuretics, beta-blockers, corticosteroids, cyclosporin, etc. Patients were prescribed only antacids, vitamin D preparations (42 patients), calcium channel blockers (28 patients), and angiotensin-converting enzyme inhibitors (22 patients). Eighty-four healthy volunteers chosen randomly from a pool of blood donors were used as controls. The two groups were comparable in age, gender, and body mass index. In both patients and controls, venous blood was obtained after a 14 h overnight fast for determination of lipid parameters. In all patients, fasting blood was obtained at least 40 h after the preceding hemodialysis.
Table 1

Clinical Characteristics of the Study Population

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Number</td>
<td>151</td>
</tr>
<tr>
<td>Age (years)</td>
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<tr>
<td>Mean</td>
<td>57</td>
</tr>
<tr>
<td>Range</td>
<td>12–81</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>75</td>
</tr>
<tr>
<td>Male</td>
<td>76</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.4 ± 1.2</td>
</tr>
<tr>
<td>Etiology of renal disease (n)</td>
<td></td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>56</td>
</tr>
<tr>
<td>Chronic pyelonephritis</td>
<td>27</td>
</tr>
<tr>
<td>Polycystic renal disease</td>
<td>19</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3</td>
</tr>
<tr>
<td>Obstructive uropathy</td>
<td>8</td>
</tr>
<tr>
<td>Unknown</td>
<td>38</td>
</tr>
<tr>
<td>Duration of hemodialysis (months)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>44.3</td>
</tr>
<tr>
<td>Range</td>
<td>1–189</td>
</tr>
</tbody>
</table>

The mean of 3 measurements performed within 1 month was regarded as the patient's representative value for each parameter. Serum cholesterol and triglycerides were determined by enzymatic colorimetric assay using an RA-1000 analyzer (Technicon Instruments Ltd), while HDL cholesterol was determined enzymatically in the supernatant after precipitation of other lipoproteins with dextran sulfate–magnesium. LDL cholesterol was calculated using the Friedewald formula (31) if fasting triglyceride levels were less than 400 mg/dL, and by ultracentrifugation if triglyceride levels exceeded 400 mg/dL. Serum Apo A1 and B were measured by immunonephelometry with the aid of a Beckman array analyser (Beckman Instruments, CA, USA). Lp(a) was measured using a monoclonal anti-Lp(a) antibody technique by the enzyme immunoassay Macra Lp(a) (Terumo Medical Corporation Diagnostic Division, Elkton, MD). The lower limit of detectability was 0.8 mg/dL. In cases of Lp(a) levels less than 0.8 mg/dL, the value of 0.8 mg/dL was used for statistical reasons. The intra-assay and the interassay coefficients of variation were less than 6%, and 10.3%, respectively. In a recent report using this monoclonal antibody, no cross-reactivity with plasminogen, LDL, VLDL, or HDL was observed (32). Values were expressed by means ±SD, except for Lp(a), which was expressed in terms of median and range. Data analysis was performed using the Mann–Whitney U test or the Student t test for group comparison of continuous variables with nonnormal or normal population distribution, respectively. Spearman correlation coefficients were determined to evaluate the relation between Lp(a) and other continuous variables. The proportions of the groups having Lp(a) lipoprotein above 25 mg/dL were compared by using χ² with Yates correction.
RESULTS

Lipid parameters in the CHD patients and in the control population are shown in Table 2. The patients had higher levels of triglycerides and lower levels of HDL cholesterol and Apo A1 compared to normal controls. Total cholesterol, LDL cholesterol, and Apo B were not significantly different between the two groups. However, CHD patients had higher ratios of total/HDL cholesterol. The median Lp(a) lipoprotein concentration in the CHD patients was significantly higher than that in the control group ($p < 0.001$). Furthermore, the prevalence of subjects with Lp(a) levels above 25 mg/dL was significantly higher in these patients compared to normal subjects (30% vs. 8%), $p < 0.001$. We selected a group of 20 CHD patients who had levels of total cholesterol and triglycerides similar to 20 normal controls. As shown in Table 3, in this group of CHD patients, median Lp(a) lipoprotein levels were again significantly higher than in the control population. In addition, CHD patients had significantly lower levels of HDL cholesterol and Apo A1 and an increased ratio of total/HDL cholesterol compared to normal controls. In Table 4 the correlation coefficients between Lp(a) and other parameters of lipoprotein metabolism are shown. A statistically significant correlation between Lp(a) levels and both LDL cholesterol and Apo B was found only in the CHD patients. No significant correlation was detected between Lp(a) levels and duration of hemodialysis ($r = -0.12$) or Lp(a) levels and the age of either patients ($r = 0.06$) or controls ($r = 0.15$). Finally, there were no differences in the levels of Lp(a) among the groups of patients classified by primary renal disease.

DISCUSSION

Our study, performed on a large number of CHD patients, indicated that they had increased serum triglyceride and decreased serum HDL cholesterol and Apo A1 concen-

<table>
<thead>
<tr>
<th>Lipid parameter</th>
<th>CHD patients (n = 151)</th>
<th>Control population (n = 84)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>202 ± 51</td>
<td>200 ± 39.6</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>193 ± 96</td>
<td>112 ± 74</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>40 ± 11</td>
<td>56 ± 14</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>121 ± 42</td>
<td>120 ± 53</td>
<td>NS</td>
</tr>
<tr>
<td>Total/HDL cholesterol</td>
<td>5 ± 1.6</td>
<td>3.6 ± 1.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Apo A1 (mg/dL)</td>
<td>127 ± 20</td>
<td>151 ± 23</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Apo B (mg/dL)</td>
<td>130 ± 39</td>
<td>128 ± 36</td>
<td>NS</td>
</tr>
<tr>
<td>Lp(a) (mg/dL)</td>
<td>13 (0.8–108)</td>
<td>6.3 (&lt; 0.8–34.5)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Note: Values are means ± SD except for Lp(a), where medians and ranges are shown. NS: not significant.
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Table 3

Lipid Parameters in 20 Patients and 20 Controls Selected by Similar Levels of Serum Total Cholesterol and Triglycerides

<table>
<thead>
<tr>
<th>Lipid parameter</th>
<th>CHD patients</th>
<th>Control population</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>204 ± 45</td>
<td>202 ± 46</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>128 ± 51</td>
<td>108 ± 53</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>48 ± 11</td>
<td>59 ± 14</td>
<td>&lt; 0.01</td>
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<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>128 ± 38</td>
<td>122 ± 37</td>
<td>NS</td>
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<tr>
<td>Total/HDL cholesterol</td>
<td>4.3 ± 1.2</td>
<td>3.6 ± 1.0</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Apo A1 (mg/dL)</td>
<td>130 ± 19</td>
<td>166 ± 26</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Apo B (mg/dL)</td>
<td>127 ± 36</td>
<td>121 ± 31</td>
<td>NS</td>
</tr>
<tr>
<td>Lp(a) (mg/dL)</td>
<td>13 (0.8–67)</td>
<td>7.5 (&lt; 0.8–34.5)</td>
<td>&lt; 0.04</td>
</tr>
</tbody>
</table>

Note. Values given are ± SD except for Lp(a), where medians and ranges are shown NS: not significant.

Table 4

Correlation Coefficients Between Lp(a) and Parameters of Lipoprotein Metabolism

<table>
<thead>
<tr>
<th>Lipid parameter (mg/dL)</th>
<th>CHD patients (n = 151)</th>
<th>Control population (n = 84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>0.14</td>
<td>0.13</td>
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<tr>
<td>Triglycerides</td>
<td>-0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.11</td>
<td>-0.01</td>
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<tr>
<td>LDL cholesterol</td>
<td>0.18*</td>
<td>0.23</td>
</tr>
<tr>
<td>Apo A1</td>
<td>0.10</td>
<td>0.14</td>
</tr>
<tr>
<td>Apo B</td>
<td>0.19*</td>
<td>0.17</td>
</tr>
</tbody>
</table>

*p < 0.05.
to previous ones, the lower Lp(a) levels observed could be owing to the fact that the Greek population may have lower levels of Lp(a). Besides, it is well known that Greeks have lower levels of total and LDL cholesterol when compared with other Europeans (35). Although Lp(a) concentrations are thought to be genetically determined to a significant extent and show little variation during adult life (36, 37), other factors such as drugs (13, 38, 39), diabetes mellitus (40–44), sex hormones (45), diet (46), alcohol (47), and renal diseases (11–22, 48–52) also affect Lp(a) levels. The main mechanisms of the increased Lp(a) levels in CHD patients are unknown. The elevated Lp(a) seen here could be due mainly to increased hepatic synthesis, as it is well known that the liver is the main site of its production (53); the plasma Lp(a) levels are mainly regulated by the hepatic synthetic rate and the elevated Lp(a) levels result from increased synthesis rather than decreased clearance (54, 55). Impaired catabolism could also contribute to the high Lp(a) levels observed. Increased hepatic synthesis has been suggested as a significant factor in the high Lp(a) levels reported in proteinuric patients in whom a loss of plasma proteins into urine, or a low plasma protein concentration, stimulates the hepatic synthesis of plasma proteins and possibly lipoproteins, including Lp(a) and other Apo B-containing lipoproteins (48, 56). Increased hepatic production of Apo B containing lipoproteins, including VLDL and Lp(a), has been regarded as the main mechanism of increased Lp(a) in CAPD patients, who like nephrotic patients lose their plasma proteins into peritoneal dialysate (18, 50, 57). However, the HD procedure does not lose plasma proteins, as the molecular weight of Lp(a) particle is 3.800 kDa (58). Increased hepatic production of Lp(a) in this population could be related to hypertriglyceridermia. Studies have shown that individuals with diet-induced hypertriglyceridermia demonstrated Lp(a) linked to Apo B in their postprandial triglyceride-rich lipoproteins (59). The observed positive correlation between Lp(a) and Apo B (Table 4) suggest that Lp(a) levels have some linkage to the metabolism of other Apo B-containing lipoproteins. However, as shown in Table 3 and confirmed previously (15), Lp(a) levels are increased even in normotriglyceridemic uremic patients. Alternatively, metabolic abnormalities commonly present in hemodialysis, such as changes in carbohydrate metabolism (60), could play a very significant role in the increased Lp(a) production. Increased glucose absorption stimulating hepatic synthesis of Lp(a) is especially common in CAPD patients and has been thought to account for the higher levels of Lp(a) among CAPD patients (18).

Conversely, excess Lp(a) could result from diminished clearance. It has been reported, though not proved, that Lp(a) may be catabolized by the LDL receptor. Theoretically when LDL levels are increased, Lp(a) binding may be competitively inhibited, resulting in less degradation of Lp(a) (55, 61). Although LDL levels of our hemodialysis patients were not increased compared to controls, the positive correlation between Lp(a) and LDL cannot rule out the possibility of decreased receptor-mediated catabolism. It is also possible that the kidneys have a regulatory role in Lp(a) metabolism, and the decline of renal function could interfere with normal catabolism and clearance of Lp(a) (48, 62). Finally, as has been stated recently, intermitent heparinization or exposure of blood to a hemodialysis membrane or use of a specific type of solution in dialysis may be partly responsible for the pathogenesis of dyslipidemia, including increased Lp(a) levels in hemodialysis patients (16).

The increased Lp(a) levels in CHD may be of great importance as it well known that Lp(a) contributes to the increased coronary heart disease commonly observed in this pop-
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The strong association between Lp(a) and early coronary heart disease is related to its atherogenic and thrombogenic properties (12, 36, 63).

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