Apolipoprotein(a) Phenotypes Predict the Risk for Carotid Atherosclerosis in Patients With End-Stage Renal Disease

Florian Kronenberg, Hermann Kathrein, Paul König, Ulrich Neyer, Wolfgang Sturm, Karl Lhotta, Ernst Gröchenig, Gerd Utermann, Hans Dieplinger

Abstract Several studies have demonstrated that atherosclerotic complications are the major cause of morbidity and mortality in hemodialysis patients. High lipoprotein(a) [Lp(a)] plasma concentrations are an independent risk factor for atherosclerosis. Patients with end-stage renal disease (ESRD) have elevated plasma concentrations of Lp(a), which are not explained by size variation at the apolipoprotein(a) [apo(a)] gene locus. The aim of our study was to investigate whether Lp(a) concentrations and/or apo(a) phenotypes are predictive of the degree of atherosclerosis in the extracranial carotid arteries in ESRD patients. Of 167 patients, 108 showed atherosclerotic plaques (65%). Univariate analysis showed that the plaque-affected group was significantly older and had a higher frequency of angina pectoris, previous myocardial infarction, or cerebrovascular accident. Furthermore, this group included significantly more patients with low-molecular-weight apo(a) isoforms (26.9% versus 8.5%, P<.005) and had significantly higher mean Lp(a) plasma concentrations (29.3±31.0 versus 19.7±25.7 mg/dL, P<.05). Lp(a) plasma concentration increased significantly with the number of affected arterial sites, from 19.7 mg/dL in patients without plaques to 40.1 mg/dL in patients with seven or eight affected sites. In patients with low-molecular-weight phenotypes, significantly more arterial sites were affected (3.62 versus 2.08, P<.001). Multivariate regression analysis showed that age, angina pectoris, and the apo(a) phenotype were the only significant predictors of the degree of atherosclerosis. We conclude that, besides age, the apo(a) phenotype is the best predictor of carotid atherosclerosis in ESRD patients and may be used for assessment of general atherosclerosis risk in this patient group. (Arterioscler Thromb. 1994;14:1405-1411.)

Keywords • Lp(a) • apo(a) phenotype • carotid atherosclerosis • B-mode ultrasound • end-stage renal disease

Patients with terminal renal insufficiency suffer from an increased morbidity and mortality related to atherosclerotic diseases.1,2 Although there undoubtedly are many contributory factors, several lipoprotein abnormalities have been suggested as a major cause of these diseases (for review, see Reference 3).

Recently, increased plasma concentrations of lipoprotein(a) [Lp(a)] have been described in end-stage renal disease (ESRD) patients.4,5 The distribution of Lp(a) plasma concentrations in the Caucasian population is highly skewed and extremely broad (range, <0.1 to >100 mg/dL),13 with mean and median concentrations of approximately 15 and 8 mg/dL, respectively.14 The apolipoprotein(a) [apo(a)] gene locus on chromosome 6q2.6-2.7 has been described as the major gene controlling Lp(a) plasma concentrations.15-17 The alleles at this highly polymorphic locus determine a protein size polymorphism of apo(a)13 that is due to varying numbers of kringle IV repeats in the apo(a) gene.15,17-19 An inverse relation exists between Lp(a) plasma concentration and the molecular weight of apo(a). Large isoforms (S3 or S4 in the original nomenclature) are expressed at low concentrations and small isoforms (S1, S2, B, or F) at high concentrations. In healthy Caucasians, about half of the variability in Lp(a) levels can be explained by this polymorphism.15-18,20

Several retrospective21-24 and two prospective25,26 case-control studies have found an association between high Lp(a) plasma levels and coronary heart disease (CHD) or myocardial infarction. This association was not confirmed by the Helsinki Heart Study27 or the Physicians’ Health Study.28 All studies relating Lp(a) levels to atherosclerotic risk may be biased by the nongenetic factors that affect Lp(a) concentrations. Recently, a multipopulation study demonstrated that the genetic apo(a) size polymorphism determines the risk for CHD through its effect on Lp(a) plasma concentrations in the general population.29,30 Several studies showed significantly elevated Lp(a) plasma concentrations in patients with symptomatic carotid atherosclerosis without ESRD31-33 and in hypercholesterolemic patients with carotid atherosclerotic plaques.34-36 Thickening of the arterial wall of the carotid arteries correlates with higher Lp(a) plasma concentrations.37,38 A recent study in hemodialysis patients described Lp(a) plasma concentrations as an independent factor contributing to the risk for atherosclerotic events.39 The aim of the present study was to investigate the predic-
tive power of the Lp(a) plasma concentration, apo(a) phenotype, and other atherosclerosis risk factors for the presence and degree of extracranial asymptomatic carotid atherosclerosis in ESRD patients.

**Methods**

**Patients**

All patients from two dialysis units (Innsbruck and Feldkirch) who were at least 25 years of age were invited to participate in the present study of atherosclerosis risk factor evaluation and B-mode ultrasound examination of the carotid arteries. Only approximately 6% of the patients refused. The study comprised 167 patients (91 men and 76 women) with a mean age of 52.8±13.4 (range, 25 to 80) years. At the time of ultrasound examination they had been undergoing hemodialysis for an average of 36.9±40.3 (range, 1 to 181) months. Treatment was performed three times weekly for an average of 4 hours. The cause of chronic renal failure was chronic glomerulonephritis in 59 patients (35%), diabetic nephropathy in 25 (15%), chronic pyelonephritis in 21 (13%), polyneuropathy in 15 (9%), and other causes in 12 (7%).

**Assessment of Carotid Atherosclerosis**

Findings were documented as a hard copy of these ultrasound images. Two experienced physicians performed the examination including the blinded evaluation of the presence or absence of atherosclerotic plaque at each site. Each arterial site was carefully scanned for the presence of plaque in anterior oblique, lateral, posterior oblique, and transverse scans. Carotid arteries were screened while the patient was in a supine position, with a pulsed Doppler (6.0-MHz frequency) for B-mode imaging and evaluation of vascular flow velocity was used. Two experienced physicians performed the examination and were unaware of patient history or laboratory findings. The cause of chronic renal failure was diabetes mellitus in 59 patients (35%), diabetic nephropathy in 25 (15%), chronic pyelonephritis in 21 (13%), and other causes in 21 (13%). The origin was unknown in 19 (12%) patients.

**Risk Factor Evaluation**

Evaluation of some risk factors (hypertension, diabetes mellitus) was based on multiple laboratory measurements at various times, as all examined patients were under observation for a long period because of the chronic renal insufficiency. Patients were classified as hypertensive when the blood pressure was greater than 95 mm Hg diastolic and/or greater than 140 mm Hg systolic (BP), and they were being treated with antihypertensive medication. Patients were considered diabetic if they were being treated for diabetes with oral hypoglycemic agents or insulin, and/or fasting glucose level was greater than 140 mg/dL. Because many of the patients had stopped smoking only recently, we decided to calculate in the univariate analysis only the rate of smokers and never-smokers. Body mass index was calculated (weight divided by height squared) as an indicator of obesity. A previous myocardial infarction or cerebrovascular accident as well as angina pectoris was self-reported and documented in the patient history.

**Assessment of Carotid Atherosclerosis**

Commercially available instrumentation (a Prisma Diasonics) and Sonolayer SA 270A (Toshiba) with a 7.5-MHz linear-array probe including the pulsed Doppler with 6.0-MHz frequency) for B-mode imaging and evaluation of vascular flow velocity was used. Two experienced physicians performed the examination and were unaware of patient history or laboratory findings. The carotid arteries were screened while the patient was in a supine position with the neck extended; vessels were examined using anterior oblique, lateral, posterior oblique, and transverse scans. Evaluation included eight different arterial sites: the common, internal, and external carotid arteries and the carotid bifurcation on each side. Each arterial site was carefully scanned for the occurrence of plaques. As previously described, we decided a priori to define plaque as a localized thickening of the vessel wall exceeding 2 mm with protrusion into the lumen. To minimize the variation introduced by intraobserver and interobserver differences, plaque at each site was defined as present or absent, independent of number, extension, and structure. All measurements were performed from "frozen" images at the end of diastole. Findings were documented as a hard copy of these images using a videoprinter.

**Laboratory Procedures**

Baseline values of all measured parameters were obtained from EDTA-plasma taken after a 12-hour overnight fast before dialysis. After low-speed centrifugation, samples were frozen and kept at −80°C pending analysis. Lp(a) quantification was performed with a double-antibody enzyme-linked immunosorbent assay (ELISA) using an affinity-purified polyclonal rabbit anti-apo(a) antibody for coating and the horseradish peroxidase–conjugated monoclonal antibody 1A2 for detection. This antibody does not cross-react with plasminogen. Lp(a)-positive serum with an intermediate size of apo(a) (S2S3) from Immuno served as a standard. Lp(a) concentrations were expressed as total Lp(a) lipoprotein mass, ignoring the presence of small amounts of "free" apo(a). When nonultracentrifugal methods are used, the percentage of "free" apo(a) in plasma has been determined as being less than 5%. Apo(a) phenotyping was performed with sodium dodecyl sulfate–polyacrylamide gel electrophoresis of plasma under reducing conditions followed by immunoblotting using the monoclonal antibody 1A2 for the detection of apo(a) phenotypes. Isolmers that did not exactly comigrate with the standards were categorized with the closest respective isoform. Of the patients, 91% showed at least one isoform, and the frequency of null types did not differ between patients with and without plaques (8.3% versus 10.2%). There was no difference in the frequency of double-band apo(a) phenotypes between these two patient groups (25.9% versus 25.4%). ApoB plasma concentrations were measured with a double-antibody ELISA using the same affinity-purified polyclonal antibody against apoB for coating and in a horseradish-labeled format for detection. ApoA-I concentrations were measured with a commercially available electroimmunodiffusion assay (Immuno). Plasma concentrations of total and high-density lipoprotein cholesterol and triglycerides were determined using commercially available kits from Boehringer Mannheim. Low-density lipoprotein was calculated with the Friedewald formula.
one of the eight arterial sites examined. When we divided patients into two groups according to the presence or absence of plaques and applied univariate statistical analysis, the group with plaques was significantly older (58.3 versus 42.0 years, \( P < .001 \)) and had a higher frequency of angina pectoris or history of previous myocardial infarction or cerebrovascular accident (Table 1). Moreover, this group had significantly higher Lp(a) plasma concentrations (29.3±31.0 versus 19.7±25.7 mg/dL, \( P < .05 \)). Patients were further dichotomized into two groups according to the presence (LMW group) or absence (HMW group) of LMW apo(a) isoforms (see "Methods"). The patient group with plaques included significantly more patients with LMW isoforms than the plaque-free group (26.9% versus 8.5%, \( P < .005 \)). This difference is mainly caused by a higher frequency of S2 isoforms (Fig 1). No other lipoprotein parameters differed significantly between the two patient groups. The prevalence of plaques was also independent of dialysis duration, sex, diabetes mellitus, hypertension, or smoking status.

The stepwise logistic regression analysis was applied to predict the plaque status (presence or absence of plaques in at least one of the eight arterial sites). The only significant predictors were age and the apo(a) phenotype (Table 2). In patients with LMW apo(a) phenotypes the estimated risk for plaques was 4.29 times higher (95% confidence interval, 1.26 to 14.56) than in those with HMW types (\( P < .02 \)).

### Results

#### Risk Factors for the Presence of Atherosclerotic Carotid Plaques in ESRD Patients

In this study 167 patients with ESRD were evaluated by B-mode ultrasonography. Of these patients, 108 (65%) showed atherosclerotic plaques at a minimum of one of the eight arterial sites examined. When we divided patients into two groups according to the presence or absence of plaques and applied univariate statistical analysis, the group with plaques was significantly older (58.3 versus 42.0 years, \( P < .001 \)) and had a higher frequency of angina pectoris or history of previous myocardial infarction or cerebrovascular accident (Table 1). Moreover, this group had significantly higher Lp(a) plasma concentrations (29.3±31.0 versus 19.7±25.7 mg/dL, \( P < .05 \)). Patients were further dichotomized into two groups according to the presence (LMW group) or absence (HMW group) of LMW apo(a) isoforms (see "Methods"). The patient group with plaques included significantly more patients with LMW isoforms than the plaque-free group (26.9% versus 8.5%, \( P < .005 \)). This difference is mainly caused by a higher frequency of S2 isoforms (Fig 1). No other lipoprotein parameters differed significantly between the two patient groups. The prevalence of plaques was also independent of dialysis duration, sex, diabetes mellitus, hypertension, or smoking status.

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#### Relation of Risk Factors to the Degree of Atherosclerosis

Next we analyzed whether Lp(a) plasma concentrations, apo(a) type, or both correlate with the degree of atherosclerosis. Lp(a) plasma concentration increased

### Table 1. Plaque Prevalence and Univariate Comparison of Lipoprotein(a) Concentrations, Apolipoprotein(a) Phenotypes, Lipid and Apolipoprotein Levels, and Other Common Risk Factors in ESRD Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Present (n=108)</th>
<th>Absent (n=59)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58.3±9.8</td>
<td>42.0±12.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Angina pectoris, %</td>
<td>33.7</td>
<td>9.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Previous myocardial infarction, %</td>
<td>13.9</td>
<td>0</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>LMW apo(a) types, %</td>
<td>26.9</td>
<td>8.5</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Lp(a), mg/dL</td>
<td>29.3±31.0</td>
<td>19.7±25.7</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Previous cerebrovascular accident, %</td>
<td>16.0</td>
<td>3.4</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.0±4.01</td>
<td>22.7±4.04</td>
<td>.058</td>
</tr>
<tr>
<td>ApoA-I, mg/dL</td>
<td>117.7±26.7</td>
<td>126.2±29.1</td>
<td>.071</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>80.2</td>
<td>69.6</td>
<td>.14</td>
</tr>
<tr>
<td>ApoB, mg/dL</td>
<td>107.8±37.0</td>
<td>100.6±35.3</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.92±1.47</td>
<td>4.75±1.42</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>0.93±0.47</td>
<td>0.92±0.31</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>2.00±1.63</td>
<td>1.84±1.26</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.03±1.13</td>
<td>3.09±1.25</td>
<td>NS</td>
</tr>
<tr>
<td>Months of dialysis</td>
<td>36.5±40.7</td>
<td>37.7±39.9</td>
<td>NS</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>52.8</td>
<td>57.6</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>22.2</td>
<td>18.6</td>
<td>NS</td>
</tr>
<tr>
<td>Smokers/never-smokers*, %</td>
<td>42/58</td>
<td>39/61</td>
<td>NS</td>
</tr>
</tbody>
</table>

LMW indicates low-molecular-weight; LMW apo(a) includes all subjects with either of the isoforms F, B, S1, or S2.
Number of Affected Arterial Sites

**FIG 2.** Bar graph shows number of plaque-affected arterial sites in accordance with mean lipoprotein(a) [Lp(a)] plasma concentrations (ANOVA, P<.005). Significantly with the number of affected arterial sites, from 19.7 mg/dL in patients without plaques to 40.1 mg/dL in patients with seven or eight affected sites (P=.005) (Fig 2). Apo(a) type was also related to the severity of carotid atherosclerosis. In patients with LMW phenotypes, significantly more arterial sites were affected by atherosclerotic plaques than in patients with HMW phenotypes (mean, 3.62 versus 2.08, P<.001) (Fig 3). When patients were divided into two age groups (separated at the median value of 54 years), this difference was significant only in the younger group (2.21 versus 0.81, P<.005). In Fig 4 the number of affected arterial sites is plotted against age for LMW and HMW phenotypes separately. This demonstrated that patients with LMW phenotypes were on average 10 years younger than patients with HMW phenotypes with the same degree of atherosclerosis of the carotid vessels. As a corollary, patients with LMW phenotypes had on average more than one additional affected arterial site compared with patients of the same age with HMW phenotypes.

We then applied multivariate analysis to determine the independence of identified risk factors. In the total group, age, angina pectoris, and the apo(a) phenotype were the only significant predictors of the number of affected arterial sites. In the younger patient group the history of previous myocardial infarction was a predictor in addition to age and apo(a) phenotype. In the elderly patient group only the occurrence of angina pectoris was significantly predictive (Table 3).

**Discussion**

In recent years Lp(a) has been proposed as an independent risk factor for CHD in different ethnic groups,25,26,29,30 but this view has recently been challenged.27,28 Patients with ESRD have an increased risk for CHD.1,2 We and others recently demonstrated that Lp(a) is elevated in ESRD patients.3 This elevation in Lp(a) is not caused by differences in apo(a) isoform frequencies.7 Rather, we observed that only patients with HMW isoforms had significantly elevated plasma Lp(a) levels, whereas patients with LMW isoforms had levels nearly identical to those in isoform-matched control subjects. In keeping with this we observed a rapid decrease of Lp(a) plasma levels after renal transplantation only in patients with HMW apo(a) phenotypes.46 This suggests a strong nongenetic effect on Lp(a) levels in patients with LMW but not HMW isoforms. These findings may obscure the predictive value of Lp(a) levels in ESRD patients.

The present study investigated the atherosclerotic status of the extracranial carotid arteries in a large group of patients with ESRD and related it to Lp(a) concentrations and apo(a) type. To define carotid atherosclerosis we applied B-mode ultrasonography. Three relevant observations were made: (1) the plaque-affected group had significantly higher Lp(a) plasma concentrations and included significantly more patients with LMW apo(a) phenotypes; (2) patients with LMW apo(a) isoforms had a significantly higher degree of
The age difference between patients with LMW and HMW phenotypes with the same degree of carotid atherosclerosis and risk factors such as hypertension, diabetes, and hypercholesterolemia was not comparable.

Numerous studies have shown that atherosclerotic disease in the carotid system reflects to a high degree the atherosclerotic situation of the coronary arteries. In different patient groups a relation between atherosclerotic disease defined by a history of angina on effort, physician-diagnosed heart attack, transient ischemic attack or stroke, or intermittent claudication, in whom apo(a) phenotype was a predictor of disease, was observed. However, in our study group, apo(a) type was not a predictor of disease, irrespective of the presence or absence of Lp(a) concentration in the statistical model. 

In the ARIC Study, the traditional atherosclerosis risk factors were not predictive in our patient group or yielded controversial results. This situation calls for predictive markers not influenced by the disease state. As shown here, this requirement is met by the genetically determined apo(a) phenotype. In the stepwise and multivariate regression analyses, besides age apo(a) type was not an independent predictor of plaque status and degree of atherosclerosis in the carotid arteries. Inclusion or exclusion of Lp(a) plasma concentrations in the statistical model had no influence on the predictive power of the apo(a) phenotype. Even when phenotype was omitted from the model, Lp(a) level reached no significance. This is in contrast to the ARIC Study, which is investigating preclinical extracranial carotid atherosclerosis (defined as arterial wall thickness) by B-mode ultrasonography. Lp(a) plasma concentration was found to be an independent predictor of case-control status, whereas apo(a) phenotype was not, irrespective of the presence or absence of Lp(a) concentration in the statistical model. There is, however, a profound difference in the selection of patients for the two studies. The cases in the ARIC Study represent a highly selected group. Exclusion criteria for the case group were evidence of symptomatic cardiovascular or cerebrovascular disease defined by a history of angina on effort, physician-diagnosed heart attack, transient ischemic attack or stroke, or intermittent claudication. Therefore, all patients with previous atherosclerotic complications were excluded from the study. In this excluded group higher Lp(a) plasma concentrations and a higher frequency of LMW phenotypes may have been present. Our study group included all patients with ESRD, and no patients were excluded because of previous disease as in the ARIC Study. Therefore, the two studies are not comparable. 

Our results seem to be in contrast to the situation in non-ESRD patients with CHD or intermittent claudication, in whom apo(a) phenotype was a predictor of disease only when Lp(a) levels were omitted from the model. Lp(a) level reached no significance.
Multivariate model. This had been taken as evidence that the effect of the apo(a) gene on disease is mediated primarily by Lp(a) level and not directly by the apo(a) type. At first glance the postulated relation between apo(a) type, Lp(a) level, and atherosclerosis seems not to apply to ESRD patients, which is counterintuitive. Here, apo(a) types and not Lp(a) levels appear as a significant predictor of atherosclerotic disease. We believe, however, that the general relation between apo(a) type, Lp(a) concentration, and atherosclerosis is the same in ESRD patients as in the general population but that it is masked by isoform-specific changes in Lp(a) levels occurring with time in ESRD patients. To explain our findings we propose a model that considers the atherogenic effect of Lp(a) as a function of dosage and duration of exposure (Fig 5): Patients with LMW phenotypes have on average higher Lp(a) plasma levels during their entire life. Patients with HMW phenotypes experience high Lp(a) levels only with the development of their chronic renal insufficiency. Even then, their mean Lp(a) levels are lower than in patients with LMW phenotypes. Therefore, patients with LMW phenotypes may have a more preinjured vascular system at the start of renal insufficiency than do patients with HMW phenotypes. The fact that premature may be important was suggested in a recent study demonstrating that atherosclerotic disease affects long-term survival only in those dialysis patients with preexisting atherosclerosis. On the basis of this preinjury, patients with LMW phenotypes may develop a rapidly progressing atherosclerosis. This may explain why apo(a) phenotype, which reflects preinjury Lp(a) level, is an excellent predictor of atherosclerosis in ESRD patients. When divided into age groups, apo(a) type was a significant predictor in young patients (<55 years) only. In elderly patients the predictive power was lost (Table 3). The reason for this is unclear, but numerous patients with LMW phenotypes and high Lp(a) plasma concentrations may have reached a degree of atherosclerosis that is inconsistent with life. Bias against high-risk patients may have contributed to these results. Many studies have shown that atherosclerotic complications are still the major cause of morbidity and mortality in hemodialysis patients. We conclude from our study that, besides age, variation in the apo(a) gene is related to the risk for atherosclerotic vascular disease in these patients. Studies that fail to find such a relation when Lp(a) levels are analyzed therefore should be considered with caution. It must be emphasized that Lp(a) level in contrast to apo(a) type is not an unchangeable genetic trait. In the present study Lp(a) levels were less predictive than was apo(a) type because of the confounding effect of renal disease on Lp(a) plasma concentrations. Such effects may also partly explain the negative results obtained in studies that related Lp(a) level and not apo(a) type to atherosclerotic vascular disease.

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