The apolipoprotein(a) size polymorphism is associated with nephrotic syndrome

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The apolipoprotein(a) size polymorphism is associated with nephrotic syndrome.

Background. The atherogenic serum lipoprotein(a) [Lp(a)] is significantly elevated in patients with nephrotic syndrome. The underlying mechanism for this elevation is poorly understood.

Methods. We investigated in 207 patients with nondiabetic nephrotic syndrome and 274 controls whether the apolipoprotein(a) [apo(a)] kringle-IV repeat polymorphism explains the elevated Lp(a) levels in these patients.

Results. Patients showed a tremendous elevation of Lp(a) concentrations when compared to controls (mean 60.4 vs. 20.0 mg/dL and median 29.8 vs. 6.4 mg/dL, \( P < 0.0001 \)). Primary and secondary causes contributed to this elevation. The primary causes became apparent by a markedly elevated number of low-molecular-weight apo(a) phenotypes which are usually associated with high Lp(a) levels. This frequency was 35.7% in patients compared to only 24.8% in controls (\( P = 0.009 \)). In addition, secondary causes by the pathogenetic mechanisms of the nephrotic syndrome itself resulted in a different increase of Lp(a) in the various apo(a) isoform groups. Based on the measured Lp(a) concentrations in each subject, we calculated separately the Lp(a) concentrations arising from the two expressed isoforms by estimating the relative proportion of the two serum isoforms in the sodium dodecyl sulfate (SDS) agarose gel electrophoresis. Low-molecular-weight isoforms were associated with 40% to 75% elevated Lp(a) concentrations when compared to matched isoforms from controls. High-molecular-weight apo(a) isoforms showed 100% to 500% elevated Lp(a) levels compared to matched isoforms from controls. The severity of the nephrotic syndrome as well as the degree of renal impairment did not influence the Lp(a) concentrations.

Key words: Lp(a), apo(a) polymorphism, nephrotic syndrome, genetics, atherosclerosis.

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Conclusion. The tremendously increased Lp(a) levels in nephrotic syndrome are caused by primary genetic as well as disease-related mechanisms.

There is a large body of evidence that high lipoprotein(a) [Lp(a)] levels are a risk factor for cardiovascular disease in the general population [1, 2]. This lipoprotein shows a high degree of genetic determination. Briefly, a size polymorphism at the apolipoprotein(a) [apo(a)] gene locus [3] originating from a varying number of kringle-IV (K-IV) repeats [4, 5] is the most important determinant of Lp(a) levels that exhibit marked interindividual variation by more than 1000-fold. Subjects who express a low number of K-IV repeats [low-molecular-weight (LMW) apo(a) phenotypes] show on average markedly higher Lp(a) concentrations than those with a high number of K-IV repeats [high molecular weight (HMW) apo(a) phenotypes] who usually have low Lp(a) concentrations. Recent studies that considered Lp(a) concentrations as well as the apo(a) size polymorphism found that the apo(a) size polymorphism determines the atherothrombotic risk not only by its allelic control of Lp(a) concentrations but also per se. Identical Lp(a) levels going in hand with either small or large apo(a) isoforms are associated with different risk. Elevated Lp(a) levels showed a higher risk for carotid stenosis [6] or coronary artery disease [7] if coinciding with small isoforms than those coinciding with large isoforms.

Numerous studies have reported that Lp(a) levels are significantly elevated in patients with nephrotic syndrome [8–18]. However, it was never systematically investigated whether and how the apo(a) kringle-IV repeat polymorphism contributes to this increase. We therefore compared the apo(a) phenotype distribution in patients and controls and considered the relative expression of the two
Table 1. Characteristics of patients with nephrotic syndrome and age- and gender-matched controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls (N = 274)</th>
<th>Nephrotic syndrome (N = 207)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years</td>
<td>44.6 ± 12.4</td>
<td>43.5 ± 16.0</td>
</tr>
<tr>
<td>Gender, females/males</td>
<td>97/177</td>
<td>76/131</td>
</tr>
<tr>
<td>Body mass index</td>
<td>26.1 ± 3.7</td>
<td>25.1 ± 3.9*</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>101 ± 27</td>
<td>73 ± 40</td>
</tr>
<tr>
<td>(mL/min)</td>
<td>[84, 97, 113]</td>
<td>[40, 68, 98]b</td>
</tr>
<tr>
<td>Creatinine mg/dL</td>
<td>0.9 ± 0.17</td>
<td>3.83 ± 1.38b</td>
</tr>
<tr>
<td>Urea mg/dL</td>
<td>31 ± 8</td>
<td>55 ± 35b</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>—</td>
<td>7.1 ± 3.6</td>
</tr>
<tr>
<td>g/24 hours/1.73 m²</td>
<td>[4.4, 6.0, 8.6]</td>
<td></td>
</tr>
<tr>
<td>Serum albumin g/dL</td>
<td>4.88 ± 0.47</td>
<td>3.01 ± 0.96b</td>
</tr>
<tr>
<td>Total protein g/dL</td>
<td>7.0 ± 0.4</td>
<td>5.9 ± 1.1b</td>
</tr>
<tr>
<td>Primary cause of renal disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Membranous nephropathy</td>
<td>51 (24.6%)</td>
<td></td>
</tr>
<tr>
<td>Minimal change nephropathy</td>
<td>34 (16.4%)</td>
<td></td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>30 (14.5%)</td>
<td></td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>30 (14.5%)</td>
<td></td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis</td>
<td>18 (8.7%)</td>
<td></td>
</tr>
<tr>
<td>Crescentic glomerulonephritis</td>
<td>5 (2.4%)</td>
<td></td>
</tr>
<tr>
<td>Nephrosclerosis</td>
<td>5 (2.4%)</td>
<td></td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>9 (4.3%)</td>
<td></td>
</tr>
<tr>
<td>Lupus nephritis</td>
<td>10 (4.8%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>15 (7.4%)</td>
<td></td>
</tr>
</tbody>
</table>

*Data are mean ± SD and [25th percentile, median, 75th percentile] where appropriate; aP < 0.001; and bP < 0.01 for comparison with controls.

Methods

Patients

The 207 patients with nephrotic syndrome included in this study came from three centers: (1) 155 (75%) were recruited at the Department of Nephrology at the University of Innsbruck during a period of 11 years (1992 to 2002); (2) 37 patients were recruited in the Munich University Hospital and in outpatient clinics in Bavaria; and (3) 15 patients were recruited at the Department of Nephrology and Rheumatology at the University of Düsseldorf. The primary cause of renal disease was diagnosed by kidney biopsy and nephrotic syndrome was defined by a 24-hours proteinuria with more than 3.5 g/24 hours. Patients with diabetic nephropathy were excluded from the study since they usually do not undergo a kidney biopsy in our centers. All patients were Caucasians and were not in need of renal replacement therapy.

Table 1 shows the clinical characteristics of patients, including the histologic diagnosis of the primary cause of renal disease.

Patients were compared to 274 age- and gender-matched controls of the same ethnic origin without renal impairment or liver disease who were recruited in 1997 from one of the PROCAM study centers [19].

Laboratory procedures

Serum and ethylenediaminetetraacetic acid (EDTA) plasma were taken after a 12-hour overnight fast. After low-speed centrifugation, samples were frozen and kept at −80°C prior to analysis [20]. Samples were measured in batches to avoid major effects of long-term storage on the measured Lp(a) levels. We calculated the creatinine clearance using the formula of Cockcroft and Gault [21].

Measurement of serum albumin, Lp(a), and apo(a) phenotyping were performed in batches centrally in a single laboratory to avoid interlaboratory differences in measurements. Serum albumin concentrations were measured by the brom-cresol green method kit from Roche (Mannheim, Germany). Lp(a) quantification was performed as described in detail [20] with a double-antibody enzyme-linked immunosorbent assay (ELISA) using an affinity-purified polyclonal apo(a) antibody for coating and the horseradish peroxidase-conjugated monoclonal 1A2 for detection. An Lp(a) positive serum from Technoclone (Vienna, Austria) with the same apo(a) isoforms served as standard throughout the study. Each sample was analyzed in duplicate, and intra- and interassay coefficients of variation were 2.7% and 6%, respectively. Apo(a) phenotyping was performed by sodium dodecyl sulfate (SDS)-agarose gel electrophoresis under reducing conditions as outlined with slight modifications [22]. Fifty nanograms of Lp(a) were applied to the gel in case of serum Lp(a) concentrations above 4 mg/dL. In case of lower concentrations, a fixed volume of 1.5 µL serum was applied to the gel. Electrophoresis was followed by immunoblotting [3] using the monoclonal antibody 1A2 for detection of apo(a) isoforms.

Calculation of the Lp(a) concentration derived from each apo(a) isoforms

In subjects expressing two apo(a) isoforms, we estimated the percentage of the two isoforms by densitometric scanning of the apo(a) bands of the immunoblots from SDS agarose gel electrophoresis. We used the Lp(a) concentrations measured by ELISA to calculate the isoform-specific amount of Lp(a) derived from each isoform by using these relative estimates [23]. For example, when an individual with 21 and 33 K-IV repeats had an Lp(a) serum concentration of 40 mg/dL measured by ELISA, and the 21 K-IV isoform accounted for 85% of the staining in the SDS agarose gel electrophoresis, we calculated the Lp(a) concentration originating from this isoform to be 34 mg/dL (40·0.85). The isoform with 33 K-IV repeats accounted for the remaining 6 mg/dL. The whole Lp(a) isoforms to calculate the apo(a) isoform-specific effects on Lp(a) levels.

METHODS

Patients

The 207 patients with nephrotic syndrome included in this study came from three centers: (1) 155 (75%) were recruited at the Department of Nephrology at the University of Innsbruck during a period of 11 years (1992 to 2002); (2) 37 patients were recruited in the Munich University Hospital and in outpatient clinics in Bavaria; and (3) 15 patients were recruited at the Department of Nephrology and Rheumatology at the University of Düsseldorf. The primary cause of renal disease was diagnosed by kidney biopsy and nephrotic syndrome was defined by a 24-hours proteinuria with more than 3.5 g/24 hours. Patients with diabetic nephropathy were excluded from the study since they usually do not undergo a kidney biopsy in our centers. All patients were Caucasians and were not in need of renal replacement therapy.

Table 1 shows the clinical characteristics of patients, including the histologic diagnosis of the primary cause of renal disease.
concentration counted for the expressed isoform in case a subject showed only one apo(a) band.

**Statistical procedures**

Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) for Windows 11.0. Univariate comparisons of continuous variables between controls and nephrotic patients were done by unpaired t test or the nonparametric Wilcoxon rank sum test in case of nonnormally distributed variables. Lp(a) levels between more than two groups were compared by the Kruskal-Wallis test. Dichotomized variables were compared using Pearson’s χ² test or the Likelihood ratio χ² test. The Spearman correlation test was used to correlate Lp(a) with proteinuria, creatinine clearance, and serum test.

Because of the high number of detectable apo(a) isoforms (>30), many phenotypes were represented only in low numbers. To account for this problem, we decided a priori to combine apo(a) isoforms in six groups according to the molecular weight of the smaller apo(a) isoforms in order to have sufficient sample sizes in each category. Furthermore, we divided apo(a) phenotypes into two subgroups according to the molecular weight of the smaller apo(a) isoforms, as done in previous works by our and other groups [6, 24–31]. The LMW group included all subjects with at least one apo(a) isoform with 11 to 22 K-IV repeats; the HMW group comprised all subjects having only isoforms with more than 22 K-IV repeats. In a subanalysis, however, we considered the effect of the second apo(a) isoform, if expressed, as described above.

**RESULTS**

**Comparison of nephrotic patients and controls**

Table 1 shows the demographic and laboratory characteristics of the investigated nephrotic patients and the age- and gender-matched healthy controls. Patients lost on average 7.1 g proteins per day in urine and showed an impaired creatinine clearance of 66 mL/min/1.73 m². As a consequence of the nephrotic syndrome, patients showed markedly decreased serum albumin concentrations when compared to controls (3.10 vs. 4.88 g/dL, P < 0.001). Most patients underwent biopsy when kidney function was still relatively well preserved (creatinine clearance 73 ± 40 mL/min).

Patients with nephrotic syndrome showed a tremendous elevation of Lp(a) serum concentrations. The mean and median concentrations were three and five times higher, respectively, when compared to controls (mean 60.4 vs. 20.0 mg/dL and median 29.8 vs. 6.4 mg/dL, respectively) (Table 2). Figure 1 shows the frequency distribution of Lp(a) levels in the investigated groups.

<table>
<thead>
<tr>
<th>Table 2. Lipoprotein(a) [Lp(a)] serum concentrations and apolipoprotein(a) [apo(a)] size polymorphism in controls and patients with nephrotic syndrome</th>
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<tr>
<td></td>
</tr>
<tr>
<td>Lp(a) mg/dL; mean ± SD [25th percentile, median, 75th percentile]</td>
</tr>
<tr>
<td>Apo(a) alleles number; (%)ab</td>
</tr>
<tr>
<td>11–19 K-IV repeats</td>
</tr>
<tr>
<td>20–22 K-IV repeats</td>
</tr>
<tr>
<td>23–25 K-IV repeats</td>
</tr>
<tr>
<td>26–28 K-IV repeats</td>
</tr>
<tr>
<td>29–31 K-IV repeats</td>
</tr>
<tr>
<td>&gt;31 K-IV repeats</td>
</tr>
<tr>
<td>Apo(a) phenotypesc</td>
</tr>
<tr>
<td>Low-molecular-weight apo(a) phenotypes number; (%)</td>
</tr>
<tr>
<td>High-molecular-weight apo(a) phenotypes number; (%)</td>
</tr>
</tbody>
</table>

aP < 0.0001 by Wilcoxon rank sum test for comparison of Lp(a) serum concentrations between patients and controls.
bMantel-Haenszel test for linear association comparing the frequencies of apo(a) phenotypes between patients and controls; χ² = 6.96, df = 1, P = 0.008.
cPearson’s χ²-test comparing the frequencies of LMW apo(a) phenotypes between patients and controls; χ² = 6.77, df = 1, P = 0.009.

Similar to earlier control groups we observed about 60% of healthy subjects having Lp(a) levels below 10 mg/dL. In nephrotic patients only 25% of the patients showed such low levels. Instead, about 50% and 30% had Lp(a) levels above 30 and 70 mg/dL, respectively. This could only be observed in 18% and 8.4% of the controls, respectively.

In controls we observed the usual frequency of LMW apo(a) phenotypes as in earlier studies. Patients with nephrotic syndrome showed a markedly elevated number of LMW apo(a) phenotypes when compared to controls (35.7% vs. 24.8%, P = 0.009) (Table 2). This higher number of LMW apo(a) phenotypes was not caused by the preponderance of a single isoform but by an elevation in the frequency of all LMW apo(a) isoforms. Next, we investigated whether an association exists between

![Fig. 1. Frequency distribution of lipoprotein(a) [Lp(a)] serum concentrations in 207 patients with nephrotic syndrome and 274 healthy controls. Pearson’s χ² test P < 0.0001.](image-url)
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Fig. 2. Influence of proteinuria and renal function on lipoprotein(a) [Lp(a)] serum concentrations in patients with nephrotic syndrome. The 10th, 25th, 50th, 75th, and 90th percentile of Lp(a) serum concentrations in patients stratified by the medians of proteinuria and creatinine clearance. No significant differences between the four groups were observed (Kruskal-Wallis test, P = 0.59).

Lp(a) concentrations and/or apo(a) phenotypes on the one hand and the five most frequent causes of renal disease. We observed no differences in the Lp(a) levels or the frequency of LMW apo(a) phenotypes between these five groups (data not shown).

The severity of the nephrotic syndrome as well as the amount of renal impairment did not influence the Lp(a) concentrations. There were no significant differences in Lp(a) levels when patients were stratified by the medians of proteinuria and creatinine clearance (P = 0.59 by Kruskal-Wallis test) (Fig. 2). A negative correlation was observed between Lp(a) levels and serum total protein (r = −0.20, P = 0.005) and serum albumin (r = −0.17, P = 0.023).

We then analyzed whether the elevation of Lp(a) in nephrotic syndrome can be observed in all apo(a) isoform groups. Patients with LMW apo(a) phenotypes showed Lp(a) levels almost twice as high as controls with the same apo(a) phenotypes (mean ± SD; median 106.2 ± 115.2 mg/dL; 79.3 vs. 56.0 ± 47.4 mg/dL; 51.1 mg/dL, P = 0.002). The relative elevation of Lp(a) was much more pronounced in patients with HMW apo(a) phenotypes who showed on average fourfold higher Lp(a) levels (mean ± SD; median 34.9 ± 46.9 mg/dL; 17.7 vs. 8.2 ± 11.2 mg/dL; 4.2 mg/dL, P < 0.0001). The subgrouping into LMW and HMW apo(a) phenotypes in a given individual, however, is based on the apo(a) isoform with the lowest molecular weight. It ignores that many subjects with an LMW apo(a) phenotype have not only one LMW, but also one HMW apo(a) isoform. Therefore, we calculated based on the measured Lp(a) concentrations in each subject separately the Lp(a) concentrations arising from the two expressed isoforms by estimating the relative proportion of the two isoforms in the sodium dodecyl sulfate (SDS) agarose gel electrophoresis (see Methods section).

DISCUSSION

Patients with nephrotic syndrome have a significantly increased burden of coronary heart disease [32, 33]. The hyperlipidemic changes in these patients might contribute to this increased risk [34]. One of the most prominent changes of the lipoprotein metabolism is experienced by Lp(a): there is no other disease condition known which produces such an extensive increase in Lp(a) levels as the nephrotic syndrome [8–18]. We therefore investigated the changes of Lp(a) in these patients in more detail by apo(a) phenotyping and estimation of apo(a) isoform-derived Lp(a) concentrations.

Primary causes for increased Lp(a) concentrations

Surprisingly, we observed primary as well as secondary reasons to contribute to the three and five times higher mean and median Lp(a) levels, respectively. The primary
or genetic reasons became obvious when we looked at the apo(a) phenotype distribution between patients and controls. Patients showed a 1.5 times higher frequency of LMW apo(a) phenotypes than controls (35.7% vs. 24.8%, \(P = 0.009\)). The obtained results in nephrotic patients are in contrast to those in nonnephrotic renal disease patients as well as dialysis patients where increased Lp(a) levels were found to be caused solely by nongenetic disease-related mechanisms [23, 26, 29, 31, 35, 36]. We are aware that case control studies include the possibility of false positive results. However, a finding by chance is not very likely due to the large number of patients and controls we investigated. Furthermore, a spurious association is improbable, since we observed in the controls of the study at hand a very similar apo(a) phenotype distribution as in our earlier studies which used controls from the same geographic regions as our nephrotic patients [31, 35, 37].

Interestingly, our finding of differences in the frequency of LMW apo(a) phenotypes between patients and controls is supported by another data set. Paying closer attention to Table 4 of the study by Wanner et al [10], one can calculate a 1.6 times higher frequency of LMW apo(a) phenotypes in 60 nephrotic patients compared to 91 controls of that study.

If this higher frequency of LMW apo(a) phenotypes in nephrotic patients indeed holds true, we might speculate that high Lp(a) levels [besides high low-density lipoprotein (LDL) cholesterol levels] caused partially by a preponderance of LMW apo(a) phenotypes have an modulating effect on proteinuria by influencing the endothelial and glomerular function. Atherogenic lipoproteins such as LDL cholesterol or Lp(a), especially when oxidized, have pronounced effects on this system. They induce the formation of oxygen radicals in arteries, in glomeruli, and in juxtaglomerular cells, which results in an inhibition of nitric oxide-mediated vasodilatation [38], stimulation of renin release, and modulation of mesangial cell growth and apoptosis [39–42]. Amelioration of oxidative stress by the use of antioxidants prevents the induction of apoptosis [42, 43]. The Heymann nephritis as rat model of human membranous glomerulopathy, a frequent cause of nephrotic syndrome in humans, clearly shows that proteinuria in this model depends on the formation of radical oxygen species. Therapeutic application of oxygen radical scavengers drastically reduces proteinuria [44, 45]. In accordance, treatment of rats with Heymann nephritis as well as of humans suffering from membranous nephropathy with probucol, a potent inhibitor of lipid peroxidations, resulted in a reduction of proteinuria [46, 47]. The treatment with lovastatin had no effect on proteinuria although it showed a similar LDL cholesterol-lowering effect [47]. Therefore, the specific antiproteinuric effect of probucol seems to be independent of the lipid-lowering effect.

An influence of high Lp(a) levels on the progression of a glomerular disease in terms of nephrotic or non-nephrotic course is in line with two observations. First, in a recent study, high Lp(a) levels predicted the future relapse in children with steroid-sensitive nephrotic syndrome [18]. Second, in patients with nonnephrotic glomerulonephritis who do not show these tremendous elevations of Lp(a), we observed an apo(a) phenotype frequency distribution that is not different from controls [23]. Until now, only one prospective study investigated the influence of Lp(a) on the progression of renal disease which was negative [48]. This study, however, was small and only 17 of the 73 patients showed a proteinuria above 3 g/24 hours.

**Secondary causes for increased Lp(a) concentrations**

The secondary causes for an Lp(a) elevation in nephrotic syndrome became apparent when we found that Lp(a) was elevated in all apo(a) isoform classes when compared to the isoform-matched controls. In principle, this was already observed in a smaller study by Wanner et al [10]. The stratification of apo(a) phenotypes in that study, however, was based on the apo(a) isoform with the most intensive immunostaining. Since the sensitivity of the apo(a) phenotyping methods significantly improved during the last 10 years, we used in the present study the immunostaining of the apo(a) bands to calculate the proportion of Lp(a) deriving from each apo(a) isoform. This analytic method diminishes the problem of categorizing patients into groups of apo(a) phenotypes depending on the smaller apo(a) isoform or on the isoform which was expressed more dominantly. Using this method, we herein clearly demonstrate that Lp(a) is elevated in all apo(a) isoform groups but show that HMW apo(a) isoforms are associated with a more pronounced relative elevation of Lp(a) than LMW apo(a) isoforms when compared to isoform-matched controls. This is in contrast to nonnephrotic patients with mild and moderate renal insufficiency who show an apo(a) isoform-specific elevation of Lp(a) meaning that Lp(a) raises only in HMW apo(a) isoforms but not in LMW isoforms [23]. This interesting but until now unexplained phenomenon was already described earlier for hemodialysis patients by our and other groups [26, 29, 31, 35, 36]. Continuous ambulatory peritoneal dialysis (CAPD) patients show an extent of Lp(a) elevation in between of hemodialysis and nephrotic patients. Besides an elevation of Lp(a) in HMW apo(a) phenotypes CAPD patients with LMW apo(a) types show a tendency to elevated Lp(a) levels [31]. Taken together, it seems that the large amount of protein loss either by dialysate in CAPD patients or in urine in nephrotic patients results in an increased production of Lp(a) by the liver. This was indeed observed in recent turnover studies in patients with nephrotic syndrome which revealed...
a similar fractional catabolic rate of Lp(a) in five patients and five controls which suggested that differences in Lp(a) levels are caused by differences in synthesis rate [49]. The number of studied patients did not allow to investigate the turnover stratified for apo(a) phenotypes. The data from the present study, however, suggest that even when Lp(a) is elevated in all apo(a) isoform groups, we can observe again that HMW apo(a) isoforms show a higher relative (but not absolute) increase in Lp(a) levels than LWM apo(a) isoforms.

Similar to other studies [8, 10, 13] we did not find any correlation between Lp(a) and the amount of protein loss or kidney function. The urinary protein loss in nephrotic syndrome seems to be already above a certain threshold where it has a linear influence on Lp(a) levels. Above this threshold neither the amount of proteinuria nor of renal function was associated with a further increase in Lp(a) concentrations. Obviously, the increased hepatic synthesis of lipoproteins, including Lp(a), dominates the serum levels independently of these two parameters. Lp(a) was only correlated with total serum protein and serum albumin. Hypoalbuminemia might result in a reduced oncotic pressure, which, in turn, stimulates the hepatic synthesis of albumin and other proteins including lipoproteins and Lp(a) [50, 51].

CONCLUSION

We show in this investigation that primary (genetic) and secondary causes are responsible for the extremely elevated Lp(a) levels in nephrotic syndrome. The preponderance of LMW apo(a) phenotypes let us speculate that Lp(a) has an influence on nephrotic proteinuria.

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