Lipoprotein(a) in the Nephrotic Syndrome: Molecular Analysis of Lipoprotein(a) and Apolipoprotein(a) Fragments in Plasma and Urine

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Abstract. Plasma levels of lipoprotein(a) (Lp(a)), an atherogenic particle, are elevated in kidney disease, which suggests a role of this organ in the metabolism of Lp(a). Additional evidence for a role of the kidney in the clearance of Lp(a) is provided by the fact that circulating N-terminal fragments of apolipoprotein(a) (apo(a)) are processed and eliminated by the renal route. To further understand the mechanism underlying such renal excretion, the levels of apo(a) fragments in plasma and urine relative to plasma Lp(a) levels were determined in patients with nephrotic syndrome (n = 15). In plasma, the absolute (24.7 ± 20.4 versus 2.16 ± 2.99 µg/ml, P < 0.0001) as well as the relative amounts of apo(a) fragments (4.6 ± 3.4% versus 2.1 ± 3.3% of total Lp(a), P < 0.0001) were significantly elevated in nephrotic patients compared with a control, normolipidemic population. In addition, urinary apo(a) excretion in patients with nephrotic syndrome was markedly elevated compared with that in control subjects (578 ± 622 versus 27.7 ± 44 ng/ml per mg creatinine, P < 0.001). However, the fractional catabolic rates of apo(a) fragments were similar in both groups (0.68 ± 0.67% and 0.62 ± 0.47% in nephrotic and control subjects, respectively), suggesting that increased plasma concentrations of apo(a) fragments in nephrotic subjects are more dependent on the rate of synthesis rather than on the catabolic rate. Molecular analysis of apo(a) immunoreactive material in urine revealed that the patterns of apo(a) fragments in nephrotic patients were distinct from those of control subjects. Full-length apo(a), large N-terminal apo(a) fragments similar in size to those present in plasma, as well as C-terminal fragments of apo(a) were detected in urine from nephrotic patients but not in urine from controls. All of these apo(a) forms were in addition to smaller N-terminal apo(a) fragments present in normal urine. This study also demonstrated the presence of Lp(a) in urine from nephrotic patients by ultracentrifugal fractionation. These data suggest that in nephrotic syndrome, Lp(a) and large fragments of apo(a) are passively filtered by the kidney through the glomerulus, whereas smaller apo(a) fragments are secreted into the urine.

Lipoprotein(a) (Lp(a)) has been identified as an independent, inherited risk factor for atherosclerotic cardiovascular disease (reviewed in reference (1). Lp(a) consists of an LDL-like particle to which apolipoprotein(a) (apo(a)) is linked by a disulfide bond. Protein sequencing and cDNA cloning revealed that apo(a) is highly homologous to plasminogen (2). Apo(a) consists of several tandemly repeated copies of kringle IV-like repeats (KIV), one copy of kringle V, and an inactive protease-like domain. The number of KIV varies between 12 and 51 and is responsible for the marked degree of size polymorphism of apo(a) (3). The plasma Lp(a) concentration varies over a

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>1000-fold range among individuals, and is partly determined by apo(a) size, to which it is inversely related.

Lp(a) that circulates in plasma originates from the liver (4). However, the mechanism by which Lp(a) is cleared from the circulation is not known. A role for the kidney in Lp(a) catabolism was first suggested by studies showing that patients with renal failure displayed increased plasma Lp(a) concentrations (5). Subsequently, Oida et al. (6) reported that fragments of apo(a) were present in human urine and that the urinary excretion of apo(a) was decreased in patients with renal dysfunction. Clearance studies in mice suggested that urinary apo(a) fragments are the product of larger fragments present in plasma that are processed and actively transported through the kidney (7). Consistent with this scenario is the observation that plasma levels of apo(a) fragments are elevated in subjects with end-stage renal disease (8,9). Finally, Kronenberg et al. (10) have shown that Lp(a) levels are lower in renal veins compared with renal arteries, thereby indicating that a fraction of Lp(a) is catabolized in the kidney.

To further understand the mechanisms underlying the catab-
olism of Lp(a) by the kidney, we examined the level and molecular composition of these fragments in the plasma and urine of patients with nephrotic syndrome and in a control group of normocholesterolemic subjects. The pattern of urinary apo(a) fragments was markedly different between patients and control subjects. For the first time, we detected the presence of both Lp(a) and C-terminal fragments of apo(a) in the urine of nephrotic patients, in addition to N-terminal fragments. We equally observed elevated plasma and urine levels of apo(a) fragments in nephrotic patients.

Materials and Methods

Subjects

We studied 15 non-diabetic subjects (seven men, eight women), presenting a primary nephrotic syndrome (Table 1). The histologic findings in these patients as determined by renal biopsy were: minimal change disease (n = 5), idiopathic extramembranous glomerulonephritis (n = 5), focal and segmental glomerulosclerosis (n = 2), and proliferative glomerulopathy (n = 1). In two patients, a biopsy sample could not be obtained. Subjects with nephrotic syndrome were compared to a control group of 40 normolipemic healthy subjects. None of the subjects was treated with cholesterol-lowering drugs.

Lipids and Lp(a) Measurements

Blood was drawn on ethylenediaminetetra-acetic acid (0.1%) after an overnight fast. Urine was collected for a 24-h period preceding blood sampling in the case of nephrotic patients, and a urine sample was collected at the same time as blood for the control group. The plasma and urine samples were stored at −20°C before analysis. Total cholesterol and triglycerides were determined by nephelometry. Lp(a) concentration in plasma was determined by enzyme-linked immunosorbent assay (ELISA) as described previously (11).

The concentration of N-terminal fragments of apo(a) in plasma and urine was determined by two different ELISA. The first ELISA has been described previously (7), and uses as capture antibody IgG-a6, and as detecting antibody IgG-a5 (a gift from Dr. S. Marcovina, University of Washington, Seattle, WA), which specifically react against KIV type 1 and 2 and KIV type 2, respectively. The second ELISA uses two monoclonal antibodies (21D5C6 and 23G3C4) kindly provided by Dr. G. Dupuy (BioMérieux, Marcy-l’Etoile, France). These antibodies recognize two different epitopes in the N-terminal region of apo(a) (12). Coefficient of variation values for this ELISA for intra- and interassays were, respectively, 4.6 and 11.8%. A close correlation was observed between measurements performed with the two ELISA assays. Accordingly, only the results obtained with the second ELISA will be presented in the Results section.

Electrophoresis and Immunoblotting

Sodium dodecyl sulfate-polyacrylamide gel electrophoresis was performed on 4 to 10% acrylamide gradient slab minigels (Mini protein II, BioRad, Ivry, France), using a discontinuous buffer system (13). Before electrophoresis, samples were combined with glycerol, bromphenol blue, and ethylenediaminetetra-acetic acid to final concentrations of 2%, 0.01%, and 0.05 mM, respectively. Reduced samples were prepared by boiling at 100°C for 4 min in the presence of 20 mM dithiothreitol and 2% sodium dodecyl sulfate. Proteins were then electrophoresed onto nitrocellulose and revealed by immunoblotting. Fragments of apo(a) were revealed using four different antibodies: a polyclonal anti-apo(a) antibody (14), a monoclonal antibody 21D5C6, a polyclonal anti-apo(a) KV antibody raised in sheep (15), and a polyclonal anti-apo(a) KV antibody raised in guinea-pig (kindly provided by BioMérieux, France). Apo B100 was detected by using a polyclonal anti apo B100 antibody. Polyclonal anti-apo(a) and 21D5C6 antibodies were peroxidase-conjugated; for the anti-apo B100 and anti-apo(a) KV antibodies, the incubation with the primary antibody was followed by incubation of the membranes with an anti-IgG antibody coupled to peroxidase. Revelation was performed by enhanced chemiluminescence (ECL, Amersham, Orsay, France).

Isolation of Lipoproteins

The density of 6 ml of urine was adjusted to 1.21 g/ml by addition of solid potassium bromide, and the samples were centrifuged for 5 h at 100,000 × g at 10°C in a bench-top ultracentrifuge (Beckman TL100; Seine St. Denis, France). The supernatant (<1.21 g/ml) and bottom (>1.21 g/ml) fractions were concentrated on Aquacid II (Calbiochem, Meudon, France), and dialyzed against phosphate-buffered saline (pH 7.5).

Heparin-Sepharose Affinity

Fractionation of plasma samples on heparin-Sepharose was performed according to Mooser et al. (16), using 1 µg of Lp(a) for 50 µl

| Table 1. Clinical characteristics of patients presenting with nephrotic syndrome and normolipidemic control subjects* |
|-----------------|-----------------|-----------------|-----------------|
| Characteristic   | Control Subjects (n = 40) | Nephrotic Patients (n = 15) | P Value         |
| Age (yr)         | 41.5 ± 11        | 45.8 ± 18.1     | NS              |
| Male/female      | 20/19            | 7/8             |                 |
| Plasma triglycerides (mmol/L) | 0.86 ± 0.5       | 3.1 ± 2.1       | <0.0001         |
| Plasma cholesterol (mmol/L) | 2.2 ± 0.41       | 8.73 ± 3.6      | <0.0001         |
| Plasma glucose (mmol/L) | ND              | 5.18 ± 1.7      |                 |
| Plasma protein (g/L) | ND              | 48.8 ± 6.9      |                 |
| Plasma creatinine (µmol/L) | ND              | 174 ± 154       |                 |
| Proteinuria (g/24 h) | ND              | 9.41 ± 7.78     |                 |
| Urinary creatinine (µmol/L) | 10.34 ± 4.36    | 7.25 ± 2.4      | 0.004           |
| Creatinine clearance (ml/min) | ND              | 74 ± 56         |                 |

* Results are expressed as mean ± SD. ND, not determined.
of resin. Apo(a) fragments were assayed in the nonretained fraction by using the ELISA assays mentioned above.

**Statistical Analyses**

Results represent the mean of at least duplicate determinations and are expressed as means ± SD. Statistical analyses were performed with the Statview TM II computer program (Abacus Concepts, Berkeley, CA). A t test was applied to assess significant differences of continuous variables between the two groups. For non-normally distributed variables, the nonparametric Mann–Whitney test was applied. Correlations were determined by the Spearman test. The statistical level of significance was P < 0.05.

**Results**

**Plasma Lipid Levels**

Table 1 lists a series of lipid parameters in nephrotic and control subjects. In keeping with previous studies (17,18), plasma cholesterol and triglyceride levels were markedly elevated in nephrotic patients. Plasma Lp(a) levels were also significantly elevated in the nephrotic patients compared with controls (Table 2). This finding is in accordance with our previous work (19) and that of others (20–23).

**Quantification of Apo(a) Fragments in Plasma**

Plasma apo(a) fragments were assayed in both groups after removal of Lp(a) using heparin-Sepharose affinity resin. The mean level of apo(a) fragments present in plasma was significantly elevated in nephrotic patients compared with control subjects (Table 2). The amounts of apo(a) fragments correlated positively with Lp(a) levels in plasma in both groups (Figure 1A). The ratio of apo(a) fragments to total Lp(a) was calculated for each individual. The relative amount of apo(a) fragments to Lp(a) was significantly increased in nephrotic patients compared with control subjects (Table 2). A significant negative correlation was observed for the control group (Figure 1B). A negative correlation was also observed for the nephrotic patients, although the relation did not attain significance (P = 0.09).

**Quantification of Apo(a) in Urine**

Urine samples were assayed for their content in apo(a) and apo(a) fragments by using two distinct ELISA assays as described in the Materials and Methods. Both ELISA used for

<p>| Table 2. Plasma and urinary levels of apo(a) in patients presenting with nephrotic syndrome and normolipidemic control subjects a |
|--------------------|------------------|------------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Subjects</th>
<th>Nephrotic Patients</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Lp(a) (mg/ml)</td>
<td>0.21 ± 0.28</td>
<td>0.71 ± 0.54</td>
<td>0.0003</td>
</tr>
<tr>
<td>median</td>
<td>0.115</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>Plasma apo(a) fragments (µg/ml)</td>
<td>2.16 ± 2.99</td>
<td>24.7 ± 20.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>median</td>
<td>1.02</td>
<td>19.9</td>
<td></td>
</tr>
<tr>
<td>Plasma apo(a) fragments/Lp(a) (%)</td>
<td>2.1 ± 3.3</td>
<td>4.6 ± 3.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Urinary apo(a) (ng/ml per mg creatinine)</td>
<td>27.7 ± 44</td>
<td>578 ± 622</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>median</td>
<td>11</td>
<td>293</td>
<td></td>
</tr>
</tbody>
</table>

*a Results are expressed as mean ± SD. apo(a), apolipoprotein (a); Lp(a), lipoprotein (a).
these determinations detected N-terminal fragments of apo(a) and full-length apo(a) but not C-terminal fragments, since the monoclonal antibodies used are directed against the N-terminal part of apo(a). Urinary levels of apo(a)-immunoreactive material normalized to urinary creatinine were considerably elevated in nephrotic patients compared with control subjects (Table 2). They were positively correlated with plasma Lp(a) levels in both populations (Figure 2A). In contrast, no correlation was found between urinary levels of apo(a) and proteinuria or creatinine clearance, or plasma and urinary creatinine. The amount of apo(a) excreted into the urine was also correlated with the level of apo(a) fragments in plasma in both the control ($r = 0.72, P < 0.001$) and the nephrotic patient groups ($r = 0.62, P = 0.04$). The fractional catabolic rate of apo(a) fragments (urinary excretion per day/total plasma apo(a) fragments $\times 100$) was calculated, and no significant difference was observed between both groups (0.68 ± 0.67% and 0.62 ± 0.47% for nephrotic and control subjects, respectively).

**Molecular Analysis of Urinary Apo(a)**

Immunoblot analysis of apo(a) in urine samples was performed for all patients with nephrotic syndrome and control subjects. Figure 3 shows the typical patterns obtained after revelation by using a polyclonal anti-apo(a) antibody. The patterns of urinary apo(a) from control subjects resembled those described previously, with a ladder of fragments ranging in size from 60 to 230 kD. In contrast, the banding pattern of apo(a)-immunoreactive material in the nephrotic patients was distinct. In addition to the bands visible for control subjects, full-length apo(a) was immunodetected as well as large apo(a) fragments (ranging in size from 230 to 500 kD). Two smaller bands were also visible (90 and 60 kD), which predominated in most urine samples, although their intensity varied from one patient to another.

A series of additional experiments was performed to characterize further the apo(a) bands that were present in urine of nephrotic patients but not in control urine. First, we performed immunoblotting of urine from patients and control subjects using a series of antibodies of well-defined specificity (Figure 4). Analysis with monoclonal antibody 21D5C6, whose epitope was mapped to the N-terminal domain of apo(a) (12), revealed a series of bands of apparent molecular mass ranging from 60 kD to approximately 500 kD for the patients and from 60 to 230 kD for the control subjects (Figure 4, lanes 2 and 6). For the control subjects, the pattern obtained with this antibody was similar to that obtained with the polyclonal anti-apo(a) antibody (Figure 4, lanes 5 and 6). In contrast, the 21D5C6 antibody revealed fewer bands than the polyclonal anti-apo(a) antibody in the urine of the patients, and specifically in the low molecular mass range (below 100 kD) (Figure 4, lanes 1 and 2). This finding constitutes a good indication that the 60- and 90-kD bands revealed by the anti-apo(a) antibody are not due...
to the accumulation of N-terminal fragments in this size range. To further characterize these bands, a sheep polyclonal anti-apo(a) KV antibody (15) was used (Figure 4, lanes 3 and 7). This antibody primarily revealed the 90- and 60-kD bands, which were not detected by using the 21D5C6 antibody and were absent from control urine. Confirmation of this result was obtained by use of a separate anti-apo(a) KV antibody raised in guinea pig (not shown). The addition of the bands revealed with 21D5C6 and the anti-apo(a) KV antibodies closely matched the pattern obtained with the polyclonal anti-apo(a) antibody. Both anti-apo(a) KV antibodies did not reveal any band in the control subjects (Figure 4, lane 7), thereby indicating that both N- and C-terminal fragments of apo(a) were present in urine of nephrotic patients, whereas only N-terminal fragments were present in control urine.

Analysis of the blots with a polyclonal anti-apo B100 antibody revealed the presence of fragments of apo B100 in urine from the patients in contrast to the control subjects (Figure 4, lanes 4 and 8). However, no intact apo B100 was clearly detectable. Thus, to determine whether apo(a) and apo B100 present in urine of nephrotic patients circulate in free form or attached to a lipoprotein moiety, samples of urine from six patients were subjected to ultracentrifugation at d < 1.21 g/ml. Figure 5 shows a typical immunoblot of apo(a) in the ultracentrifugal fractions. The d < 1.21 g/ml fraction of urine from the patients contained a band that was revealed by application of a polyclonal anti-apo(a) antibody, clearly indicating the presence of Lp(a) particles in the urine of nephrotic patients. The bottom fraction contained all of the other apo(a) fragments present in urine, indicating that they were free of lipids. No Lp(a) was detected in control urine samples (Figure 5, right panel).

Finally, we compared the banding pattern of urinary apo(a) with that of the heparin-unbound fraction in plasma after removal of Lp(a) (Figure 6). As expected, apo(a) fragments in control urine were markedly smaller than apo(a) fragments detected in plasma. In contrast, the size of the larger apo(a) fragments present in urine from nephrotic subjects was similar to the size of apo(a) fragments in plasma, suggesting that large apo(a) fragments present in plasma are filtered unprocessed into the urine of nephrotic patients.
Discussion

We presently demonstrate, for the first time, that the proportion of apo(a) fragments relative to Lp(a) is elevated in plasma from subjects with nephrotic syndrome, and that not only N-terminal apo(a) fragments, but also Lp(a) particles, apo B100, and C-terminal fragments of apo(a) are present in the urine of these patients. We therefore provide evidence of qualitative differences in the composition of apo(a)-immuno-reactive material in nephrotic patients compared to that described previously for healthy subjects (7).

In the first part of this study, we confirmed previous studies showing that plasma Lp(a) levels are markedly increased in patients with nephrotic syndrome (19–23). We also quantified the concentration of apo(a) fragments in plasma and urine of nephrotic patients and control subjects. The most intriguing result concerned the elevated proportion of apo(a) fragments relative to Lp(a) in the plasma of nephrotic patients compared with control subjects. This result was unexpected and paradoxical, since we also observed that the concentration of apo(a) fragments was greatly increased in urine of nephrotic patients (Table 2). It has been shown that Lp(a) levels are more dependent on the rate of synthesis of apo(a) rather than on its catabolic rate, in healthy subjects (24), as well as in nephrotic patients (25). Consequently, the increased concentration of apo(a) fragments in plasma may also be the result of increased synthesis in nephrotic patients, since the fractional catabolic rate that we calculated (see Results) was similar in nephrotic and control subjects. An elevation in plasma levels of apo(a) fragments has also been reported in patients with end-stage renal disease (8,9), as a result of the limited capacity of the kidney to excrete apo(a) fragments that subsequently accumulate in plasma. This explanation may not be valid in the case of nephrotic patients, since we observed that their urinary excretion of apo(a) fragments was considerably elevated. This result is in contrast to those obtained in the case of end-stage renal disease patients (6) and of patients with proteinuria (26). In the latter study, most patients also presented renal insufficiency. We believe that the distinct results in our present study compared with those of Oida et al. (6) can be attributed to the difference in the populations studied, our population of nephrotic patients presenting only mild (if any) renal insufficiency. In addition, we found no relationship between urinary creatinine levels or creatinine clearance and the level of apo(a) fragments in the urine of nephrotic patients, thereby confirming our observations. This finding may suggest that part of the urinary content of apo(a) fragments in nephrotic patients may result from passive filtration. In healthy subjects, plasma apo(a) fragments undergo processing that leads to a reduction of their size in urine (16). This process was markedly attenuated in the case of apo(a) fragments from the nephrotic patients. Large apo(a) fragments were observed in plasma and urine (Figure 6). This latter result also argues in favor of a passive filtration of the large fragments of apo(a) and of Lp(a) in nephrotic syndrome. However, it cannot be ruled out that the presence of smaller fragments in urine may result from a secretory mechanism.

In the second part of this study, we examined the qualitative profiles of apo(a) fragments in urine of nephrotic patients compared to those in control subjects. The pattern of urinary fragments of apo(a) was distinct in the two populations. As expected, control subjects exhibited a ladder of fragments ranging from 60 to 230 kD; this pattern was remarkably constant from one control subject to the other. In contrast, the urine of nephrotic patients presented a strikingly different pattern. One major difference was the presence of Lp(a) as demonstrated by ultracentrifugal fractionation (Figure 5). The presence of Lp(a) as a particle in the urine of nephrotic patients has never been documented before. This observation suggests that very large particles (>2 to 3 × 10^6 kD) are filtered through the damaged nephrotic glomerulus to be excreted into urine, in agreement with a previous study that reported the presence of LDL and HDL particles in urine of nephrotic patients (27). The other major difference between control and nephrotic urine concerns the presence of two intense bands of 60 and 90 kD, which were revealed by an anti-apo(a) KV antibody and not by the antibody specific to the N-terminal part of apo(a) (Figure 4). This finding suggested that these bands could correspond to the C-terminal end of apo(a). We detected such fragments in every sample of urine from nephrotic patients, but in none of those from control subjects. This result contrasts with the observation of Kostner et al. (28), who detected trace amounts of a fragment reacting with an anti-apo(a) KV antibody in urine of healthy subjects, smaller than those that we have found in urine of nephrotic patients. Such a discrepancy can be explained by differences in the reactivity of the anti-apo(a) KV antibodies used in the two studies. Although our antibody presents marked specificity for the C-terminal domain of apo(a), it cannot be completely excluded that the anti-apo(a) KV immunoreactive bands could originate from unknown proteins that cross-react with this antibody. In our experiments, the anti-apo(a) KV-immunoreactive material was abundant in urinary samples of nephrotic patients. The presence of such quantities of C-terminal fragments in urine seems to be a characteristic of nephrotic syndrome, since Oida et al. (6) did not detect the presence of such fragments in the urine of patients with renal insufficiency. Up to now, C-terminal fragments of apo(a) have never been detected in plasma, and indeed, despite an intensive search, we have been unable to detect them. Consequently, their presence in urine cannot be explained, as is the case for N-terminal fragments, by their elimination from plasma. It is plausible that in the case of nephrotic patients, these fragments could originate from urinary degradation of apo(a) and/or Lp(a), which are equally present in their urine. The urinary C-terminal fragments can also be generated by the kidney through cellular proteolysis of Lp(a) and/or apo(a) or another mechanism. Kronenberg et al. (10) found an equal amount of N-terminal fragments in renal veins and arteries, suggesting that urinary fragments did not originate from their counterparts in plasma, or alternatively, that the kidney released similar amounts of apo(a) fragments in plasma as it excreted into the urine. In this case, and in contrast to N-terminal fragments, C-terminal fragments would be prin-
chloroform/methanol/acetone. The supernatant was removed and the pellet was dissolved in 1 ml of 0.5 M sodium chloride. The solution was then dialyzed against distilled water and stored at -20°C until use. The protein content of the dialyzed solution was determined by the bicinchoninic acid (BCA) method (Pierce, Rockford, IL).

5. Apo(a) Fragments in Nephrotic Syndrome

In conclusion, we have detected the presence of Lp(a), apo(a), and both N-terminal and C-terminal fragments of apo(a) in the urine of nephrotic patients. These results suggest that large fragments of apo(a) and Lp(a) are passively eliminated by renal filtration, whereas the smaller apo(a) fragments are actively secreted. However, the finely tuned mechanisms implicated in the excretion of apo(a) by the kidney remain to be determined.

Acknowledgments

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