Symptomatic antiproteinuric treatment decreases serum lipoprotein (a) concentration in patients with glomerular proteinuria

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Abstract. Elevated serum levels of the atherogenic and thrombogenic lipoprotein (a) (Lp(a)) have been recognized as a feature of the nephrotic syndrome associated hyperlipidaemia. To examine a possible relationship between serum Lp(a) concentration and proteinuria, serum albumin, or blood pressure, we studied nine patients with nephrotic-range proteinuria both at baseline and after various forms of antihypertensive and antiproteinuric treatment. In fixed order, patients received conventional antihypertensive treatment (either a-methyldopa or clonidine), subsequently ACE-inhibition therapy (lisinopril), ACE inhibition combined with an NSAID (indomethacin), and finally NSAID plus conventional antihypertensive therapy. Measurements were performed at the end of each 2-month study period.

When compared to controls (n=29), proteinuric patients before treatment showed increased levels of total cholesterol, very-low and low-density lipoprotein (VLDL+LDL) cholesterol, triglycerides and apolipoprotein B (apoB), while high-density lipoprotein (HDL) HDL cholesterol was lower. Lp(a) was significantly higher in patients (107 (95% CI: 55-208) mg/l) as compared to controls (25 (13-49) mg/l, P<0.01). Conventional antihypertensive treatment did not reduce proteinuria, while Lp(a) remained unaffected. ACE-inhibitor treatment lowered proteinuria, raised serum albumin, while La(a) tended to fall (−11 ±8%). Addition of an NSAID induced a further fall in proteinuria and a rise in serum albumin. Lp(a) now fell by 40±5% from baseline values (P<0.01). Both serum total, HDL and VLDL+LDL cholesterol fell significantly. Finally, during subsequent single therapy with NSAID plus conventional antihypertensive treatment, Lp(a) returned towards values obtained during single therapy with ACE inhibition. Multiple regression analysis showed a strong relation of Lp(a) with the amount of proteinuria (P=0.001), while serum albumin did not independently contribute to Lp(a) levels (P=0.2).

In conclusion, effective symptomatic antiproteinuric treatment decreases serum Lp(a) levels in patients with glomerular proteinuria. Our data suggests that renal protein leakage plays a more important role in the metabolic regulation of this lipoprotein than serum albumin level, and that antiproteinuric treatment may be of benefit in reducing the increased risk of thrombosis and atherosclerosis observed in this patient category.

Key words: ACE inhibition; albumin; nephrotic syndrome; proteinuria; lipoprotein (a); non-steroidal anti-inflammatory drugs

Introduction

The nephrotic syndrome is associated with changes in lipoprotein profile. Among these changes are an increase in serum total cholesterol, very-low and low-density-lipoprotein (VLDL and LDL) cholesterol, and triglycerides [1-4]. Recent studies have shown that serum lipoprotein(a) (Lp(a)) is also elevated in proteinuric patients [5-8]. Lp(a) is an LDL-like particle that contains apolipoprotein(a), which is covalently linked to apolipoprotein B-100 [9]. Its concentration is to a large extent genetically determined [10]. The level of Lp(a) varies widely among individuals, but is rather stable within normal persons [11]. Intercultural differences have been reported, while Lp(a) levels are not related to gender [12]. High levels of this lipoprotein are considered to be an independent risk factor of coronary heart disease [13,14], and Lp(a) is thought to possess thrombogenic properties because of a strong structural homology between apolipoprotein(a) and plasminogen [15,16]. The elevated level of Lp(a) in patients with the nephrotic syndrome may thus be related to the increased risk of thrombosis and cardiovascular disease observed in these patients [17,18].

The pathophysiological mechanism responsible for
the increased Lp(a) concentration in the nephrotic syndrome is poorly understood. Some cross-sectional studies report a correlation of Lp(a) with urinary protein excretion [5,7]. Others found Lp(a) levels to be lowered after remission of nephrotic syndrome [6,19]. Although it appears difficult to influence elevated levels of Lp(a) with lipid lowering agents [20–22], it is thus possible that nephrotic syndrome associated Lp(a) hyperlipidaemia can be lowered by antiproteinuric treatment. Indeed, Keilani et al. recently found that antihypertensive treatment with ACE inhibition lowered proteinuria and Lp(a) [23]. To examine the possible relationships between Lp(a) concentration and blood pressure, proteinuria and serum albumin in more detail, we studied patients with nephrotic range proteinuria, both before and after various forms of blood-pressure-lowering and antiproteinuric treatment. Patients were studied first at baseline (I), subsequently during conventional antihypertensive therapy to investigate the effect on Lp(a) levels of blood-pressure-lowering without proteinuria changes (II). Thereafter, patients were studied during ACE inhibition to investigate the effect of blood-pressure and proteinuria lowering (III), during the combination of ACE inhibition and an NSAID to ensure a more pronounced antiproteinuric effect than on ACE inhibition single treatment (IV), and finally during antiproteinuric treatment with an NSAID to investigate whether possible changes in Lp(a) are indeed proteinuria- and not drug-related (V). Measurements were performed at the end of each 2-month study period.

Subjects and methods

Patients and protocol

Nine non-diabetic patients with biopsy-proven glomerulopathy participated in this study. Entry criteria were stable proteinuria in excess of 2.5 g/day, and creatinine clearance of more than 50 ml/min. Patients using hypolipidaemic agents or with a history of familial hyperlipidaemia were not accepted. Patients were matched with healthy controls with respect to age, body mass index (BMI) and oral contraceptive use. All subjects gave informed consent to participate in the protocol, which was approved by the local Medical Ethical Committee.

The control subjects were studied once, whereas proteinuric patients were studied during five study periods, each lasting 2 months. Measurements were performed at the end of study periods. First, baseline data of controls and patients were compared. Patients did not receive medication except one, who received diuretic treatment with frusemide at a constant dose during the entire protocol. Second, to test whether blood-pressure-lowering itself influences Lp(a), patients were studied while receiving conventional antihypertensive treatment with clonidine (3 patients, median dose 450 μg/day) or α-methyldopa (5 patients, median dose 750 mg/day). This medication on its own has only minor effects on proteinuria [24], and on serum total cholesterol [25]. Third, patients were studied after antiproteinuric treatment with ACE inhibition (lisinopril 10 mg/day). Fourth, all patients received the NSAID indomethacin (150 mg/day), additional to ACE inhibition. This combined therapy was given to induce a further decrease in urinary protein excretion [26]. In the fifth period NSAID treatment was continued, while ACE-inhibitor therapy was replaced by the same antihypertensive medication as in the second period.

At the end of each study period, venous blood for the determination of serum lipids and albumin was obtained from each subject. Blood was drawn after a 12-h fast, before medication was taken. Furthermore, proteinuria and blood pressure were determined at the end of each period. Throughout the study a sodium-restricted diet of 50 mmol daily was prescribed to enhance the antiproteinuric effect of ACE inhibition therapy [27]. The participants were advised not to change the dietary intake of fat and cholesterol.

Laboratory and clinical procedures

Venous blood was collected into vacuum tubes. Erythrocytes were removed by centrifugation at 3000 r.p.m. for 15 min within 1 h of collection. Serum samples were frozen at — 20°C until analysed. Lp(a) levels were quantified using a commercially available enzyme-linked immunosorbent assay (Tint-Elize Lp(a), Biopool AB, Umeå, Sweden, cat. no. 610221) [28]. The cross-reactivity of the Lp(a) antibodies with LDL-cholesterol and plasminogen are known to be negligible. The intra- and interassay coefficients of variation are below 10%.

The detection limit of the assay was 1 mg/l. Total cholesterol and triglycerides were assayed enzymatically. Cholesterol was measured in whole serum and in the HDL-containing supernatant fraction after precipitation of apolipoprotein-B-containing lipoproteins with polyethylene glycol–6000 [29]. VLDL + LDL lipids were calculated as the difference between plasma and the HDL-containing supernatant fraction. Apolipoproteins A, and B were determined by immunoturbidimetry using commercially available kits (Boehringer Mannheim, FRG, cat. nos. 726478 and 726494 respectively). Lipid and apolipoprotein determinations of each patient were assayed in one run. Serum creatinine, total protein and albumin were measured on a SMA-C autoanalyzer (Technicon Instruments Inc., Tarrytown, NY, USA). Urinary protein was determined at the end of each period in two consecutive 24-h urine collections by the pyrogallol–red-molybdate method [30]. All laboratory determinations were carried out on blinded samples. Blood pressure was recorded with an automated device (Dinamap®) in patients and by the auscultatory method in controls. MAP was calculated as the sum of two-thirds of the diastolic blood and one-third of the systolic blood pressure. BMI was calculated as weight (in kilograms) divided by height (in metres) squared.

Statistical analysis

Data are presented as mean±SE. Because of the skewed distribution of Lp(a) concentration, data on this parameter are given as geometric mean with 95% confidence interval (CI). To compare baseline Lp(a) levels between patients and controls the Mann–Whitney U test was used, while Student’s t test for unpaired data was used for comparison of other baseline characteristics. To test whether Lp(a) levels showed significant changes between study periods, Friedman’s non-parametric analysis of variance was applied. For other parameters parametric analysis of variance was employed. Duncan’s method was used to correct for multiple comparisons. One patient could not be studied during conventional antihypertensive therapy because his nephrotic syndrome necessitated immediate antiproteinuric treatment. To calcu-
late a mean value of parameters during conventional antihypertensive treatment, the corresponding baseline values of this patient was substituted. To evaluate relationships between variables Pearson’s correlation coefficients were calculated. Multiple regression analysis was performed to assess parameters that independently contributed to Lp(a) and apolipoprotein B levels. 
P values of less than 0.05 (two-sided) were considered significant.

Results

Patients (n = 9) were well matched with controls (n = 29) with regard to gender (2F/7M versus 7F/22M, difference \( P = 0.91 \)); age (39 ± 2 years versus 38 ± 4 years, difference \( P = 0.80 \)); and BMI (24.4 ± 0.5 kg/m\(^2\) versus 24.6 ± 1.0 kg/m\(^2\), difference \( P = 0.85 \)). Serum creatinine and blood pressure tended to be higher in patients when compared to controls, reflecting the presence of renal disease (respectively 92 ± 3 \( \mu \)mol/l versus 126 ± 17 \( \mu \)mol/l, difference \( P = 0.11 \) and 98 ± 1 mmHg versus 106 ± 4, difference \( P = 0.10 \)). Histological diagnosis in the patient group was IgA nephropathy (n = 5), membranous glomerulopathy (n = 2), and membranoproliferative glomerulonephritis (n = 2). All studied subjects were Caucasian.

Table 1 provides the principal study parameters in controls and proteinuric patients, both at baseline and during the follow-up periods. Individual Lp(a) levels of patients during the different phases of the protocol are shown in Figure 1. Baseline serum albumin concentration was significantly lower in the proteinuric patients. Baseline serum levels of total cholesterol, VLDL + LDL cholesterol, triglycerides, and apolipoprotein-B were significantly elevated in patients, compared to controls. In contrast, HDL cholesterol was significantly lower, while serum lipoprotein A, was not different from controls. The level of protein A, was not different from controls. The level of protein A, was not different from controls. The level of protein A, was not different from controls.

Table 1. Study parameters in controls and proteinuric patients at baseline and during different antihypertensive and antiproteinuric treatment regimens

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls (n = 29)</th>
<th>Proteinuric patients (n = 9)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Conventional</td>
</tr>
<tr>
<td>Proteinuria (g/24 h)</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>98 ± 1</td>
<td>98 ± 1</td>
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<tr>
<td>Serum albumin (g/l)</td>
<td>48.4 ± 0.5</td>
<td>32.4 ± 2.0²</td>
</tr>
<tr>
<td>Serum creatinine (μmol/l)</td>
<td>92 ± 3</td>
<td>126 ± 17</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.98 ± 0.14</td>
<td>6.97 ± 0.46²</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.45 ± 0.12</td>
<td>2.35 ± 0.36²</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.15 ± 0.04</td>
<td>0.86 ± 0.06³</td>
</tr>
<tr>
<td>VLDL + LDL cholesterol</td>
<td>3.82 ± 0.15</td>
<td>6.11 ± 0.50³</td>
</tr>
<tr>
<td>Apolipoprotein A(_1) (g/l)</td>
<td>1.52 ± 0.06</td>
<td>1.69 ± 0.05</td>
</tr>
<tr>
<td>Apolipoprotein B (g/l)</td>
<td>0.71 ± 0.03</td>
<td>1.24 ± 0.09²</td>
</tr>
<tr>
<td>Apolipoprotein A(_1)/B</td>
<td>2.34 ± 0.22</td>
<td>1.42 ± 0.11²</td>
</tr>
<tr>
<td>Lp(a) (mg/l)</td>
<td>25 ± (13-49)</td>
<td>107² (55-208)</td>
</tr>
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</table>

Data in mean ± SE and in geometric mean (95% confidence interval).

Abbreviations: Conventional, conventional antihypertensive treatment; ACEi, ACE inhibition; NSAID, non-steroidal anti-inflammatory drug; MAP, mean arterial pressure; HDL, high-density lipoprotein; VLDL, very-low-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein (a).

\( *: P < 0.05; \quad ²: P < 0.01 \) patients at baseline versus controls.

\( ³: P < 0.05; \quad ⁴: P < 0.01 \) patients vs baseline.

![Fig. 1. Lp(a) concentration in nine proteinuric patients at baseline, during conventional antihypertensive treatment, and during antiproteinuric treatment with ACE inhibition (ACEi), a combination of ACE-inhibition and NSAID, and NSAID plus conventional antihypertensive therapy respectively. A patient not studied during conventional antihypertensive treatment, is visualized by the open circle. Horizontal bars represent geometric means during the respective study periods. *: \( P < 0.05 \); **: \( P < 0.01 \) patients vs baseline.](https://academic.oup.com/ndt/article-abstract/9/3/244/1858583)
of Lp(a) was significantly higher in the patient group, compared to the control group. Lp(a) was at or below the detection limit of 1 mg/l in five control subjects, but in none of the patients. When the control and patient groups were analysed separately, no significant correlations could be demonstrated between baseline Lp(a) concentration and serum albumin, proteinuria or the various lipid parameters. However, when controls and patients were combined, a negative correlation was observed between Lp(a) and serum albumin \((n = 38, r = 0.42, P = 0.01)\). When multiple regression analysis was performed in the combined groups with log Lp(a) as dependent variable, it was found that Lp(a) was not related to clinical parameters, such as age, sex, BMI, blood pressure or serum creatinine, whereas the negative relation with serum albumin was near significant \((P = 0.06)\).

A significant decrease in MAP was observed during conventional antihypertensive treatment, while proteinuria and serum total cholesterol remained essentially unaltered. Serum albumin increased slightly, and Lp(a) increased non-significantly.

Treatment with ACE inhibition resulted in a fall in MAP. In addition a reduction of 59.2 ± 7.1% in urinary protein excretion \((P < 0.05)\) was observed. As a result serum albumin levels rose. Furthermore serum total cholesterol and apolipoprotein-B tended to decrease, while the apolipoprotein ratio A\(_1\)/B tended to increase. Lp(a) did fall numerically, but the fall was not statistically significant \((-11.4 ± 7.6\%)\).

Subsequently, an NSAID was added, while leaving the dose of the ACE inhibitor unchanged. This resulted in a further decrease in proteinuria and increase in serum albumin. At the end of this period cholesterol had decreased in all serum lipoprotein fractions, among which was HDL cholesterol. Furthermore, apolipoprotein B was significantly reduced. The ratio of apolipoprotein A\(_1\)/B tended to increase. Lp(a) fell significantly during combined therapy by 40.4 ± 5.4\% \((P < 0.01)\). This fall in Lp(a) concentration was similar in the three histological diagnosis groups (IgA 39\%, MGP 45\% and MPGN 39\%).

During therapy with NSAID and conventional antihypertensive therapy, mean proteinuria rose to a value comparable to that obtained in the ACE inhibition period. Also most of the lipid parameters, including Lp(a), returned towards values as measured during treatment with ACE inhibition alone.

To evaluate possible relations between blood pressure, proteinuria, serum albumin concentration with changes in Lp(a) levels in these patients, multiple regression analysis was performed with log Lp(a) as dependent variable and with blood pressure, serum albumin, and proteinuria as possible independent variables, and Lp(a) as dependent variable. In this analysis each patient was included as a separate categorical variable to take account of the fact that each patient was studied on five occasions. This model appeared highly predictive for Lp(a) levels, as the multiple \(r\) was 0.94. Patient category strongly contributed to the level of Lp(a) \((P < 0.001)\), indicating that the concentration of Lp(a) was individually determined. Furthermore the concentration of Lp(a) was related to proteinuria \((P = 0.001)\). Serum albumin and blood pressure did not independently contribute to Lp(a) levels \((P = 0.24, P = 0.06\) respectively). When apolipoprotein B was added to this model, no relationship was found between Lp(a) and apolipoprotein B \((P = 0.47)\). The individual relationships of Lp(a) with urinary protein excretion are in Figure 2.

In addition, multiple regression analysis demonstrated that apolipoprotein B was also determined by patient category \((P < 0.001)\), and by urinary protein excretion \((P = 0.02)\), but not by serum albumin \((P = 0.48)\) or MAP \((P = 0.80)\). The multiple \(r\) of this model was 0.87. When Lp(a) was added to this model, no relationship between apolipoprotein B and Lp(a) \((P = 0.47)\) was observed.

**Discussion**

In the present study we confirmed that non-diabetic patients with nephrotic range proteinuria have higher serum levels of Lp(a) when compared to healthy
controls. Blood-pressure-lowering therapy alone did not significantly alter Lp(a), whereas symptomatic antiproteinuric treatment with ACE inhibition, NSAIDs, and their combination lowered Lp(a) levels. A strong positive correlation was found between the level of Lp(a) and the amount of proteinuria, while serum albumin did not independently contribute to Lp(a) levels.

Lipoprotein abnormalities associated with the nephrotic syndrome have been extensively studied. Several authors have reported increases in total cholesterol, VLDL + LDL cholesterol, and triglycerides, similar to our findings [1-4]. Data on HDL cholesterol are less consistent, as HDL cholesterol was found to be reduced [31,32, present study], normal [1] or even elevated [3]. In addition elevated levels of Lp(a) have recently been recognized as a feature of nephrotic-syndrome-associated hyperlipidaemia [5-8]. In primary hypercholesterolaemia, lowering Lp(a) levels appeared to be difficult [20-22]. This issue has not yet been studied in detail in patients with the nephrotic syndrome. A few studies report that complete remission of the nephrotic syndrome, either spontaneously or induced by immunosuppressive drugs, coincides with a fall in Lp(a) [6,19]. Our report clearly corroborates that symptomatic antiproteinuric treatment can lower Lp(a) levels in patients with nephrotic range proteinuria, and that this effect depends upon the reduction in proteinuria, regardless of the type of drug used. In this respect it is of interest that a recent study showed that symptomatic antiproteinuric treatment with the ACE inhibitor fosinopril did not uniformly reduce Lp(a), while improving other lipid abnormalities [23]. However, in the subgroup of patients that showed a good antiproteinuric response, a significant decrease in Lp(a) was observed. In that study, in contrast to ours, no correlation was found between Lp(a) and proteinuria, neither in the entire study population, nor in the subgroup of good responders. In addition we found that antiproteinuric treatment lowered HDL-cholesterol. The fall in HDL-cholesterol seems to be counterbalanced though, by the concomitant fall in VLDL + LDL cholesterol, whereas the apolipoprotein A1/B ratio tended to improve. The clinical significance of these changes is unclear.

The mechanisms responsible for the elevated Lp(a) levels in patients with proteinuria are not well characterized. Among healthy individuals genetically determined factors have been found to account for a major proportion of the variation in Lp(a) [10]. This is in accordance with the present results obtained by multiple regression analysis, showing that Lp(a) levels are individually determined. It is generally assumed that Lp(a) is synthesized in the liver, but little is known about its catabolism. The hepatic LDL receptor seems to be involved in Lp(a) clearance from the circulation, since Lp(a) levels are elevated in heterozygote patients with familial hypercholesterolaemia who have one defective LDL receptor gene [33], while Lp(a) is decreased in transgenic mice overexpressing the LDL receptor Lp(a) [34]. However, both the lack of effect on Lp(a) of cholesterol synthesis inhibitors that cause upregulation of LDL receptors [21,22], and the observation that the levels of apolipoprotein B and Lp(a) are not interrelated, suggest that other pathways are more important in Lp(a) metabolism. Accordingly, Lp(a) concentration has been shown to be more closely related with Lp(a) production than with Lp(a) catabolism [35]. In the nephrotic syndrome the hepatic production of lipoproteins is assumed to be increased parallel with enhanced protein synthesis [1,4]. Although many studies showed a negative correlation between serum albumin or plasma oncotic pressure and the level of apolipoprotein-B-containing lipoproteins, it has been demonstrated that the concentration of cholesterol is related primarily to urinary protein leakage, rather than to increased hepatic albumin synthesis [36,37]. At baseline we observed a negative correlation between baseline Lp(a) and serum albumin, but only when patients and controls were combined. Multiple regression analysis of data obtained during the different study periods revealed that Lp(a) levels were closely related to the amount of urinary protein excretion, whereas the relationship with serum albumin was not significant. Thus it seems plausible to postulate that renal protein leakage plays a more important role in the metabolic regulation of Lp(a) than hypoalbuminemia per se. Furthermore, the absence of an interrelation between the levels of Lp(a) and apolipoprotein B suggests that in the nephrotic syndrome Lp(a) and LDL levels are regulated by different mechanisms, although the magnitude of proteinuria is a common determinant of both.

The level of Lp(a) has been shown to be an independent risk-factor for cardiovascular disease, particularly when present in concentrations of more than 300 mg/l [13,14]. When both LDL and Lp(a) are elevated, the cardiovascular risk increases even more [38]. Since Lp(a) has also been related to the development of thrombosis [15], an elevated concentration of Lp(a) might contribute to the assumed increased risk for atherosclerosis and thrombosis in proteinuric patients [17,18]. Of note is the fact that the presently measured Lp(a) levels were found to be rather low both in controls and in patients when compared to other studies. Since Lp(a) distribution in the general population is highly skewed, this discrepancy may be due just to coincidence. However, because Lp(a) levels are for a large part genetically determined [10], differences between regional populations may be expected. A direct comparison of clinical studies is difficult moreover, since the various assays available provide different values of Lp(a) [39]. In addition, it is possible that our sample storage procedure has influenced the apparent serum Lp(a) concentration. Recent laboratory experiments have shown that storage, both at -20°C and at -70°C, results in a minor fall in Lp(a) levels over time, when measured with the presently used enzyme-linked immunosorbent assay [39]. However, since patients were compared with controls from the same region, were studied in parallel, and all samples were stored under similar conditions and assayed in
Lp(a) levels in proteinuric patients

one run, it is not likely that our conclusions will be influenced.

Another aspect of interest is that several animal studies have shown that hyperlipidaemia may play a role in the progression of renal disease [40]. Accordingly, a recent report showed marked deposition of apo(a) and apoB-100 in the mesangium of patients with severe proteinuria and glomerulosclerosis, leading the authors to conclude that Lp(a) hyperlipidaemia may participate in the persistence and progression of renal damage [41]. Taken together these observations suggest that lowering serum levels of Lp(a) in proteinuric patients may be of benefit in the long term. Since the present study shows that lipoprotein profile of the nephrotic syndrome is not fully normalized with antiproteinuric treatment, the combination of lipid-lowering drugs and antiproteinuric treatment may deserve further attention.

In conclusion, in patients with nephrotic range proteinuria serum Lp(a) concentration is found to be elevated when compared to healthy controls. Effective antiproteinuric treatment significantly lowered Lp(a) levels. This suggests that renal protein leakage plays an important role in the metabolic regulation of this lipoprotein. Antiproteinuric treatment, by means of lowering Lp(a) concentration, may thus possibly exert a beneficial effect on the increased risk for thrombosis and atherosclerosis observed in patients with the nephrotic syndrome.

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