Complex Apolipoprotein B-Containing Lipoprotein Particles Are Associated with a Higher Rate of Progression of Human Chronic Renal Insufficiency

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Abstract. Chronic renal failure is characterized by specific alterations of the lipoprotein metabolism. It has been suggested that renal dyslipoproteinemia contributes to the progression of renal dysfunction. The objective of this study was to investigate the impact of different apoB-containing lipoprotein families on the progressive decline of renal function in patients with moderately advanced chronic renal failure. As part of a larger prospective study, 44 adult nondiabetic patients with primary chronic renal disease were followed with repeated GFR measurements for an average of 2.4 (SD 1.0) yr. Patients' characteristic variables, including plasma levels of lipids, apolipoproteins (apo), and apoA- and apoB-containing lipoprotein families (LP), were determined at the beginning of the observation period. The baseline variables were prospectively related, using linear regression, to the rate of progression (ΔGFR). The patient study group had a mean GFR at baseline of 40.3 (SD 16.7) ml/min per 1.73 m² body surface area. The average rate of progression was a yearly decline in GFR of −3.2 (SD 5.1) ml/min per 1.73 m² body surface area. A strong association was observed between the plasma concentration of complex, triglyceride-rich apoB-containing lipoproteins (LP-Bc) and the rate of progression (r = 0.43, P < 0.01), whereas there was no association between the cholesterol-rich apoB-containing lipoproteins (LP-B) and ΔGFR. The association between the levels of LP-Bc and the rate of progression was not dependent on the baseline values of GFR, BP, and the degree of proteinuria. The results of this study extend earlier observations regarding the importance of renal dyslipoproteinemia for progressive renal insufficiency. In particular, elevated levels of intact or partially metabolized triglyceride-rich apoB-containing lipoproteins of intermediate- and low-density ranges seem to promote the progression of human renal insufficiency.

Chronic renal insufficiency, already at the early stages of renal functional impairment, is accompanied by specific lipoprotein abnormalities (1). Although the clinical significance of these abnormalities remains to be clarified, it has been suggested that renal dyslipoproteinemia may contribute not only to an accelerated development of atherosclerosis (1–3), but also to the progression of renal insufficiency (1,4). In fact, the hypothesis that some lipid and/or lipoprotein abnormalities may exert a nephrotoxic influence has already been strongly supported by several animal (1,3) and human (1,4–10) studies on the progression of renal dysfunction.

Renal dyslipoproteinemia is characterized by moderately increased levels and marked compositional changes of apolipoprotein (apo) B-containing lipoproteins of very low and low densities, and reduced levels and abnormal composition of apoA-containing lipoproteins of high densities (11,12). Recently, we have reported in a prospective study of nondiabetic patients with primary chronic renal disease that elevated plasma concentrations of apoB and LDL cholesterol at entry of follow-up correlate with the progression of renal insufficiency (13); in contrast, there was no evidence for a similar involvement of reduced levels of apoA-I or HDL cholesterol.

ApoB-containing lipoproteins consist of five major families of discrete lipoprotein particles differentiated and defined on the basis of apolipoprotein composition as predominantly cholesterol-rich lipoprotein B (LP-B) and lipoprotein B:E (LP-B:E) and triglyceride-rich lipoprotein B:C (LP-B:C), lipoprotein B:C:E (LP-B:C:E) and lipoprotein A-II:B:C:D:E (LP-A-II:B:C:D:E, or abbreviated LP-A-II:B complex) (Figure 1). The latter three lipoprotein families are referred to as complex apoB-containing lipoproteins, or LP-Bc. Because of the wide distribution of apoB-containing lipoprotein families along their characteristic density spectrum (d, 0.92 to 1.063 g/ml), it was not possible to establish, based on the plasma levels of apoB or LDL cholesterol (d, 1.006 to 1.063 g/ml), whether the contribution of this class of lipoproteins to the progression of renal insufficiency was related to the content of cholesterol-rich LP-B or triglyceride-rich LP-Bc particles.

This report is based on a prospective study (13), and its specific purpose was to evaluate the role of cholesterol-rich
LP-B and triglyceride-rich LP-Bc particles as contributors to the progression of renal insufficiency.

Materials and Methods

Patients

From 1990 to the end of 1991, 77 patients with chronic primary renal disease and a GFR between 15 and 75 ml/min per 1.73 m² body surface area (BSA) were included in a prospective, long-term observational study. The study design and the characteristics of the patient population have been described previously in detail (13). Patients treated with any type of lipid-lowering agents were excluded, and no dietary advice counseling regarding protein or energy intake was given to any of the patients. In a subset of this patient population consisting of 44 patients, the analysis of lipoprotein profile was extended to include the determination of the apoA- and apoB-containing lipoprotein families. These specific determinations were performed in samples collected either at the 6-, 12-, or 18-mo checkup visit (see also below). The selection of 44 patients was not based on any demographic or clinical criteria but on the availability of lipoprotein particle data for this subset and not for the entire patient population. The concentrations of apoA- and apoB-containing lipoprotein families were related to the subsequent rate of progression as assessed by repeated measurements of GFR.

There were 13 female and 31 male patients. Twenty-four (55%) of the patients had chronic glomerulonephritis, six (14%) had interstitial nephritis, five (11%) had adult polycystic kidney disease, and seven (16%) had nephrosclerosis as the underlying chronic renal disease. In the remaining two (4%) patients, the renal disorder could not be adequately diagnosed. The mean age of patients at the time of the lipoprotein particle determination, i.e., at the baseline, was 51.6 (SD 12.7 yr; range, 30 to 69 yr). Their mean body weight was 79.7 (SD 16.3) kg. Forty patients (91%) were on antihypertensive medication. Thirty-two (73%) were treated with an angiotensin-converting enzyme (ACE) inhibitor. The average baseline BP was 138.2 (SD 17.2)/84.9 (SD 10.1) mmHg. The BP remained stable during follow-up: 138.4 (SD 17.5)/85.5 (SD 9.6) mmHg at the 24-mo checkup and 137.3 (SD 20.2)/83.6 (SD 8.7) mmHg at the 36-mo checkup. The mean total urinary protein excretion at baseline was 1.4 (SD 1.5) g/24 h. Only three patients had nephrotic-range proteinuria (i.e., >3.5 g/24 h; range, 4.0 to 6.2 g/24 h), but none of the patients had edema or subnormal serum albumin levels.

Renal Function

GFR was determined as the plasma or renal clearance of ⁵¹Cr-ethylenediaminetetra-acetic acid (EDTA) (14). The renal clearance method was used when the GFR value was <20 ml/min per 1.73 m² BSA. GFR was determined at the beginning of follow-up and then at 3- or 6-mo intervals. The individual rate of progression of renal insufficiency was calculated as the slope of GFR versus time plot (linear regression). The progression rate was expressed as the change in GFR ($\Delta$GFR ml/min per 1.73 m² BSA per year).

Lipid and Apolipoprotein Analyses

At the beginning of the study and at regular 6-mo intervals during the follow-up period, blood samples were drawn after an overnight fast by antecubital venipuncture into EDTA-containing Vacutainer tubes, and plasma samples were recovered by low-speed centrifugation (1000 x g) for 10 min at 4°C. A preservative solution (0.13% $\epsilon$-aminocaproic acid and 0.1% thiomersal) was added (10 µl/ml) to all plasma samples, which were then shipped in the fresh state by express air freight to Oklahoma City for lipid and lipoprotein analyses. At the Lipid and Lipoprotein Laboratory, the samples were analyzed within a week after they had been drawn to avoid any possible adverse effects due to freezing and subsequent thawing of individual samples. Total cholesterol, triglycerides, and lipoprotein cholesterol concentrations were determined by enzymatic procedures as described previously (15). HDL cholesterol was measured after the precipitation of apolipoprotein families in whole plasma by heparin-manganese chloride (16); VLDL cholesterol was assumed to equal one-fifth of the plasma triglyceride concentration, and the LDL cholesterol was determined by difference according to the method of Friedewald et al. (17). Cholesterol, triglyceride, and HDL cholesterol

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**CLASSIFICATION OF PLASMA LIPOPROTEINS**

<table>
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</table>

Apo B - CONTAINING LIPOPROTEINS

LP-B

LP-B:C

LP-B:C:E

LP-B:C

Apo A - CONTAINING LIPOPROTEINS

LP-A-I

LP-A-I:II

LP-A-II

Figure 1. The relationship between major lipoprotein density classes and individual apoA- and apoB-containing lipoprotein families. The lines under the lipoprotein families indicate their distribution along the density spectrum. Revised and reproduced with the permission of Am J Kidney Dis (see reference 1).
Determination of ApoA- and ApoB-Containing Lipoprotein Families

The two major apoA-containing lipoprotein families, LP-A-I and LP-A-I:A-II, were quantified in plasma samples from either the 6-, 12-, or 18-mo checkup. This was done using a modified differential electroimmunoassay described by Parra et al. (23). Briefly, polyclonal antisera to apoA-I and apoA-II were mixed with agarose in Tris-barbital buffer, pH 8.5, and the mixture was poured onto a strip of film. Plasma samples were applied to wells punched out in each film, and the plates were run for 6 h at 12 V/cm with Tris-barbital buffer, pH 8.5. By using anti-apoA-II serum in excess over anti-apoA-I serum, LP-A-I:A-II particles formed short rockets near the wells. The LP-A-I particles migrated beyond the LP-A-I:A-II particles, forming well delineated rockets. The concentration of apoA-I in LP-A-I particles was determined by measuring the area of LP-A-I rockets with a digitizer, and the levels of LP-A-I particles were expressed in terms of their apoA-I concentration (mg/dl). The concentration of LP-A-I:A-II particles was calculated by subtracting apoA-I levels of LP-A-I particles from apoA-I levels of whole plasma. LP-A-I particles isolated by immunoaffinity chromatography served as the primary standard, and a plasma sample of a known concentration of LP-A-I as the secondary standard. The within- and between-assay coefficients of variation for LP-A-I assay were 3.1 and 4.0%, respectively; the corresponding coefficients of variation for the measurements of LP-A-I:A-II were 1.2 and 1.5%, respectively.

Two major classes of apoB-containing lipoprotein families, LP-B and LP-Bc, were isolated from whole plasma by immunoaffinity chromatography on an anti-apoC-III immunosorber, according to a previously described procedure (24). Plasma samples (0.2 to 0.4 ml) were applied to the immunosorber and incubated for 12 h at room temperature (20°C). The unretained fraction was eluted with 0.05 mol/L Tris-HCl buffer, pH 7.4, containing 0.5 mol/L NaCl and 1.5 mg/ml EDTA. After the column was washed with this buffer, the retained fraction was eluted with 3 mol/L NaSCN, pH 7.4. The unretained fraction contained LP-B and small amounts of LP-B:E particles, whereas the retained fraction consisted of LP-Bc particles including LP-B:C, LP-B:C:E, and LP-A-II:B:C:D:E. If the unretained fraction tested positively for apoC-III, it was chromatographed until free of apoC-III. Whole plasma and retained and unretained fractions were analyzed for apoB, and the levels of apoB-containing lipoproteins were expressed in terms of respective apoB contents in milligrams per deciliter. The apoB content of the anti-apoC-III unretained fraction corresponded to LP-B (and small amounts of LP-B:E) particles and that of the anti-apoC-III retained fraction corresponded to LP-Bc particles. The concentrations of apoB in apoB-containing lipoproteins were calculated on the basis of plasma apoB values and the percent distribution of apoB in retained and unretained fractions. The recoveries of apoB from the immunosorber ranged from 80 to 90% of applied apoB. The interassay coefficients of variation were 6.2% for the measurement of LP-B and 8.7% for the assay of LP-Bc.

Other Clinical Variables

Parathyroid hormone levels were determined every 6 mo during the follow-up and were measured as intact parathyroid hormone. BP was recorded every 3 mo and measured after 5 min of supine rest.

Statistical Analyses

Standard statistics were used to illustrate the salient features of the data. The association between baseline variables and the rate of progression (ΔGFR) was analyzed by linear regression analysis and the Spearman rank correlation test. Because there was no qualitative difference in outcome between these methods, only the results of the former are presented. P values <0.05 were considered statistically significant. As stated earlier, the first GFR used for calculating the rate of progression was the GFR measurement that corresponded in time to the determination of lipoprotein families.

Results

The average GFR value at the beginning of the follow-up period was 40.3 (SD 16.7) ml/min per 1.73 m² BSA. The average time of follow-up was 2.4 (SD 1.0) yr, and the mean rate of progression during this observation period was –3.2 (SD 5.1) ml/min per 1.73 m² BSA per year. Thus, there was a wide interindividual variation in the progression rate.

The diastolic BP values tended to be associated with the progression rate (r = 0.28, P = 0.06), whereas neither the initial GFR values nor higher urinary protein excretion rates were, statistically, significantly correlated with a higher rate of progression (Table 1). Among plasma lipids and apolipoproteins, only the levels of LDL cholesterol (r = 0.29, P = 0.06) and apoE (r = 0.29, P = 0.06) were close to being significantly associated with the rate of progression, followed by apoA-II (r = 0.24, NS) and apoB (r = 0.19, NS). There was no statistically significant association between the levels of apoA-containing lipoprotein families, LP-A-I and LP-A-I:A-II, and the progression rate. However, there was a statistically significant correlation between the plasma concentrations of triglyceride-rich LP-Bc particles and the subsequent rate of progression (r = 0.43, P = 0.004). In contrast, the levels of cholesterol-rich LP-B particles did not correlate with the progression of renal insufficiency (Table 1, Figure 2). Elevated concentrations of LP-Bc particles were associated with a higher progression rate independent of high or low levels of LP-B (Figure 3). The association between the plasma concentration of LP-Bc and the change in renal function (ΔGFR) thus was not dependent of initial GFR values, urinary protein excretion rates, or BP values at baseline.

Discussion

Results of our previous studies have shown that elevated levels of apoB-containing lipoproteins are of prognostic importance in patients with progressive chronic renal insufficiency (7,13). We have now demonstrated by direct measurement of apoB-containing lipoproteins that the role of these lipoproteins in the progression of renal insufficiency most likely depends on intact and/or partially delipidized triglyceride-rich lipoprotein particles rather than cholesterol-rich lipoprotein particles.
Table 1. Clinical and lipoprotein characteristics of 44 nondiabetic patients with chronic renal disease prospectively followed for up to 4 y

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients</th>
<th>Correlation Coefficient</th>
<th>P Value</th>
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<tbody>
<tr>
<td>No. of patients</td>
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<tr>
<td>ΔGFR (ml/min/1.73 m² BSA per year)</td>
<td>-3.2 (5.1)</td>
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<tr>
<td>Follow-up (years)</td>
<td>2.4 (1.0)</td>
<td>0.16</td>
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<td>GFR at start (ml/min/1.73 m² BSA)</td>
<td>40.3 (16.7)</td>
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<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>138.2 (17.2)</td>
<td>0.16</td>
<td>&gt;0.20</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>84.9 (10.1)</td>
<td>0.28</td>
<td>0.06</td>
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<td>Proteinuria (g/24 h)</td>
<td>1.4 (1.5)</td>
<td>0.14</td>
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<td>Lipids (mmol/L)</td>
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<tr>
<td>total cholesterol</td>
<td>6.4 (1.4)</td>
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<td>&gt;0.20</td>
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<td>triglycerides</td>
<td>1.9 (1.1)</td>
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<td>VLDL cholesterol</td>
<td>0.8 (0.4)</td>
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<td>LDL cholesterol</td>
<td>4.6 (1.2)</td>
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<td>HDL cholesterol</td>
<td>1.0 (0.3)</td>
<td>0.15</td>
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<td>Apolipoproteins (mg/100 ml)</td>
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<tr>
<td>apoA-I</td>
<td>112.4 (21.7)</td>
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<td>apoA-II</td>
<td>61.9 (13.6)</td>
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<td>apoB</td>
<td>129.7 (32.2)</td>
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<td>apoC-III</td>
<td>19.9 (7.1)</td>
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<td>apoE</td>
<td>17.8 (7.6)</td>
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<td>apoC-III-HS</td>
<td>6.1 (2.9)</td>
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<td>apoC-III-HP</td>
<td>11.8 (6.7)</td>
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<td>Lipoprotein particles (mg/100 ml)</td>
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<td>LP-A-I</td>
<td>36.1 (9.7)</td>
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<td>75.6 (17.9)</td>
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<tr>
<td>LP-B</td>
<td>114.1 (27.2)</td>
<td>0.08</td>
<td>&gt;0.20</td>
</tr>
<tr>
<td>LP-Bc</td>
<td>15.6 (8.8)</td>
<td>0.43</td>
<td>&lt;0.01</td>
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*Results are given as mean (SD). BSA, body surface area.

Patients in the present study represented a subset of nondiabetic patients with chronic renal insufficiency participating in our prospective study (13), the primary objective of which was to explore the possible role of renal dyslipoproteinemia (1) in the progression of renal dysfunction. This subgroup of patients was representative of unselected adult asymptomatic subjects with moderately advanced renal insufficiency due to primary renal disease with characteristic alterations in the apolipoprotein rather than the lipid pattern (1,13). The lipid and apolipoprotein profiles, other clinical and demographic characteristics, and the distribution of the underlying renal diseases did not differ in the present subgroup from that of the total patient population (13). All patients have been closely monitored.

Figure 2. Rate of progression of renal insufficiency (ΔGFR = decline in GFR ml/min per 1.73 m² per year) in relation to the initial level of apolipoprotein B, LP-B, and LP-Bc in 44 nondiabetic patients followed for an average of 2.4 yr.
during the follow-up and managed according to recommended treatment strategies. Nine of 10 patients were on active antihypertensive drug therapy, with the majority receiving an ACE inhibitor.

Thus far, studies of the prognostic role of hyperlipidemia in progressive renal disease have focused on the impact of elevated plasma lipids (5,6,8,9,10). However, most patients with renal dyslipoproteinemia, which occurs in the early stages of renal insufficiency, have unchanged or only moderately elevated plasma lipid levels (1). Because renal dyslipoproteinemia is predominantly reflected by an abnormal apolipoprotein rather than lipid profile (1), it is necessary to analyze specific lipoprotein abnormalities also in terms of apolipoprotein and lipoprotein particle composition. The importance of apolipoprotein profiling is based on the notion that apolipoproteins are the essential constituents responsible for the structural stability and functional properties of lipoprotein particles (25). Furthermore, as chemically unique constituents, apolipoproteins are also the most suitable markers for differentiating and classifying plasma lipoproteins (26). Accordingly, the apoA- and apoB-containing lipoproteins represent the two main classes of lipoproteins defined by the apolipoprotein composition. As stated previously, the former consist of three and the latter of five distinct lipoprotein families (Figure 1). It has been shown previously that decreased levels of apoA-I and apoA-II, normal or slightly elevated levels of apoB, and increased levels of apoC-III are the characteristic features of apolipoprotein profile in patients with renal insufficiency (1). In terms of lipoprotein families, the renal dyslipoproteinemia has been characterized by decreased levels of LP-A-I:A-II (12) and increased concentrations of intact or partially delipidized triglyceride-rich LP-Bc particles (11). Depending on the extent of delipidization, LP-Bc particles have densities characteristic of IDL and/or LDL.

Previously, we have reported that elevated levels of apoB-containing lipoproteins seem to promote a faster rate of decline in renal function of patients with moderately advanced renal insufficiency (7,13). The present findings extend those observations and indicate that of the apoB-containing lipoproteins, it is the triglyceride-rich LP-Bc particles that are most strongly associated with a faster rate of progression of the renal dysfunction. As evident from Figures 2 and 3, the impact of elevated plasma concentrations of simple, cholesterol-rich LP-B particles seems to be marginal. This also suggests that our previous observations of an association between high plasma levels of apoB and the rate of progression can now be explained by increased plasma concentrations of the complex LP-Bc particles. Although the underlying mechanism(s) responsible for the accumulation of these lipoprotein particles has not been established with certainty, it is reasonable to assume that it may be due at least partially to a delayed catabolism of triglyceride-rich lipoproteins (1).

Our previous analyses (13) have shown that LDL cholesterol and apoB levels were significantly associated with a more rapid decline in renal function. The lack of a statistically significant association between these variables and the progression rate found in the present study is most likely due to a smaller number of patients in this than in the previous study (44 versus 73 patients). However, the association between the levels of LDL cholesterol and the progression rate is in accordance with the present finding of a strong relationship between the concentration of LP-Bc particles and the rate of decline in renal function. Because the LDL cholesterol levels were estimated by the Friedewald formula (17), the IDL cholesterol

![Figure 3. Rate of progression of renal insufficiency (decline in GFR ml/min per 1.73 m² per year) in relation to high and low levels of LP-B and LP-Bc in 44 patients with moderately advanced renal failure. The cutoff points for LP-B and LP-Bc particles were the respective median levels of 110.0 and 13.5 mg/dl.](image)
levels were also included in this measurement. Thus, the calculated LDL cholesterol encompasses cholesterol content of both LP-B and the majority of LP-Bc particles.

There are now several clinical observational studies suggesting that renal dyslipoproteinemia is an important contributory factor to progressive human renal disease (1, 4-10). Studies based on animal models of renal insufficiency have suggested that the composition of circulating lipoproteins may be an important determinant of their nephrotoxic potential, and that increased concentrations of some abnormal lipoprotein particles may be more prone to cause renal injury than the elevated levels of normal particles (27, 28). Results of the present study are in full agreement with this hypothesis, and for the first time provide evidence from a prospective study that the accumulation of structurally or functionally altered lipoprotein particles is also of prognostic importance in human chronic renal disease. Furthermore, these results suggest that some lipoprotein particles belonging to the LP-Bc family are particularly nephrotoxic.

Complex apoB-containing lipoproteins of intermediate and low densities not only may promote kidney damage through interactions with glomerular and/or tubulointerstitial tissues, but also may play a role in the development of atherosclerosis (29-31). Recently, the Monitored Atherosclerosis Regression Study (MARS) provided further support for the atherogenic potential of triglyceride-rich lipoproteins by showing a significant association of these lipoproteins with the progression of small atherosclerotic lesions (32). Furthermore, the significant role of LP-Bc in the progression of atherosclerosis was confirmed by direct measurements of these particles in a subset of MARS patients (33).

The importance of these lipoprotein abnormalities for both the accelerated decline in renal function and development of premature atherosclerosis is of particular interest, because analogous pathophysiologic mechanisms have been proposed to be operative in both glomerulosclerosis and atherosclerosis (3, 27). Whether the renal dyslipoproteinemia also contributes to accelerated atherosclerosis in patients with chronic renal disease and the well documented increase in cardiovascular morbidity and mortality in patients with end-stage renal disease (34) remains to be proven. However, many reports indicate that this could be the case (2). Theoretically, because renal dyslipoproteinemia is characterized by the accumulation of triglyceride-rich and cholesterol-rich apoB-containing lipoproteins, patients with chronic renal disease should be at a high risk for atherosclerotic complications.

Elevated BP and proteinuria are well established risk factors for accelerated decline in renal function (35, 36). The lack of statistically significant associations between these risk factors and the rate of progression in the present study may be explained, at least in part, by the extensive use of treatment with ACE inhibitors, which are effective BP-lowering agents with antiproteinuric properties. Furthermore, only three patients in this study group had nephrotic-range proteinuria at the beginning of the follow-up period, resulting in a rather low average urinary protein excretion rate of 1.4 g/24 h in the present subset of patients. This is in contrast to the higher urinary protein excretion rate, due to relatively more patients with a higher degree of proteinuria, in the whole study population (13). Furthermore, the narrow range of a rather modest absolute level of proteinuria in this study group makes it more difficult to show a relation between proteinuria and the rate of decline in renal function. This is in agreement with the observations of the Modification of Diet in Renal Disease Study, in which a lower degree of proteinuria is not associated with the rate of progression, regardless of the BP control (37). These findings further strengthen the notion that the adverse effects of renal dyslipoproteinemia on the progression of renal insufficiency is not dependent on the degree of proteinuria (38).

In conclusion, the results of this study extend our previous findings that lipoprotein abnormalities caused by renal insufficiency may influence the progression of renal failure in human chronic renal disease. Specifically, it seems that some of the intact or partially metabolized triglyceride-rich LP-Bc particles are mainly responsible for promoting the progression of renal insufficiency. However, at present it is not known whether lipid-lowering therapy can reduce the rate of progression. A lipid-lowering clinical intervention trial in patients with renal insufficiency is therefore needed to establish whether renal dyslipidemia is a causal factor in the process of glomerulosclerosis and chronic progressive renal failure in human chronic renal disease.

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References


