Abnormal Concentrations of CII, CIII, and E Apolipoproteins among Apolipoprotein B-Containing, B-Free, and A-I-Containing Lipoprotein Particles in Hemodialysis Patients

Neji Alayed and Regis Reboucet

Serum concentrations of total cholesterol, triglycerides, and apolipoproteins (apo) A-I, B, CII, CIII, and E in 36 hemodialysis patients and nine anephric patients were compared with the concentrations in 34 normolipidemic subjects. The dialysis patients displayed a moderate hypertriglyceridemia (1.94 ± 0.12 vs 1.09 ± 0.11 mmol/L in controls, mean ± SEM; P < 0.001), apo CII concentrations were also increased (130.2 ± 2.1 vs 108.4 ± 0.7 mg/L; P < 0.001), whereas apo CII (34.5 ± 0.5 vs 36 ± 0.5 mg/L; P < 0.05), apo E (22.7 ± 0.3 vs 27.9 ± 0.2 mg/L; P < 0.001), and apo A-I (1.18 ± 0.05 vs 1.31 ± 0.04 g/L; P < 0.05) were decreased. Concentrations of serum apo B were normal (0.86 ± 0.03 vs 0.97 ± 0.07 g/L). In the hemodialysis patients, apo CII concentrations were increased in apo B-containing lipoproteins (30.1 ± 0.5 vs 25.0 ± 0.1 mg/L; P < 0.001), whereas CII and E were decreased below control values (14.4 ± 0.2 vs 16.8 ± 0.1, and 8.2 ± 0.2 vs 11.4 ± 0.1 mg/L, respectively; P < 0.001 each). By calculation, non-B-containing lipoproteins in the hemodialysis group had increased concentrations of apo CII (100.1 ± 2.1 vs 83.3 ± 0.7 mg/L; P < 0.001) and decreased amounts of apo E (14.5 ± 0.4 vs 16.4 ± 0.3 mg/L; P < 0.001); apo CII content was unchanged (20.1 ± 0.5 vs 19.3 ± 0.5 mg/L). Results for apo CII, CIII, and E among apo A-I-containing lipoproteins in both normolipidemic and hemodialysis groups were similar to those in non-B-containing lipoproteins. Finally, the sole significant (P < 0.01) difference between the anephric and hemodialysis groups was the lower apo E concentrations in the former group. Accumulation of triglyceride-rich lipoproteins in hemodialysis patients may thus be related to the enrichment of apo CII in apo B-containing lipoproteins and to a marked decrease in the apo CII and E contents.

Additional Keyphrases: chronic renal failure · uremia · hypertriglyceridemia · enzyme immunoassay

Chronic renal failure is clearly associated with a disturbance in lipid metabolism. Numerous studies have been devoted to evaluation of the plasma lipid profile in this pathological state (1–5). The mild hypertriglyceridemia of chronic renal failure is considered to be due to an increase in concentrations of circulating very-low-density lipoproteins (VLDL) and their metabolic products (6, 7). The cholesterol content of low-density lipoproteins (LDL) is normal, whereas that of high-density lipoproteins (HDL) is decreased (4, 8–10).

Over recent years, apolipoproteins have been receiving increasing attention in view of their important role in the structural integrity and functional specificity of lipoprotein particles. Most studies have focused on the major apolipoproteins of LDL [i.e., apolipoprotein B (apo B)] and HDL (i.e., apo A-I) so as to understand further the mechanisms underlying the atherogenicity of certain dyslipoproteinemic states (II–17). Serum concentrations of apo A-I in uremic patients are generally thought to be less than in control subjects (7–10, 18–22), whereas those of apo B are normal (19–21, 23) or also decreased (22). Minor apolipoproteins have received less attention, although the C proteins and apo E play an important role in the catabolism of triglyceride-rich lipoproteins (TRL) (24).

The hydrolysis of lipoprotein triglycerides by lipoprotein lipase is stimulated by apo CII (24, 25) and inhibited by apo CIII, at least under certain in vitro experimental conditions (26–28). Apo E is considered to be the signal mediating the hepatic removal of cholesterol-laden HDL, subfractions and chylomicron remnants from the circulation (29, 30). Apo CIII also reportedly inhibits the apoE-mediated clearance of TRL by the liver (31, 32). The normal catabolism of lipoproteins implicates the transfer and exchange of apo CII, apo CIII, and apo E from HDL to VLDL and chylomicrons, and from chylomicrons and VLDL to HDL before and during lipolysis by lipoprotein lipase (33). Thus, an alteration in the total concentrations of these three apolipoproteins in plasma, and especially of their relative proportions within TRL, could affect the clearance rate of these particles. Until now, few studies have been performed to evaluate the concentrations in serum of apo CII, CIII, and E in uremic subjects by use of specific immunoassays (21, 22, 34).

The present study was undertaken to provide more information on the distribution of apo CII, CIII, and E in apo B-containing as well as in non-B-containing and in apo A-I-containing lipoproteins in sera of hemodialysis and anephric patients. We have approached this question by applying a new, specific, enzyme-linked immunosorbent assay (ELISA) technique (35).

Materials and Methods

Patients

Groups of 36 hemodialysis patients and of nine anephric patients were investigated; results were com-

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Nonstandard abbreviations: apo, apolipoprotein; TRL, triglyceride-rich lipoproteins; VLDL, IDL, HDL, very-low-, intermediate-, and high-density lipoproteins; ELISA, enzyme-linked immunosorbent assay; and PHLA, post-heparin lipolytic activity.
pared with those obtained in 34 healthy normolipidemic blood donors. Our group of hemodialysis patients consisted of 13 women and 23 men, a mean (SEM) age of 36.3 ± 3.1 years and a length of dialysis of 10 (SEM 5.3) years.

The diagnosis of renal failure was chronic glomerulonephritis in 15 patients, polycystic kidney disease in three, chronic interstitial nephritis in 14, and another or unknown diagnosis in four patients. In this latter group, only five patients were receiving beta-blocking agents for anti-hypertensive treatment. Patients were selected according to their mean serum concentrations of creatinine and urea: 1023 (SEM 47.6) μmol/L and 32.24 (SEM 2.41) mmol/L, respectively. These patients did not present with diabetes mellitus, thyroid dysfunction, or biochemically evident hepatic dysfunction.

The group of nine anephric patients consisted of six men and three women, mean age 43 (SEM 5) years and duration of dialysis 15 (SEM 5) years. Their mean serum concentrations of creatinine and urea were 1263 (SEM 12) and 42 (SEM 6) mmol/L, respectively.

The healthy group of blood donors comprised 15 women and 19 men; they were selected according to their cholesterol (<7.00 mmol/L) and triglyceride (<2.00 mmol/L) concentrations and had a mean age of 35.39 (SEM 2.5) years.

Blood was drawn, after overnight fasting, into Vacutainer Tubes (Becton-Dickinson Vacutainer, Meylan, France) by antecubital venipuncture—typically before a hemodialysis session in patients. Serum samples, obtained by low-speed centrifugation, were stored at 4 °C until use.

Lipid and Apolipoprotein Analyses

We quantified total cholesterol and triglyceride concentrations in serum by using enzymatic methods (Triglyceride GPO-PAP kit, Boehringer, Mannheim, F.R.G.; and Cholesterol Enzymatic Color kit, Biotrol, Paris, France) with a Hitachi 705 analyzer (Hitachi Ltd., Tokyo, Japan).

Serum concentrations of apo A-I and apo B were determined immunoturbidimetrically (36) with a Monarch 200 Model 760 (Instrumentation Laboratory Inc., Lexington, MA) and commercial antibodies (Hoechst-Behring, Rueil-Malmaison, France).

Apo CII, CIII, and E were measured in total serum, in apo B-containing lipoproteins, and in apo A-I-containing lipoproteins, with use of ELISA involving antibodies that had been prepared and purified in our laboratory (35, 37). Briefly, we coated 96-well microtiter plates (Nunc, Polylabo, Strasbourg, France) with each purified antibody, 500 ng/well (100 μL of a 5 mg/L solution per well), and incubated overnight at 4 °C. After three successive washings, we pipetted onto the wells 100 μL of three different dilutions of each serum sample in phosphate-buffered saline (10 mmol/L, pH 7.4) containing 1 mL of Tween 20 per liter, and then incubated the plates for 2 h at 37 °C. After three washes with phosphate-buffered saline containing 5 mL of Tween 20 per liter, we pipetted into each well 100 μL of the corresponding 1000-fold-diluted peroxidase-labeled antibody and incubated for a further 2 h at 37 °C. Finally, we pipetted 100 μL of substrate solution into previously washed plates and allowed color development to proceed at room temperature for 20 min; 50 μL of 3.7 mmol/L NaCN reagent was added to stop the reaction and the absorbance at 415 nm was recorded.

Before determining the apo CII, CIII, or E associated with the apo B-containing lipoprotein particles, we coated the plates with BL7, 500 ng/well (per well, 100 μL of a 5 mg/L solution), a monoclonal anti-ape B antibody produced in mice (Sanofi Research Center, Montpellier, France) and characterized by its similar affinity for VLDL and LDL (35, 38, 39). Similarly, the amounts of apo CII, CIII, or E associated with the apo A-I-containing lipoprotein particles were determined by coating plates with 4A12, 500 ng/well (100 μL of a 5 mg/L solution), a monoclonal anti-ape A-I antibody produced in mice (Sanofi Research Center) (40).

Other steps in this ELISA were performed as described above, with peroxidase-labeled anti-ape CII, anti-ape CIII, or anti-ape E antibodies, as appropriate, in the last step, to measure the corresponding apolipoproteins in apo B- and in apo-A-I-containing lipoprotein particles. The protein concentrations of purified antibodies and purified apolipoproteins used for construction of the standard curves were determined by use of the classic Lowry technique, with bovine serum albumin as standard (41). The standard curves were established with purified apo CII, CIII, and E (42) and were used to calculate the concentrations of apo CII, CIII, and E in whole serum and in apo-B- and in apo-A-I-containing lipoproteins.

Each determination was made in triplicate. For each group of subjects, values are presented as mean ± SEM. We compared two values by using Student’s t-test. Correlation between two independent values was evaluated by linear regression.

Results

Serum triglyceride concentration was significantly greater in hemodialysis patients than in control subjects (Table 1). In contrast, total serum cholesterol and apo B concentrations did not differ between these groups: apo B concentrations, determined in patients and in controls by both immunoturbidimetric and ELISA techniques, yielded values of 0.86 ± 0.027 vs 0.97 ± 0.097 g/L and 0.93 ± 0.059 vs 1.010 ± 0.086 g/L, respectively. Thus, quantification of apo B by two different methods confirmed that serum apo B concentrations in our hemodialysis patients were within the normal range, and that the two methods gave similar results for both the patients and the control group.

Concentrations of apo A-I in serum were significantly lower in the hemodialysis patients (P <0.05) than in the control group, whereas total serum apo CII was slightly (4.4%) but significantly (P <0.05) decreased in the former group, and total serum apo E was markedly (18.6%) decreased (P <0.001). Finally, total concentrations of apo CIII in serum were 20.1% higher in hemo-
Table 1. Total Lipid and Apolipoprotein Concentrations in Serum of Hemodialysis Patients and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Control subjects (n = 34)</th>
<th>Hemodialysis patients (n = 36)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.08 ± 0.11</td>
<td>1.94 ± 0.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.16 ± 0.19</td>
<td>4.97 ± 0.26</td>
<td>NS</td>
</tr>
<tr>
<td>Apo A-I, g/L</td>
<td>1.31 ± 0.03</td>
<td>1.18 ± 0.04</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Apo B, g/L</td>
<td>0.97 ± 0.07</td>
<td>0.86 ± 0.03</td>
<td>NS</td>
</tr>
<tr>
<td>Apo CII, mg/L</td>
<td>38.1 ± 0.52</td>
<td>34.5 ± 0.54</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Apo CIII, mg/L</td>
<td>108.4 ± 0.68</td>
<td>130.2 ± 2.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apo E, mg/L</td>
<td>27.9 ± 0.23</td>
<td>22.7 ± 0.35</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NS, not significant.

dialysis patients than in healthy subjects (P <0.001).

The contents of apo CII, CIII, and E in apo B-containing lipoproteins, in apo B-free (non-B-containing) lipoproteins, and in apo A-I-containing lipoprotein particles are indicated in Table 2. We observed significantly decreased concentrations of apo CII and apo E (by 14.3% and 19.5%, respectively; P <0.001) in the apo B-containing lipoproteins in the hemodialysis group; such alterations were associated with a significant increase in the amounts of apo CIII (20.4%; P <0.001) in these same particles. The content of apo CII in non-B-containing as well as in apo A-I-containing lipoproteins was similar in hemodialysis patients and controls, whereas apo CIII content was significantly increased, and apo E significantly decreased (each P <0.001), in both groups in comparison with the contents of the apo B-containing lipoproteins. Figure 1 shows the ratios between the contents of apo CII, CIII, and E in apo B-containing lipoproteins and the corresponding total apolipoprotein concentrations in serum. The ratios of B-CII/total apo CII and of B-E/total apo E were diminished in the hemodialysis patients: 42.0% ± 0.9% vs 46.0% ± 0.9% (P <0.001) and 36.4% ± 0.9% vs 41.1% ± 0.6% (P <0.001), respectively. By contrast, the ratio of B-CIII/total apo CIII was similar in both groups (23.3% ± 0.5% vs 23.1% ± 0.2%). The ratios of apo CII/apo CIII concentrations were determined in total serum, in apo B-containing, in apo B-free, and in apo A-I-containing lipoproteins (Figure 2). All ratios were significantly less in the hemodialysis patients than in the control group.

However, the most marked decrease (27.7%) occurred in the B-CII/B-CIII ratio (P <0.01). When comparing values in men with those in women, we found that, in the control group, only serum triglyceride concentrations were significantly lower in women than in men (0.84 ± 0.10 vs 1.30 ± 0.17 mmol/L; P <0.05). In hemodialysis patients, total apo CII (133.6 ± 2.7 vs 124.3 ± 2.7 mg/L) and non-B-CIII (103.8 ± 2.6 vs 93.6 ± 2.5 mg/L) were higher in men than in women, although the ratio of B-CII/total apo CIII was significantly higher in the women than in the men in this group.

As Table 3 shows, the most pronounced difference between anephric patients and our hemodialysis group was the marked decrease in total serum apo E (9.7%; P <0.01), especially in the apo B-containing lipoprotein particles (20.7%; P <0.001), in the former group.

Subdividing the hemodialysis patients according to whether their triglyceride concentrations were less than (n = 17) or greater than 1.85 mmol/L (n = 19) revealed

Table 2. Concentrations of Apo CII, CIII, and E among Various Lipoprotein Particles in Hemodialysis Patients and Control Subjects

<table>
<thead>
<tr>
<th>Apolipoprotein *</th>
<th>Control subjects</th>
<th>Hemodialysis patients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CII in B LP</td>
<td>16.8 ± 0.13</td>
<td>14.4 ± 0.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CII in A-I LP</td>
<td>19.5 ± 0.52</td>
<td>20.2 ± 0.54</td>
<td>NS</td>
</tr>
<tr>
<td>CII in non-B LP</td>
<td>19.3 ± 0.53</td>
<td>20.1 ± 0.54</td>
<td>NS</td>
</tr>
<tr>
<td>CII in B LP</td>
<td>25.0 ± 0.13</td>
<td>30.1 ± 0.55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CIII in A-I LP</td>
<td>83.1 ± 0.67</td>
<td>102.1 ± 2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CIII in non-B LP</td>
<td>83.3 ± 0.67</td>
<td>100.1 ± 2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E in B LP</td>
<td>11.4 ± 0.09</td>
<td>8.21 ± 0.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E in A-I LP</td>
<td>16.4 ± 0.29</td>
<td>13.5 ± 0.37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E in non-B LP</td>
<td>16.4 ± 0.28</td>
<td>14.5 ± 0.37</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* in lipoprotein particles containing apo B (B LP), containing no apo B (non-B LP), or containing apo A-I (A-I BP).

<sup>b</sup>n as in Table 1.

NS, not significant.

Fig. 2. Ratios of apo CII/apo CIII in total serum, in apo B-containing lipoproteins, in apo B-free lipoproteins, and in apo A-I-containing lipoproteins in 34 control subjects (C) and in 36 hemodialysis patients (A).

Fig. 1. Ratios of the concentrations of apo CII, CIII, and E in apo B-containing lipoproteins to the corresponding apolipoprotein concentrations in total serum from 34 controls (C) and from 36 hemodialysis patients (A).

Data taken from Tables 1 and 2.
Table 3. Concentrations of Lipid and Apo CII, CIII, and E in Total Serum and among Various Lipoprotein Particles in Anephric Patients and Other Hemodialysis Patients

<table>
<thead>
<tr>
<th></th>
<th>Anephric patients</th>
<th>Hemodialysis patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SEM</td>
<td>Mean ± SEM</td>
</tr>
<tr>
<td></td>
<td>(n = 8)</td>
<td>(n = 38)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>2.51 ± 0.19</td>
<td>1.94 ± 0.12</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.80 ± 0.32</td>
<td>4.97 ± 0.26</td>
</tr>
<tr>
<td>Apo A-I, g/L</td>
<td>1.13 ± 0.09</td>
<td>1.18 ± 0.04</td>
</tr>
<tr>
<td>Apo B, g/L</td>
<td>0.82 ± 0.08</td>
<td>0.86 ± 0.03</td>
</tr>
<tr>
<td>CII in sera, mg/L</td>
<td>33.3 ± 0.73</td>
<td>34.5 ± 0.54</td>
</tr>
<tr>
<td>CII in B LP, mg/L</td>
<td>14.2 ± 0.62</td>
<td>14.4 ± 0.24</td>
</tr>
<tr>
<td>CII in A-I LP, mg/L</td>
<td>19.8 ± 0.34</td>
<td>20.2 ± 0.54</td>
</tr>
<tr>
<td>CII in non-B LP, mg/L</td>
<td>19.1 ± 1.20</td>
<td>20.1 ± 0.54</td>
</tr>
<tr>
<td>CIII in sera, mg/L</td>
<td>135.4 ± 1.5</td>
<td>130.2 ± 2.1</td>
</tr>
<tr>
<td>CIII in B LP, mg/L</td>
<td>30.6 ± 0.47</td>
<td>30.1 ± 0.51</td>
</tr>
<tr>
<td>CIII in A-I LP, mg/L</td>
<td>106.3 ± 2.1</td>
<td>102.1 ± 2.3</td>
</tr>
<tr>
<td>CIII in non-B LP, mg/L</td>
<td>104.8 ± 1.6</td>
<td>100.1 ± 2.0</td>
</tr>
<tr>
<td>E in sera*</td>
<td>20.9 ± 0.75</td>
<td>22.7 ± 0.35</td>
</tr>
<tr>
<td>E in B LP*</td>
<td>6.68 ± 0.28</td>
<td>8.20 ± 0.16</td>
</tr>
<tr>
<td>E in A-I LP, mg/L</td>
<td>13.22 ± 0.9</td>
<td>13.53 ± 0.3</td>
</tr>
<tr>
<td>E in non-B LP, mg/L</td>
<td>14.22 ± 0.5</td>
<td>14.50 ± 0.3</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2. *P < 0.01. **P < 0.001.

no significant differences. However, this observation could be related to their moderate degree of hypertriglyceridemia in association with small variation in triglyceride concentrations between the two groups.

We established correlations among variables separately in control subjects and in hemodialysis patients. No correlation could be found between triglyceride concentrations and the concentrations of apo CII, CIII, or E in either total serum or in apo B-containing lipoprotein particles. The apo CII and E concentrations were significantly correlated in both control and hemodialysis groups (r = 0.355 and 0.550, respectively, each P < 0.05), whereas only the apo CIII concentrations in hemodialysis patients were significantly correlated with those of apo CII and E (r = 0.447, P < 0.01, and r = 0.386, P < 0.02, respectively). Finally, for the CII, CIII, and E apolipoproteins in the apo B-containing lipoproteins, apo CIII and E concentrations in hemodialysis patients were significantly correlated (r = 0.364, P < 0.05).

Discussion

Patients with chronic renal failure and who undergo regular hemodialysis display a high prevalence of atherosclerotic disease (43–46). However, it is still uncertain whether uremic patients are more prone to develop such disease (47), although they frequently exhibit a more rapid progression of already existing disease (48). Plasma lipid profiles in chronic renal failure have been widely studied (1–5), but only few apolipoprotein profiles have been described (21, 22, 34). In agreement with previous reports, we have observed that hemodialysis patients display moderate hypertriglyceridemia, normal concentrations of total serum cholesterol (1–5, 21, 22, 34, 48), subnormal apo B, and decreased apo A-I (6, 21, 34, 48, 50). Furthermore, concentrations of triglycerides and cholesterol were increased in serum of anephric patients.

Regarding the minor apolipoproteins, our patients showed markedly increased total serum concentrations of apo CIII, with characteristic decreases in apo CII and E as described by others (21, 22, 34, 51, 52). Studies of the distribution of these apolipoproteins among apo B-containing and apo B-free lipoproteins, as originally suggested by Attman et al. (21), allow a more precise characterization of the uremic dyslipidemias and their role in the progression of atherosclerotic disease in patients with chronic renal failure. To our knowledge, the only published report on this describes apo CIII distribution between apo B-containing and apo B-free lipoprotein particles (22). In fact, both our own studies and those of Parsy et al. (22) show increased concentrations of apo CIII among the apo B-containing lipoproteins; however, in disagreement with the latter authors (22), we observed that the increase in total serum apo CIII in hemodialysis patients was almost equally distributed between the apo B-containing and the apo B-free lipoproteins (20.4% and 20.1%, respectively). The discrepancies between these two reports are most probably due to the lack of specificity of the precipitation methods that were used to separate the apo B-containing from the apo B-free lipoproteins prior to the determination of apo CIII concentrations among these lipoprotein particles. Moreover, several reports indicate the presence of apo B-containing lipoproteins in the supernate and apo A-I-containing lipoproteins in the precipitate (53–55).

In addition to the use of a specific immunological method for the separation of apo B-containing lipoproteins from the apo B-free lipoproteins prior to the determination of CII, CIII, and E concentrations among these particles, we have obtained original information on the CII and E apolipoprotein concentrations in these two lipoprotein classes. Our results indicate that the decreased apo CII content of total serum is focused only on the apo B-containing lipoproteins, whereas the reduction in total serum apo E concentration occurred within apo B-containing and apo B-free lipoprotein particles at the same time, but was more pronounced in the apo B-containing lipoproteins (28% vs 11.6%). The latter observations are also true for anephric patients, but the more marked decrease in apo E in this group may confirm a role of the kidney in apo E synthesis and supports the possibility that a reduced renal parenchyma contributes less to the serum pool of apo E than in normal subjects, as already proposed by Blum et al. (56) and Attman et al. (21). Moreover, the more marked hypertriglyceridemia of these patients than in other hemodialysis subjects may suggest a role for apo E in the dyslipidemias of hemodialysis patients.

However, it remains to be established whether the more marked reduction in anephric apo E concentrations contributes to their increased risk.
Numerous studies have indicated that both impaired removal and increased production of TRL particles contribute to the hypertriglyceridemia of chronic renal failure (3, 50, 57–60). However, more recent studies suggest that a defective removal of TRL in such patients may be a more significant contributing factor than increased production (3, 7, 21–23). This view is supported by studies demonstrating reduced plasma post-heparin lipolytic activity (PHLA) and decreased clearance of triglycerides in chronic renal failure (4, 60–65). Moreover, findings such as reduced fractional turnover rates of VLDL triglycerides (18, 61) and absolute and (or) relative increases in the triglycerides content of VLDL, LDL, and HDL (2, 6), the identification of apo B-48 in VLDL, increased concentrations of apo A-IV in VLDL and LDL and of apo C and E in LDL (6) also suggest incomplete degradation and (or) uptake of TRL and consequent accumulation of remnant particles. Furthermore, Gonen et al. (66) have reported that LDL from hemodialysis patients have abnormal composition and are less readily taken up and degraded by fibroblasts than are normal LDL. Moreover, patients presenting familial hypertriglyceridemia (66, 67) and diabetes mellitus (68, 69), and who exhibit an overproduction of triglyceride-enriched VLDL, are characterized not only by increased concentrations of apo CII but also by increased concentrations of apo B and E (70).

This situation is unlikely to be the case in hemodialysis patients. Thus, overproduction of triglyceride-rich VLDL may play only a minor role in hypertriglyceridemia of hemodialysis patients (21). However, an overproduction of apo B-free lipoprotein particles enriched in apo CIII and devoid of E and CII remains possible in our patients. In fact, the existence of lipoprotein particles possessing apo CIII as their principal apolipoprotein has already been suggested by Attman et al. (34).

Because the dyslipidemia of hemodialysis patients is essentially limited to the TRL particle, our findings on the concentrations of apo CII, CIII, and E in apo B-containing and in apo B-free lipoproteins should provide a better understanding of the role of these apolipoproteins in the hemodialysis dyslipidemias.

In fact, in light of our findings documenting an increase of apo CIII in apo B-containing lipoproteins from hemodialysis patients and of a reduced PHLA associated with decreased remnant clearance (4, 23, 60–65), and in view of the inhibitory role of apo CIII on lipoprotein lipase activity (26–28) and on the hepatic uptake of TRL particles (31, 32, 70), we think that apo CIII may play a key role in the hypertriglyceridemia of hemodialysis patients. However, when anephric patients were compared with the hemodialysis group, their more marked hypertriglyceridemia was not associated with a significant increase in apo CIII.

Because apo CII is the activator of lipoprotein lipase (24, 25) and because reduction in PHLA in hemodialysis patients is associated with a decreased apo CII content in apo B-containing lipoprotein, it is possible that reduction in apo CII may contribute to the hypertriglyceridemia of hemodialysis patients. The origin of the low apo CII concentrations in this patient group could be related to the apo B-containing lipoprotein triglycerides and their enrichment in apo C-III. In this context Windler and Havel (71) suggested that preferential loss of apo CII during remnant formation may result in the termination of triglyceride hydrolysis prior to complete removal of triglycerides from chylomicrons and VLDL. These authors also showed that incubation of remnants with unfractionated rat apo C proteins involved enrichment with apo CIII but not with apo CII (32, 71). However, we did not detect enrichment in C-II in either apo B-free or apo A-I-containing lipoproteins in our patients. The accumulation of remnant particles in hemodialysis patients (4, 60–65) and the fact that they display a reduced content of apo E, especially among the apo B-containing lipoproteins, suggest a possible role for apo E in hypertriglyceridemia of hemodialysis patients. Moreover, when comparing anephric patients with the hemodialysis group, we found that their more marked hypertriglyceridemia was associated with a significant decrease in apo E concentrations in total serum, especially in apo B-containing lipoproteins (P <0.01 and 0.001, respectively). Windler and Havel (71) showed that remnant particles enriched in apo CII are deficient in apo E (32, 71). Finally, determination of the apo CII, CIII, and E concentrations among apo A-I-containing lipoproteins (namely, A-I CII, A-I CIII, and A-I E) has indicated that apo B-free CII, CIII, or E might correspond to apo A-I containing CII, CIII, or E, respectively. In fact this could not be the case, because results obtained from a preliminary study indicate the simultaneous presence of particles containing A-I and B. This suggestion has also been proposed by others (33, 55). Thus, determination of CII, CIII, and E apolipoprotein concentrations among the various A-I and B lipoprotein particles would be necessary to evaluate whether apo B-free CII, CIII, or E corresponds to apo A-I containing A-I CII, A-I CIII, or A-I E, respectively, as suggested by our results.

We conclude that the increased apo CIII content of apo B-containing lipoproteins, associated with the decreased amounts of apo CII and E among these same particles, may lead to an impaired catabolism and (or) disturbed hepatic uptake of TRL. Such a metabolic dysfunction, rather than TRL overproduction, appears to be responsible for hypertriglyceridemia in hemodialysis patients and may be one of the major risk factors for the accelerated atherosclerotic disease typical of hemodialysis patients.

References


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