SHORT COMMUNICATION

Acute Changes in Concentrations of Apolipoproteins A-I, B, C-II and Lipoprotein(a) in Serum Covering the Period from Directly Before to 48 Hours After Chronic Haemodialysis

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Summary: This study reports the changes in total cholesterol, triacylglycerols, apolipoproteins A-I, B, C-II and (a) before, directly after and 48 hours after chronic renal dialysis on 46 non-selected patients (20 male, 26 female; time since first dialysis 1–203 months (median 22 months), median age 52 years, range 25–82 years). Thirty six of the 46 patients (17 men and 19 women) suffered from hypertension. There were no sex-linked differences in any analyte except cholesterol, which was significantly higher in women than in men at all times.

The apolipoproteins were determined with immunoluminometric assays. Apolipoprotein C-II was determined as the apolipoprotein C-II : apolipoprotein B complex. Lipoprotein(a) was determined using two antibodies directed against apolipoprotein(a).

Significant increases (p < 0.05) in serum concentrations before and after dialysis were seen for all analytes with the exception of cholesterol (no significant change) and apolipoprotein C-II (significant decrease). The median increases were: cholesterol 5%, triacylglycerols 28%, apolipoprotein A-I 19%, apolipoprotein B 11%, apolipoprotein C-II −39%, lipoprotein(a) [all patients 21% < 300 mg/l 8%, > 300 mg/l 163%].

The values 48 hours after dialysis were not significantly different from the value before dialysis for cholesterol (−5%), apolipoprotein B (0%) and lipoprotein(a) (−2% – all patients). Statistically significant lower concentrations of apolipoprotein C-II (−28%) (p < 0.01) and triacylglycerols (−19%) (p < 0.01) were observed, but not investigated further.

The behaviour of lipoprotein(a) was not correlated with any of the other analytes except triacylglycerols, where a statistically significant negative correlation was seen in all groups. Apolipoprotein B and apolipoprotein C-II, triacylglycerol and apolipoprotein C-II, and apolipoprotein B and triacylglycerol concentrations were correlated at all three sampling times. Lipoprotein(a) correlated with cholesterol only directly after dialysis, whereas cholesterol and triacylglycerols correlated before and 48 hours after dialysis, but not directly after dialysis. None of the analytes correlated with the time since the first dialysis, i.e. with the length of time on dialysis.

The results showed that dialysis by no means had a uniform effect on the lipid analytes studied, and that those patients with elevated lipoprotein(a) were subject to elevations of this analyte directly after dialysis, which were on average more than three times those before dialysis. The clinical relevance of these findings must be investigated further. The results indicate that it is important to standardise the blood sampling time for dialysis patients as results obtained before, during, and immediately after dialysis may vary significantly.

Introduction

The association between chronic haemodialysis and increased risk of cardiovascular disease is well known, especially with respect to recent results for (apo)lipoprotein(a) (1–3). Lipoprotein(a) has been described as an independent risk factor in atherogenic processes (1, 4–6), although some authors still question the direct action of lipoprotein(a) in the development of venous thrombosis (7).

This article describes the behaviour of several analytes directly concerned with lipid metabolism in patients undergoing chronic renal dialysis. Blood sampling times were directly before and after haemodialysis and again 48 hours after dialysis.

Materials and Methods

Patients

Forty six patients were studied, who were undergoing chronic renal haemodialysis. There was no prior selection. The median age of the patients was 52 years and the median length of time since commencement of chronic haemodialysis 22 months (range 1 month to 17 years). The distribution of the sexes was 20/46 male and 26/46 female.

The patients were dialysed three times per week using conventional haemodialysis. None was receiving continuous ambulatory peritoneal dialysis.

Analysis of lipid analytes

Triacylglycerols and total cholesterol were analysed enzymatically using reagents from Boehringer-Mannheim (Mannheim, Germany).
The apolipoproteins were assayed using two-site immunoluminometric assays described in detail elsewhere (8). Apolipoprotein A-I and apolipoprotein B were analysed as such (using standards from Immuno, Heidelberg, Germany), apolipoprotein C-II as apolipoprotein C-II : apolipoprotein B complex (using an apolipoprotein C-II standard, supplied by Immuno), and lipoprotein(a) using standards from Immuno. Although apolipoprotein(a) was detected, the results were given as lipoprotein(a) because of the standards used and the concordance of results with an assay using an apolipoprotein(a) : apolipoprotein B antibody combination (9).

Statistics

Non-parametric statistics were used throughout the study. The median was used as central tendency; comparisons were made with the Wilcoxon signed rank test for dependent variables, the Mann-Whitney U-test for independent variables and correlations were made using the Spearman rank correlation coefficient.

Results and Discussion

Table 1 shows the median values of the analytes measured for all analytes, both for all patients and for males and females separately. Significant differences between male and female at the level p ≤ 0.05 are shown in the footnotes of table 1. Table 2 shows the behaviour of those patients with lipoprotein(a) values below and above 300 mg/l.

A negative correlation between lipoprotein(a) and triacylglycerols was unexpectedly found, with correlation coefficients (r) between -0.287 and -0.409 and p values between 0.005 and 0.05. The correlation existed for males and females as well as for the whole group. There was no such correlation between lipoprotein(a) and cholesterol, with p > 0.4 in all cases. Apart from this statistically significant negative correlation with triacylglycerols, lipoprotein(a) correlated with none of the other analytes, not even apolipoprotein B.

The increases seen in lipoprotein(a) concentrations after dialysis were especially dramatic in those patients with lipoprotein(a) values above 300 mg/l (tab. 2). Although the concentrations rose significantly in all patients (p < 0.01), the changes seen in those patients with elevated lipoprotein(a) were on average above three times the pre-dialysis levels. This means that the effect of dialysis led to a transient worsening of the situation. During long periods of dialysis this cyclic effect may contribute to the worsening of the vascular situation seen in many long-term dialysis patients. The source of the increase in lipoprotein(a) remains speculative, but it may come from the blood vessel walls, being leached out from deposits during dialysis. This explanation is logical, when one compares these results with those from repeated hepatorenal extracorporeal low density lipoprotein precipitation (HELP apheresis), which leads to a stepwise lowering of lipoprotein(a) over a period of time, together with an improvement of vascular integrity and lessening of plaques and associated lipoprotein(a). The disproportionate increases in lipoprotein(a) in patients with concentrations over 300 mg/l could not be explained by haemodilution effects alone and there was no correlation between increases in lipoprotein(a) and either albumin or total protein.

Dialysis led to a significant decrease in apolipoprotein C-II : apolipoprotein B complexes, which may also result in a negative influence on the metabolism of VLDL. Increases in apolipoprotein A-I after dialysis were not accompanied by corresponding increases in apolipoprotein B, leading to an increase in the apolipoprotein A-I : apolipoprotein B ratio. Both cholesterol and triacylglycerols increased significantly during dialysis, so that haemodilution appears to have a generally negative effect on changes in serum concentrations of lipid analytes.

Many studies on dialysis patients have concentrated on the treatment of hyperlipidaemia using different medication regimes to influence the synthesis of fats, such as hydroxymethyl-glutaryl-CoA reductase inhibitors (9) and other lipid-lowering agents such as fibric acids (10). Other groups favour a low-protein diet with substitution of the essential amino acids, although this seems to be only effective on patients with Fredrickson Type IV hyperlipoproteinaemia (11). Sustained release bezafibrate treatment has been claimed to correct lipid abnormalities in continuous ambulatory peritoneal dialysis patients, although lipid levels tended to return to baseline values within 4 weeks after cessation of therapy (12). Lipoprotein(a) concentrations were not measured in this study.

Tab. 1 Median values and ranges for all analytes measured in 46 patients (20 males and 26 females).

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Before dialysis</th>
<th>After dialysis</th>
<th>48 h after dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipoprotein(a) all (mg/l)</td>
<td>182</td>
<td>220</td>
<td>180</td>
</tr>
<tr>
<td>Lipoprotein(a) males (mg/l)</td>
<td>182 (1.8–2816)</td>
<td>210 (20.6–2609)</td>
<td>160 (17.1–1192)</td>
</tr>
<tr>
<td>Lipoprotein(a) females (mg/l)</td>
<td>174 (2.8–2588)</td>
<td>248 (11.7–3527)</td>
<td>198 (5.0–1176)</td>
</tr>
<tr>
<td>Apolipoprotein C-II all (mg/l)</td>
<td>37.0</td>
<td>22.6</td>
<td>28.3</td>
</tr>
<tr>
<td>Apolipoprotein C-II males (mg/l)</td>
<td>28.1 (4.1–194)</td>
<td>22.5 (5.7–45.8)</td>
<td>27.4 (5.1–105)</td>
</tr>
<tr>
<td>Apolipoprotein C-II females (mg/l)</td>
<td>43.2 (14.2–109)</td>
<td>22.6 (5.9–75.5)</td>
<td>29.8 (19.8–75.6)</td>
</tr>
<tr>
<td>Apolipoprotein A-I all (g/l)</td>
<td>1.08</td>
<td>1.28</td>
<td>1.08</td>
</tr>
<tr>
<td>Apolipoprotein A-I males (g/l)</td>
<td>1.03 (0.79–1.74)</td>
<td>1.13 (0.80–2.22)</td>
<td>1.14 (0.63–1.64)</td>
</tr>
<tr>
<td>Apolipoprotein A-I females (g/l)</td>
<td>1.20 (0.79–2.16)</td>
<td>1.42 (0.86–2.37)</td>
<td>1.05 (0.72–1.95)</td>
</tr>
<tr>
<td>Apolipoprotein B all (g/l)</td>
<td>1.02</td>
<td>1.12</td>
<td>1.02</td>
</tr>
<tr>
<td>Apolipoprotein B males (g/l)</td>
<td>1.00 (0.43–1.32)</td>
<td>1.10 (0.68–1.51)</td>
<td>2.33 (0.55–1.42)</td>
</tr>
<tr>
<td>Apolipoprotein B females (g/l)</td>
<td>1.08 (0.78–1.70)</td>
<td>1.22 (0.84–2.61)</td>
<td>1.20 (0.72–2.19)</td>
</tr>
<tr>
<td>Cholesterol all (mmol/l)</td>
<td>6.76</td>
<td>7.13</td>
<td>6.38</td>
</tr>
<tr>
<td>Cholesterol males (mmol/l)</td>
<td>6.32 (3.53–8.27)</td>
<td>6.27 (4.96–8.41)</td>
<td>5.24 (2.50–8.77)</td>
</tr>
<tr>
<td>Cholesterol females (mmol/l)</td>
<td>7.04 (4.42–14.1)</td>
<td>7.64 (4.55–9.94)</td>
<td>6.85 (4.48–16.1)</td>
</tr>
<tr>
<td>Triacylglycerols all</td>
<td>2.74</td>
<td>3.52</td>
<td>2.22</td>
</tr>
<tr>
<td>Triacylglycerols males</td>
<td>2.46 (1.19–5.48)</td>
<td>2.93 (1.23–9.27)</td>
<td>1.98 (0.90–7.88)</td>
</tr>
<tr>
<td>Triacylglycerols females</td>
<td>2.74 (0.83–12.9)</td>
<td>3.95 (1.05–10.7)</td>
<td>2.33 (0.64–14.4)</td>
</tr>
</tbody>
</table>

Ranges in parentheses.

Cholesterol levels were significantly higher in females than in males.

Before dialysis p = 0.05, after dialysis p = 0.01, 48 h after dialysis p = 0.03.
There appeared to be no direct correlation between length of time on dialysis and lipoprotein(a) concentrations in the present study. There was a significant correlation between the lipoprotein(a) concentrations and the problems experienced by patients during dialysis. Those patients with low lipoprotein(a) levels were on average those with minor problems. This subjective assessment was carried out by the nephrologist, before he knew the lipoprotein(a) values. Two patients who have been dialysed for over 15 years have lipoprotein(a) values under 10 mg/l, live active lives and have no problems with haemodialysis. Three other patients who have lipoprotein(a) values above 1150 mg/l present with regular problems, especially with vasoregulation during and after dialysis.

In an American study of the causes of accelerated atherosclerosis in end-stage renal disease patients, apolipoprotein A-I and apolipoprotein B, but not lipoprotein(a) levels, were analysed, together with other clinical chemical analytes (13). This study was initiated as the majority of patients treated for chronic renal failure die of cardio-vascular complications. The same group studied the relationship between apolipoprotein clearance rates and susceptibility to atherosclerotic changes in patients undergoing continuous ambulatory peritoneal dialysis (14). Again, lipoprotein(a) was not measured.

The results of the present study tend to show that renal dialysis has an acute negative effect on lipid metabolism, and may go partly toward explaining why many patients on haemodialysis tend toward a worsening of cardiovascular function. The results are also interesting, as 34/46 patients had been on renal dialysis for less than 5 years.

The lipoprotein(a) concentrations in the serum of patients who have to undergo chronic renal dialysis may be of additional help in forecasting cardiovascular problems during dialysis. Correction of hyperlipidaemia in patients undergoing renal dialysis, where necessary, may reduce the cumulative acute negative effects of dialysis described in this study.

This study is not presented as a long-term observation on dialysis patients. It reveals, however, that acute changes occur during haemodialysis. The results presented warrant further investigation, especially as renal dialysis patients are known to have an elevated frequency of lipid metabolism disturbances. Whether the reduction of apolipoprotein C-II : B complexes is sufficient to alter the lipoprotein lipase activity must also be followed up.

References
