The Serum Lipids Levels may be Underestimated in Patients on Hemodialysis

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Abstract

Objective Although lipid disorders are a well-known risk factor for cardiovascular disease (CVD) in the general population, the optimal management with lipid-lowering therapy to reduce CVD risks and mortality in hemodialysis (HD) patients remains controversial. In the clinical setting, dyslipidemia can be diagnosed based on the detection of elevated lipid concentrations at the beginning of HD. This study investigated changes in the levels of serum lipids during a single HD session.

Methods The serum total cholesterol, triglyceride and high-density lipoprotein (HDL) cholesterol levels were measured in 31 HD patients at zero, two and four hours after the beginning of a single HD session. The data were analyzed using the Wilcoxon signed-rank test, a linear mixed model and Spearman’s rank correlation analysis.

Results The serum total cholesterol, HDL cholesterol and non-HDL cholesterol levels increased significantly during the HD session. Even after the lipid parameters were corrected for changes in the total protein level, the total cholesterol and HDL cholesterol levels increased, whereas the non-HDL cholesterol levels did not change significantly. The percentage change in the serum levels of these lipid fractions correlated strongly with the percentage change in the ultrafiltration volume per body weight. In contrast, the serum triglyceride levels were decreased significantly at two hours compared with the levels noted at the beginning of HD and gradually increased at four hours.

Conclusion The serum lipid levels are influenced significantly by HD treatment and ultrafiltration. Evaluating the degree of dyslipidemia at the beginning of a HD session may therefore underestimate the levels of serum lipids in HD patients with a large amount of weight gain, thus resulting in the use of insufficient lipid-lowering therapy.

Key words: lipid disorder, hemodialysis, cardiovascular disease, ultrafiltration volume, heparin

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Introduction

Cardiovascular disease (CVD) is the most common cause of morbidity and mortality in patients with chronic kidney disease (CKD). This increased risk for CVD correlates directly with a decline in the estimated glomerular filtration rate. Currently, the impact of albuminuria is assessed in association with the onset of CVD events, with the combined effects of these factors conferring an enhanced risk of CVD (1). Importantly, mortality from CVD in patients with CKD is 1.4-3.7-fold higher than that observed in the general population (2) and increases to 10-30-fold in hemodialysis (HD) patients (3). Strict management of risk factors is therefore required in HD patients in order to prevent the acceleration of CVD (4).

Lipid disorders are an established risk factor for CVD (5, 6), and lipid-modulating therapies, including the administration of statins, have been shown to reduce cardiovascular events and mortality in the general population (7).
However, the relationship between cholesterol and increased CVD risks has been difficult to establish in CKD patients, especially those undergoing HD treatment. Recent large clinical trials have shown that statins have little or no benefit in preventing primary CVD in patients on HD. In the Die Deutsche Diabetes Dialysis (4D) trial (8) and A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) study (9), both of which were randomized controlled trials (RCTs) performed in HD patients, statins failed to show significant benefits for primary CVD prevention. Meanwhile, in the Study of Heart and Renal Protection (SHARP) trial (10), another RCT including both CKD patients treated with and without dialysis, the administration of a statin and ezetimibe resulted in a 17% reduction in major atherosclerotic events compared with a placebo. Furthermore, a recent meta-analysis showed that statin therapy lowers the rate of cardiovascular events in patients in earlier stages of CKD, although these drugs have little or no effect in patients on dialysis (11, 12). The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines suggest that treatment with statins or a combination of statin/ezetimibe should not be initiated in adults with dialysis-dependent CKD (13). As a consequence, the use of lipid-lowering therapy to reduce CVD risks and mortality in HD patients is not considered to be beneficial.

The characteristics of HD patients with dyslipidemia are different from those observed in the general population. For example, dyslipidemia in CKD patients is characterized by an increased concentration of apo-CIII in very-low-density lipoprotein (VLDL), resulting in the inhibition of lipoprotein lipase (LPL) (14, 15). In addition to LPL, the hepatic lipase activity is known to be lower in HD patients than in normal subjects (16, 17). Therefore, HD patients are considered to be in a state of impaired catabolism of both intermediate-density lipoprotein (IDL) and low-density lipoprotein (LDL) (18). Recently, it has also been reported that cholesterol synthesis is decreased in HD patients, whereas intestinal cholesterol absorption is increased (19). As Shoji et al. reported, these changes are observed in the clinical setting as an elevated IDL cholesterol level and decreased high-density lipoprotein (HDL) cholesterol level (20). However, the influence of single HD sessions on lipid metabolism should be considered when choosing lipid-lowering therapy in HD patients.

Clinically, dyslipidemia is diagnosed based on the detection of increased lipid concentrations at the beginning of HD, whereas the effects of the HD session on lipid metabolism are ignored in such patients. In this study, we assessed changes in the serum levels of total cholesterol, non-HDL cholesterol, HDL cholesterol and triglycerides (TG) during a single HD session. In addition, we investigated the relationships between the serum lipid levels and percentage change in the ultrafiltration volume.

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### Materials and Methods

#### Patients

This observational study enrolled 31 clinically stable Japanese patients treated at Chuou Naika Clinic (Kure, Japan) who had undergone HD three times a week for over three months. We excluded patients <18 years of age and those who had undergone kidney transplantation or limb amputation. Twenty patients received polysulfone dialyzers, four received polymethyl methacrylate dialyzers, three received polyacrylonitrile dialyzers, two received cellulose triacetate dialyzers, one received polyethersulfone dialyzers and one received ethylene vinyl alcohol dialyzers. For anticoagulation, bolus and continuous infusions of unfractionated heparin were administered in 26 patients, while dalteparin was infused in five patients. The patients were treated with HD three times a week (four hours per session) using bicarbonate dialysate. All subjects provided their informed consent to participate in this study, which was conducted in accordance with the Declaration of Helsinki.

#### Biochemical parameters

All patients began the HD sessions in the morning and consumed a meal within two hours of the start of HD. Blood samples were collected during the first hemodialysis session of the week. The serum albumin and C-reactive protein (CRP) levels were measured in the blood samples collected at the beginning of HD. We also evaluated the single-pool Kt/V values using the formula reported by Shinzato et al. (21). The serum total cholesterol, HDL cholesterol, TG and total protein levels were measured at zero, two and four hours after the start of each single HD session. The serum total cholesterol levels were measured using the Biancore Liquid T-CHO II kit (TOYOBO, Osaka, Japan), the TG levels were measured using the L Type Triglyceride H kit (Wako, Osaka, Japan) and the HDL cholesterol levels were measured using the METABOLEAD HDL-C kit (Kyowa Medex, Tokyo, Japan). The lipid parameters were measured three times during three separate hemodialysis sessions, and the mean values were calculated for use in the analyses.

#### Statistical analysis

The variables were expressed as the mean ± standard deviation or median and interquartile range (25-75th percentiles). The data were analyzed using the Wilcoxon signed-rank test, a linear mixed model and Spearman’s rank correlation analysis, with a p value of <0.05 indicating a statistically significant difference. Multiple comparisons were made using the Bonferroni method. All analyses were carried out using the Statistical Package for the Social Sciences (SPSS) software program [Version 21.0, International Business Machines (IBM), Armonk, USA].
Results

The clinical characteristics of the 31 HD patients included in the study are summarized in Table 1. The study group included 10 men and 21 women, with a mean age of 70.2±10.5 years and median duration of hemodialysis of 12.6 (9.4-21.6) years. Nine (29.0%) of the 31 patients had diabetes mellitus, eight patients (25.8%) were on statin therapy, seven patients (22.6%) were on sevelamer hydrochloride therapy and five patients (16.1%) were on ethyl icosapentate therapy. The mean Kt/V of the HD session was 1.67±0.30.

We next examined the influence of the ultrafiltration volume on the serum lipid levels. Consequently, the percentage change in the serum levels of total cholesterol, HDL cholesterol and non-HDL cholesterol correlated strongly with the percentage change in the ultrafiltration volume per body weight (Fig. 5).

Discussion

This study provides evidence that the serum total cholesterol, non-HDL cholesterol, and HDL cholesterol levels increase significantly during single HD sessions, whereas the TG level decreases. Our data show that, even after compensating for changes in the total protein level, the total cholesterol and HDL cholesterol levels increase during HD sessions, whereas the non-HDL level does not change significantly. Spearman’s rank correlation analysis demonstrated that the percentage change in the serum levels of these lipid fractions correlated significantly with the percentage change in the ultrafiltration volume per body weight. These findings imply that evaluating the degree of dyslipidemia at the beginning of the HD session may underestimate the levels of serum lipids due to the effects of ultrafiltration in HD patients, resulting in the use of insufficient lipid-lowering therapy.

Because lipids are insoluble in blood, they are transported in the circulatory system within lipoproteins. The molecular weight of HDL particles ranges from 175 to 500 kDa, while that of chylomicrons, VLDL, IDL and LDL is much larger. These lipids are therefore not dialyzable during HD sessions, indicating that changes in the lipoprotein concentrations are influenced by the ultrafiltration volume. In fact, our data confirm that the percentage changes in these lipids correlate with the percentage change in the ultrafiltration volume.

In this study, the mean change was 19.3 mg/dL for total cholesterol, 9.3 mg/dL for HDL-cholesterol and 10.0 mg/dL for non-HDL cholesterol, which is equivalent to an increase of 11.5%, 16.1% and 9.1%, respectively, compared with the levels noted at the beginning of HD. These findings suggest that the HDL-cholesterol level is affected to a greater extent by HD sessions. In addition, the HDL cholesterol level corrected for changes in the total protein level increased significantly during each HD session. This finding raises the possibility that the increase in the HDL cholesterol level is due to the effects of ultrafiltration as well as HD per sé. In fact, the HDL cholesterol levels are generally lower in HD pa-

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### Table 1. Demographic Characteristics of the Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>32.3</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>70.2 ± 10.5</td>
</tr>
<tr>
<td>Duration of hemodialysis (yr)</td>
<td>12.6 (9.4-21.6)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>29.0</td>
</tr>
<tr>
<td>Statin therapy (%)</td>
<td>25.8</td>
</tr>
<tr>
<td>Sevelamer hydrochloride therapy (%)</td>
<td>22.6</td>
</tr>
<tr>
<td>Ethyl icosapentate therapy (%)</td>
<td>16.1</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>20.5 ± 3.4</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.5 ± 0.4</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>0.41 ± 0.99</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.67 ± 0.30</td>
</tr>
<tr>
<td>Dry body weight (kg)</td>
<td>48.6 ± 10.3</td>
</tr>
<tr>
<td>UV (L)</td>
<td>1.5 ± 0.6</td>
</tr>
<tr>
<td>% change in UV per body weight</td>
<td>3.1 ±1.1</td>
</tr>
</tbody>
</table>

The data are expressed as the mean ± standard deviation or median (interquartile range) for continuous variables and percentage for categorical variables. CRP: C-reactive protein, UV: ultrafiltration volume.
Figure 1. Time course of the serum total cholesterol levels during the hemodialysis sessions. The data are expressed as the mean ± standard deviation (n=31). *p<0.01: Wilcoxon signed-rank test, †p<0.01: linear mixed model.

Figure 2. Time course of the serum high-density lipoprotein (HDL) cholesterol levels during the hemodialysis sessions. The data are expressed as the mean ± standard deviation (n=31). *p<0.01: Wilcoxon signed-rank test, †p<0.01: linear mixed model.

Patients than in non-uremic individuals (20), indicating that HD sessions may attenuate the tendency toward lower HDL cholesterol levels in HD patients. Although the mechanisms underlying these findings are unknown, it is possible that a decreased TG level attenuates the cholesteryl ester transfer protein activity, resulting in an elevated HDL cholesterol level. In contrast, the serum non-HDL cholesterol levels remained unchanged after correcting for variations in total protein in this study, suggesting that the reduction in non-HDL cholesterol is primarily influenced by ultrafiltration.

Although the timing of the HD sessions and meals was standardized in this study, the TG levels were found to be significantly decreased after two hours compared with those seen at the beginning of HD and gradually increased after four hours. These findings may be explained by the effects of the bolus and continuous infusions of heparin used as an anticoagulant to prevent clotting in extracorporeal devices. LPL is a major enzyme responsible for hydrolyzing TG in circulating lipoproteins and is released from binding sites at the vascular endothelium following the injection of heparin.
Figure 3. Time course of the serum non-HDL cholesterol levels during the hemodialysis sessions. The data are expressed as the mean ± standard deviation (n=31). *p<0.01: Wilcoxon signed-rank test, †p<0.01: linear mixed model

Table 2. Time Course of the Plasma Lipid Parameters Corrected for the Total Protein Levels

<table>
<thead>
<tr>
<th></th>
<th>0 h</th>
<th>2 h</th>
<th>4 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol/total protein (mg/g)</td>
<td>26.5 ± 6.0</td>
<td>26.9 ± 6.0*</td>
<td>27.3 ± 6.2†</td>
</tr>
<tr>
<td>HDL cholesterol/total protein (mg/g)</td>
<td>9.1 ± 3.1</td>
<td>9.7 ± 3.1*</td>
<td>9.8 ± 3.2*</td>
</tr>
<tr>
<td>Non-HDL cholesterol/total protein (mg/g)</td>
<td>17.3 ± 4.8</td>
<td>17.1 ± 4.8</td>
<td>17.4 ± 5.0</td>
</tr>
</tbody>
</table>

*p<0.01 versus zero hours, †p<0.01 versus two hours; linear mixed model (n=31)

Figure 4. Time course of the serum triglyceride levels during the hemodialysis sessions. The data are expressed as the mean ± standard deviation (n=31). *p<0.01: Wilcoxon signed-rank test, †p<0.01: linear mixed model
Interestingly, Näström et al. reported that the TG level decreases during the first hour of dialysis and then increases continuously from baseline to three hours after the HD session following the use of a single bolus infusion of dalteparin at the start of the session as well as bolus and continuous infusions of unfractionated heparin (22).

The Japanese Society for Dialysis Therapy guidelines suggest a control target level of non-HDL for the primary prevention of ischemic heart disease of <150 mg/dL (23). In the current study, three (9.7%) of the 31 patients had a non-HDL level of ≥150 mg/dL at the start of HD, whereas six patients (19.4%) had a non-HDL level of ≥150 mg/dL at the end of HD. These results raise the possibility that assessing lipid parameters at the beginning of the HD session underestimates the serum lipid levels, especially in patients with good nutrition and/or those who exhibit a large amount of weight gain between HD sessions.

It has been demonstrated that HD patients experience a vicious circle of malnutrition, inflammation and atherosclerotic CVD (i.e., MIA syndrome) (24). Iseki et al. reported that low plasma albumin (3.5-3.9 g/dL) and plasma total cholesterol levels were significant predictors of death in a cohort of 1,167 Japanese HD patients. Moreover, there was a positive relationship between the risk of death and the total cholesterol level in a subgroup of this cohort with a serum albumin level of ≥4.5 g/dL (25). An observational cohort study of Japanese HD patients also demonstrated that a low HDL cholesterol level and high non-HDL cholesterol level are both significant predictors of incident CVD (26).

Meanwhile, the SHARP trial reported that the excess risk of myopathy in patients is 0.02% per year and there are no new safety concerns regarding lipid-lowering therapy (10).
These findings indicate that hyperlipidemia is a potential therapeutic target in hemodialysis patients. The present study is associated with some limitations. Because this study is observational, the exact reasons why the above changes occurred remain unclear. None of the patients fasted, and the lipid content and caloric value of their meals were not uniform. These facts do not exclude the possibility of postprandial changes in lipid profiles rather than the effects of hemodialysis. Furthermore, five patients received dalteparin for anticoagulation, which may have had different effects on lipid metabolism than those caused by unfractionated heparin. However, even after excluding the patients who received dalteparin from the analysis, the results remained consistent with the findings of the analyses of the entire study group. In addition, we were unable to investigate the inter-dialytic serum lipid levels, despite the possibility that the lipid parameters at the end of the HD sessions may have been affected by other factors, such as plasma refilling after HD. Further studies are therefore required to confirm the long-term effects of dialysis-related conditions on CVD and mortality risks in HD patients and establish lipid-lowering strategies for this population.

**Conclusion**

In summary, we herein confirmed that the serum lipid levels are significantly influenced by HD treatment. Evaluating the degree of dyslipidemia at the beginning of the HD session may underestimate the levels of serum lipids in HD patients with a large amount of weight gain, resulting in the use of insufficient lipid-lowering therapy.

The authors state that they have no Conflict of Interest (COI).

**References**


25. Isci K, Yamazato M, Tozawa M, Takishita S. Hypocholesterolemia is a significant predictor of death in a cohort of chronic