Research Article

Plasma Levels of Coronary Risk Biomarkers in Chronic Kidney Disease Patients Undergoing Maintenance Hemodialysis Treatment

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Abstract

Objective: Coronary heart disease (CAD) is the commonest complication in patients with chronic kidney disease (CKD) under hemodialysis (HD). Coronary risk biomarkers, namely, plasma levels of lipids, apo(lipo)proteins, oxidized (ox)-low-density lipoprotein (LDL), and adiponectin were compared between HD patients and age, sex, and body mass index-matched controls.

Methods and results: Eighty HD patients and 80 controls were enrolled. Plasma levels of apoproteins were measured with a turbidimetric immunoassay. Ox-LDL and adiponectin were measured by an enzyme-linked immunoassay. Plasma levels of LDL-cholesterol (C), high-density lipoprotein (HDL)-C, apoprotein (apo) B, apo A1, and ox-LDL were lower in HD patients than controls (p < 0.0001). Ratios of LDL-C/ox-LDL were higher in HD subjects than in controls (p < 0.0001). Plasma levels of remnant-like lipoprotein particle cholesterol that is equivalent to triglyceride-rich lipoprotein remnant were higher in HD patients (p < 0.0001). Plasma levels of adiponectin were higher and the abdominal circumference/adiponectin ratio was lower in HD patients than in controls (p < 0.0001).

Conclusion: Plasma levels of LDL-C, ox-LDL, and adiponectin should not be used as coronary risk biomarkers in HD patients. However, high levels of remnant-like lipoprotein particle cholesterol represent a significant coronary risk in HD patients.

INTRODUCTION

A high plasma level of remnant-like lipoprotein particle cholesterol (RLP-C), which is equivalent to the remnant of triglyceride (TG)-rich lipoprotein, is a biomarker for coronary artery disease (CAD) risk in patients with chronic kidney disease (CKD) undergoing maintenance hemodialysis (HD) [1]. In addition, in the general population, elevated plasma oxidized (ox)-low-density lipoprotein (LDL) and low levels of adiponectin are associated with an increased risk of CAD [2-9]. Therefore, it is possible that plasma ox-LDL and/or adiponectin levels could serve as distinct biomarkers for CAD risk in HD patients, independent of patient comorbidities such as hypertension, diabetes mellitus (DM), and dyslipoproteinemia, but this has not been fully investigated.

In order to determine the usefulness of ox-LDL or adiponectin as CAD risk biomarkers in HD patients, a number of factors need to be considered. Compared to large, less dense LDL, small dense LDL, which is apo(lipo)protein B rich, is easily oxidizable and more atherogenic [11-17]. Therefore, the ratios of the type of plasma LDL present should be considered when determining the potential atherogenicity of ox-LDL. However, the relationship between plasma ox-LDL levels and small dense LDL abundance has not been well defined in HD subjects. In addition, unlike in the general population, plasma levels of adiponectin are high
in patients with CKD undergoing maintenance HD [18-21]. Obesity is the most influential factor affecting plasma levels of adiponectin and a comparison of the influence of adiponectin on CAD risk in HD patients should, therefore, be made in obesity-matched subjects.

The aim of this study was to measure the plasma levels of lipids, apo(lipo)proteins, ox-LDL, and adiponectin in patients with CKD undergoing maintenance HD and in sex, age, and body mass index (BMI)-matched controls, to identify putative CAD risk biomarkers.

**MATERIALS AND METHODS**

This study was approved by the ethics committee of Hiratsuka Lifestyle-related Disease and Hemodialysis Clinic and conformed to the ethics guidelines of Tokai University Hospital. Informed consent was provided by all participants.

**Subjects and study protocol**

Patients with CKD received maintenance HD 3 times a week for 4 hours at the Hirotsuka Life-style-related Disease and Hemodialysis Clinic. Controls included healthy individuals attending the Health Evaluation and Promotion Center, Tokai University Hospital. The body length, body weight, abdominal circumference, and blood pressure of each individual were measured before blood samples were collected after a 12-hour fasting period.

**Laboratory procedures**

Plasma creatinine, fasting plasma glucose, lipid, and glycated hemoglobin (HbA1c) levels were measured using autoanalyzers. Plasma apoprotein concentrations were measured using an automated turbidimetric immunoassay [22]. Serum RLP-C concentration was determined by immunoprecipitation using monoclonal antibodies against apo(proteins) B-100 and Al [23]. Malondialdehyde-modified LDL was designated as ox-LDL Ox-LDL was estimated by an enzyme-linked immunosorbent assay, using monoclonal antibodies against malondialdehyde-modified LDL and apo B [24]. Plasma adiponectin levels were measured by an enzyme-linked immunosorbent assay as described by Arita et al [25].

**Statistical analysis**

Comparisons between the HD and control groups were made using an unpaired t-test. A comparison of the complication rate of DM was performed using the chi-square test.

**RESULTS**

Subject demographics are shown in Table 1. Sex, age, and BMI were matched between both groups. BMI was matched but abdominal circumference was significantly larger in HD patients than among the controls. Fasting plasma glucose and HbA1c were significantly higher in the HD group than the control group, mostly likely because 47.5% of HD patients had well-controlled DM (HbA1c < 6.5%). Systolic blood pressure was significantly higher in HD patients than in the controls, but diastolic blood pressure did not differ between the groups.

Plasma total cholesterol, LDL-C, apo B, and high-density lipoprotein (HDL)-C concentrations, and the LDL-C/apo B and HDL-C/apo Al ratios were significantly lower in HD patients than in the controls (p < 0.0001) (Table 2). However, the plasma HDL-C and apo Al levels were within the normal range in HD patients. Despite there being no difference in plasma TG levels between the two groups, plasma RLP-C was significantly higher in the HD patients than in the controls (p < 0.0001) (Table 2).

The plasma concentration of ox-LDL was significantly lower in HD patients than in the controls (p < 0.0001). The ratios of LDL-C/ox-LDL and apo B/ox-LDL were significantly higher in HD patients than in the controls (p < 0.0001) (Table 2).

Plasma levels of adiponectin were significantly elevated in HD patients compared to the controls (p < 0.0001). The ratio of BMI/adiponectin and abdominal circumference/adiponectin were significantly lower in HD patients than in the controls (p < 0.0001). The plasma creatinine/adiponectin ratio was significantly higher in HD patients than in the controls (p < 0.0001) (Table 2).

**DISCUSSION**

HD patients exhibited significantly higher plasma RLP-C levels than healthy individuals, which is consistent with previous reports confirming that elevated RLP-C is a risk factor for CAD in HD patients [1,26]. Despite significant differences between HD patients and healthy individuals, none of the other factors investigated were representative biomarkers of CAD risk.

Compared with individuals in the control group, the abdominal circumference in HD patients was larger, even though the BMI was same; however, this is most likely because of an increase in body fluid especially in patients with polycystic kidney disease. Furthermore, it has been suggested that abdominal circumference is not a reliable indicator for the accurate assessment of visceral fat volume in HD patients [27]. Therefore, abdominal circumference could not be considered as an accurate biomarker of CAD risk.

<table>
<thead>
<tr>
<th>Table 1: Subject demographics.</th>
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<tbody>
<tr>
<td><strong>Hemodialysis group</strong></td>
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<td>---------------------------</td>
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<tr>
<td>Number</td>
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<tr>
<td>Sex (Male/Female)</td>
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<td>Age (years)</td>
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<td>BMI (kg/m²)</td>
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<td>Abdominal circumference (cm)</td>
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<td>Systolic BP (mmHg)</td>
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<td>HbA1c (%)</td>
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<tr>
<td>DM N (%)</td>
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<td>HD duration (months)</td>
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Notes:

1 Statistical significance by unpaired t-test (HD patients vs. controls)
2 Mean ± standard deviation
3 Chi-square test

Abbreviations: BMI: Body-Mass Index; BP: Blood Pressure; FPS: Fasting Plasma Glucose; Hba1c: Glycated Hemoglobin; DM: Diabetes Mellitus; HD: Hemodialysis
Here, HD patients demonstrated significantly lower plasma LDL-C and apo B levels and a lower LDL-C/apo B ratio compared with healthy individuals. Previous ultracentrifugal analysis of plasma lipoproteins in HD patients revealed that plasma LDL largely comprised less-dense fractions in TGs and the complication rate of DM and CAD-matched HD patients and controls [26]. In this study, the enrichment of apo B in the LDL of HD patients might be induced by the high complication rate of DM and ox-LDL-poor LDL in HD patients.

From the data, it could not be determined whether plasma HDL-C levels represent a biomarker of CAD risk because although HDL-C was lower in HD patients it was within the normal range. In contrast, the plasma HDL-C level was unusually high in the control group. Accordingly, an increase in apo AI-rich HDL in HD patients resulted in a lower HDL-C/apo AI ratio in the HD group. This finding might indicate that there was a higher proportion of HDL2 than HDL in the plasma of HD patients [28,29], providing a more atherosclerosis-protective HDL in HD patients than in the controls.

Plasma levels of ox-LDL and adiponectin were not CAD risk markers in CKD patients under HD treatment. The LDL-C/ox-LDL and apo B/ox-LDL ratios were higher in the HD group because of the unexpectedly low level of ox-LDL in HD patients.

Plasma adiponectin levels are determined by the balance between the rate of synthesis in the adipose tissue and the removal from blood circulation. Here, the plasma adiponectin levels were significantly higher in HD patients than in the controls, which is concordant with previous studies [18-21]. In addition, the BMI/adiponectin and abdominal circumference/adiponectin ratios were lower in HD patients than in controls. The lower ratios in HD patients could be explained by a higher adiponectin synthesis rate. However, it should also be noted that about half of the HD patients were diabetic and it has been suggested that plasma adiponectin levels are low in diabetic patients [30,31]. Therefore, it is possible that reduced clearance of adiponectin from the circulation in HD patients might contribute, in part, to elevated plasma levels adiponectin. Furthermore, in patients with proteinuria, plasma adiponectin levels are reduced, suggesting that the kidney might play a functional role in adiponectin clearance [32].

CONCLUSION

In agreement with previous studies, plasma RLP-C levels acted as a CAD risk biomarker in HD patients. Although plasma levels of ox-LDL were lower than native LDL in HD patients and plasma levels of adiponectin were higher in HD patients, neither acted as a biomarker for CAD risk in patients with CKD undergoing HD.

REFERENCES

Homma et al. (2014)

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