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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 Hiratsuka Life style-related Diseases 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 AI [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 AI ratios were significantly lower in HD patients than in the controls (p <0.0001) (Table 2). However, the plasma HDL-C and apo AI 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).

Table 1: Subject demographics.

	Hemodialysis group	Control group	P[1]
Number	80	80	
Sex (Male/Female)	(42/38)	(42/38)	
Age (years)	68.4 ± 10.0[2]	68.1 ± 9.6	
BMI[3] (kg/m^2)	20.8 ± 3.3	21.2 ± 2.8	
Abdominal circumference (cm)	82.4 ± 11.6	79.2 ± 8.4	0.0234
Systolic BP[3] (mmHg)	153 ± 16	127 ± 21	<0.0001
Diastolic BP (mmHg)	74 ± 10	76 ± 11	0.0763
Creatinine (mg/dL)	9.7 ± 2.6	0.8 ± 0.2	<0.0001
FPS[3] (mg/dL)	127 ± 42	101 ± 14	<0.0001
HbA1c (%)	5.5 ± 0.7	5.2 ± 0.5	0.0032
DM[3] N (%)	38 (47.5)	0(0)	<0.0001[4]
HD[3] duration (months)	60.2 ± 65.6	0	<0.0001

[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

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 2: Comparison of plasma levels of lipids, apo(lipo)proteins, ox-LDL, and adiponectin between hemodialysis patients and controls.

	Hemodialysis group	Control group	p[1]
Total cholesterol (mg/dL)	159 ± 36[2]	211 ± 32	<0.0001
Triglycerides (mg/dL)	98 ± 48	103 ± 49	0.2800
LDL- cholesterol (mg/dL)	80 ± 25	123 ± 27	<0.0001
HDL-cholesterol (mg/dL)	47 ± 16	74 ± 21	<0.0001
RLP-cholesterol (mg/dL)	6.70 ± 4.46	4.03 ± 1.31	<0.0001
Apolipoprotein AI (mg/dL)	125 ± 27	159 ± 29	<0.0001
Apolipoprotein B (mg/dL)	76 ± 25	93 ± 19	<0.0001
Apolipoprotein E (mg/dL)	3.75 ± 0.74	4.51 ± 1.13	<0.0001
LDL-C[3]/apo[3] B	1.05 ± 0.20	1.31 ± 0.11	<0.0001
HDL-C/apo AI	0.37 ± 0.11	0.46 ± 0.07	<0.0001
Ox-LDL (U/L)	59.4 ± 23.0	112.9 ± 37.8	<0.0001
LDL-C/ox-LDL	1.45 ± 0.49	1.18 ± 0.34	<0.0001
Apo B/ox-LDL	1.39 ± 0.49	0.89 ± 0.23	<0.0001
Adiponectin (μg/mL)	25.6 ± 12.2	15.4 ± 9.5	<0.0001
BMI/adiponectin	1.11 ± 0.89	2.03 ± 1.55	<0.0001
Abdominal circum/adiponectin	3.73 ± 2.81	7.51 ± 5.27	<0.0001
Creatinine/ adiponectin	0.50 ± 0.33	0.07 ± 0.05	<0.0001

[1]Unpaired t-test

[2]Mean ± standard deviation

Abbreviations: RLP-C: Remnant-Like Lipoprotein Particle Cholesterol; BMI: Body Mass Index; C: Cholesterol; Apo: Apolipoprotein; Ox: Oxidized; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; Circum: Circumference

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

1. Homma K, Homma Y, Yamaguchi S, Shiina Y, Wakino S, Hayashi K, et al. Triglyceride-rich lipoproteins in chronic kidney disease patients undergoing maintenance hemodialysis treatment. Int J Clin Pract 2012; 66: 394-398.

2. Lehtimaki T, Lehtinen S, Solakivi T, Nikkilä M, Jaakkola O, Jokela H, et al. Autoantibodies against oxidized low density lipoprotein in patients with angiographically verified coronary artery disease. Arterioscler Thromb Vasc Biol 1999; 19: 23-27.

3. Toshima S, Hasegawa A, Kurabayashi M, Itabe H, Takano T, Sugano J, et al. Circulating oxidized low density lipoprotein levels. A biochemical risk marker for coronary heart disease. Arterioscler Thromb Vasc Biol 2000; 20: 2243-2247.

4. Ehara S, Ueda M, Naruko T, Haze K, Itoh A, Otsuka M, et al. Elevated levels of oxidized low density lipoprotein show a positive relationship with the severity of acute coronary syndromes. Circulation 2001; 103: 1955-1960.

5. Holvert P, Harris TB, Tracy RP, Verhamme P, Newman AB, Rubin SM, et al. Association of high coronary heart disease risk status with circulating oxidized LDL in the well-functioning elderly: findings from the Health, Aging, and Body Composition study. Arterioscler Thromb Vasc Biol 2003; 23: 1444-1448.

6. Weinbrenner T, Cladellas M, Covas MI, Fitó M, Tomás M, Sentí M, et al. High oxidative stress in patients with stable coronary heart disease. Atherosclerosis 2003; 168: 99-106.

7. Ishigaki Y, Oka Y, Katagiri H. Circulating oxidized LDL: a biomarker and a pathogenic factor. Curr Opin Lipidol 2009; 20: 363-369.

8. Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB. Plasma adiponectin levels and risk of myocardial infarction in men. JAMA 2004; 291: 1730-1737.

9. Côté M, Cartier A, Reuwer AQ, Arsenault BJ, Lemieux I, Després JP, et al. Adiponectin and risk of coronary heart disease in apparently healthy men and women (from the EPIC-Norfolk Prospective Population Study). Am J Cardiol 2011; 108: 367-373.

10. Gardener H, Sjoberg C, Crisby M, Goldberg R, Mendez A, Wright CB, et al. Adiponectin and carotid intima-media thickness in the northern Manhattan study. Stroke 2012; 43: 1123-1125.

11. Crouse JR, Parks JS, Schey HM, Kahl FR. Studies of low density lipoprotein molecular weight in human beings with coronary artery disease. J Lipid Res 1985; 26: 566-574.

12. Hulthe J, Bokemark L, Wikstrand J, Fagergerg B. The metabolic syndrome, LDL particle size, and atherosclerosis: the Atherosclerosis and Insulin Resistance (AIR) Study. Arterioscler Thromb Vasc Biol 2000; 20: 2140-2147.

13. El Harchaoui K, van der Steeg WA, Stroes ES, Kuivenhoven JA, Otvos JD, Wareham NJ, et al. Value of low-density lipoprotein particle number and size as predictors of coronary artery disease in apparently healthy men and women: The EPIC-Norfolk Prospective Population Study. J Am Coll Cardiol 2007; 49: 547-553.

14. Teng B, Sniderman AD, Soutar AK, Thompson GR. Metabolic basis of hyperapobetalipoproteinemia. Turnover of apolipoprotein B, in low density lipoprotein and its precursors and subfractions compared with normal and familial hypercholesterolemia. J Clin Invest 1986; 77: 663-672.

15. Hunt SC, Wu LL, Hopkins PN, Stults BM, Kuida H, Ramirez ME, et al. Apolipoprotein, low density lipoprotein subfractions, and insulin associations with familial combined hyperlipidemia. Study of Utah patients with familial dyslipidemic hypertension. Arteriosclerosis 1989; 9: 335-344.

16. De Graaj J, Hak-Lemmers HL, Hectors MP, Demacker PN, Hendriks JC, Stalenhoef AF. Enhanced susceptibility to in vitro oxidation of the dense low density lipoprotein subfraction in healthy subjects. Arterioscler Thromb 1991; 11: 298-306.

17. Tribble DL, Holl LG, Wood PD, Krauss RM. Variation in oxidative susceptibility among six low density lipoprotein subfractions of differing density and particle size. Atherosclerosis 1992; 93: 189-199.

18. Zoccali C, Mallamaci F, Tripepi G, Benedetto FA, Cutrupi S, Parlongo S, et al. Adiponectin, metabolic risk factors, and cardiovascular events among patients with end-stage renal disease. J Am Soc Nephrol 2002; 13: 134-141.

19. Guebre-Egziabher F, Bernhard J, Funahashi T, Hadj-Aissa A, Fouque D. Adiponectin in chronic kidney disease is related more to metabolic disturbances than to decline in renal function. Nephrol Dial Transplant 2005; 20: 129-134.

20. Menon V, Li L, Wang X, Greene T, Balakrishnan V, Madero M, et al. Adiponectin and mortality in patients with chronic kidney disease. J Am Soc Nephrol 2006; 17: 2599-2606.

21. Drechsler C, Krane V, Winkler K, Dekker FW, Wanner C. Changes in adiponectin and the risk of sudden death, stroke, myocardial infarction, and mortality in hemodialysis patients. Kidney Int 2009; 76: 567-575.

22. Noma A, Hata Y, Goto Y. Quantification of serum apolipoprotein A-I, A-II, B, C-II, C-III, and E by turbidimetric immunoassay: reference values, and age- and sex-related differences. Clin Chim Acta 1991; 199: 147-157.

23. Nakajima K, Saito T, Tamura A, Suzuki M, Nakano T, Adachi M, et al. Cholesterol in remnant-like lipoproteins in human serum using monoclonal anti apo B-100 and anti apo A-I immunoaffinity mixed gels. Clin Chim Acta 1993; 223: 53-71.

24. Kotani K, Maekawa M, Kanno T, Kondo A, Toda N, Manabe M. Distribution of immunoreactive malondialdehyde-modified low-density lipoprotein in human serum. Biochim Biophys Acta 1994; 1215: 121-125.

25. Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 1999; 257: 79-83.

26. Homma K, Homma Y, Shiina Y, Wakino S, Suzuki M, Fujishima S, et al. Skew of plasma low- and high-density lipoprotein distributions to less dense subfractions in normotriglyceridemic chronic kidney disease patients on maintenance hemodialysis treatment. Nephron Clin Pract 2013; 123: 41-45.

27. Examination Committee of Criteria for 'Obesity Disease' in Japan; Japan Society for the Study of Obesity. New criteria for 'obesity disease' in Japan. Circ J. 2002; 66: 987-992.

28. Johansson J, Carlson LA, Landou C, Hamsten A. High density lipoproteins and coronary atherosclerosis. A strong inverse relation with the largest particles is confined to normotriglyceridemic patients. Arterioscler Thromb 1991; 11: 174-182.

29. Katzel LI, Coon PJ, Sidney JB, Gottlieb SO, Krauss RM, Goldberg AP. Reduced HDL2 cholesterol subspecies and elevated postheparin hepatic lipase activity in older men with abdominal obesity and asymptomatic myocardial ischemia. Arterioscler Thromb 1992; 12: 814-823.

30. Snehalatha C, Mukesh B, Simon M, Viswanathan V, Haffner SM, Ramachandran A. Plasma adiponectin is an independent predictor of type 2 diabetes in Asian Indians. Diabetes Care 2003; 26: 3226-3229.

31. Li S, Shin HJ, Ding EL, Van Dam RM. Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA 2009; 302: 179-188.

32. Ahima RS. Linking adiponectin to proteinuria. J Clin Invest 2008; 118: 1619-1622.

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