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Relationship Between Cardiovascular Events and Serum Lipid and Plasma Fatty Acid Profile in Maintenance Hemodialysis Patients With Diabetic Mellitus

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Abstract. *Background/Aim: Cardiovascular disease (CVD) is a frequent complication in hemodialysis (HD) patients, especially when the underlying disease is diabetes mellitus (DM). In this study, we investigated cardiovascular events and lipid and fatty acid profile in maintenance HD patients with diabetic kidney disease (DKD). Patients and Methods: The subjects were 123 patients undergoing HD at Oyokyo Kidney Research Institute Hirosaki Hospital, who were considered to have DKD as the underlying cause of dialysis induction. Among these patients, the lipid and fatty acid profile were examined in two groups, CVD group (n=53) and non-CVD group (n=70), according to the presence or absence of a history of cardiovascular events (coronary artery disease, stroke, arteriosclerosis obliterans, valvular disease, and aortic disease). For serum lipid profile, the levels of total-cholesterol (T-C), triglycerides (TG), high density lipoprotein-cholesterol (HDL-C), and low density lipoprotein-cholesterol (LDL-C) were measured, and for fatty acid balance, 24 fractions of fatty acid composition in plasma total lipids were measured. These markers were compared between the CVD and non-CVD groups. Results: The levels of T-C and TG were significantly lower in the CVD group compared with the non-CVD group (147.7±36.9 mg/dl vs. 159.2±35.6 mg/dl, p<0.05, 120.2±65.7 mg/dl vs. 143.8±124.4 mg/dl, p<0.05). In the plasma fatty acid composition, alpha-linolenic acid (ALA) and docosapentaenoic acid (DPA) were significantly lower in the CVD group compared with the non-CVD group (0.74±0.26 wt% vs. 0.84±0.31 wt%, p<0.05; 0.61±0.21 wt% vs. 0.70±0.30 wt%, p<0.05). Conclusion: Abnormal fatty acid balance, especially low levels of ALA and DPA, rather than serum lipids, are more likely the factors associated with cardiovascular events in maintenance HD patients with underlying DKD.*

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Cardiovascular disease (CVD) is a major common complication in patients with end-stage renal disease (ESRD) on hemodialysis (HD) (1). Because diabetic kidney disease (DKD) is the most common cause of ESRD, a large number of HD patients have DM. Since DM is a major risk factor for CVD, it is especially frequent in HD patients with DM (2, 3).

There are many known reports on the relationship between CVD and plasma fatty acid composition, and low levels of n-3 fatty acids in the blood are known to be a risk for CVD (4, 5). However, there are few reports that discussed the relationship between a risk for CVD and plasma fatty acid composition in HD patients with DM (6, 7). In the present study, we examined the relationship between CVD and these risk factors, examples serum lipids and plasma fatty acid profile in HD patients with DM.

Patients and Methods

Among patients receiving maintenance dialysis at the Oyokyo Kidney Research Institute Hirosaki Hospital, 123 patients with diabetic kidney disease (DKD) were entered in this study. They

were divided into two groups: the CVD group (n=53) and the non-CVD group (n=70) according to the existence of past cardiovascular events (coronary artery disease, stroke, arteriosclerosis obliterans, valvular disease, and aortic disease), and the blood lipid and fatty acid profile of each patient was examined and compared between the two groups. Total-cholesterol (T-C), triglyceride (TG), high density-lipoprotein cholesterol (HDL-C), and low density lipoprotein-cholesterol (LDL-C) levels as serum lipid profile, and 24 fractions of fatty acid composition in plasma total lipids were measured by gas chromatography at SRL Inc. (Tokyo, Japan).

The present study was carried out using the cohort of the clinical study currently performed from 2019, as "Assessment of the pathophysiology and risk of cardiovascular disease in hemodialysis patients by cardiovascular disease biomarkers" (the Ethical Review Board of Hirosaki University Graduate School of Medicine, approval number 2018-154). The patients were entered to the study on receiving their written informed consent after provided with the information about the present study. This study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN ID 000036598).

The data are expressed as the means±SD. Comparison of the data between the two groups (CVD and non-CVD group) was analyzed by chi-square test and paired *t*-test. *p*-Values<0.05 were considered statistically significant.

Results

The patients' backgrounds are shown in Table I. One hundred and twenty-three patients were enrolled in the present study. Their mean age was 65.0 years old. Their complications included coronary artery disease (n=32), stroke (n=16), and arteriosclerosis obliterans (n=16). The most common drugs administered to the patients were erythropoiesis stimulating agents (ESA, n=102), phosphorus binders (n=90), and activated vitamin D_3 (n=102).

Comparison of the background data between the CVD and non-CVD groups is shown in Table II. In the CVD group, there was a significantly higher proportion of males. In terms of drugs administered, a significantly lower percentage of the CVD group received ESAs and renin angiotensin system (RAS) inhibitors compared with the non-CVD group.

The biochemical examination results in the CVD and non-CVD groups are shown in Table III. The levels of albumin, creatinine, T-C, and TG in the CVD group were significantly lower compared with those in the non-CVD group. Serum calcium levels were significantly lower in the CVD group than those in the non-CVD group, but albumin-corrected calcium levels were not significantly different between the two groups.

Comparison of plasma fatty acid composition between the CVD and non-CVD group is shown in Table IV. The levels of alpha-linolenic acid (ALA) and docosapentaenoic acid (DPA) were significantly lower in the CVD group compared with those in the non-CVD group. Other fatty acids were not significantly different between the two groups.

There were no significant differences in the ratios of eicosapentaenoic acid (EPA)/arachidonic acid (AA), [EPA + docosahexaenoic acid (DHA)]/AA, or n-6/n-3 between the two groups (Table V).

Table I. *Patient background.*

Patient number (n)	123
Male	86 (70.0%)
Age (years)	65.0±12.2
Dialysis duration (months)	63.8±52.9
Coronary artery diseases	32 (26.0%)
Stroke	16 (13.0%)
Arteriosclerosis obliterans	16 (13.0%)
Erythropoiesis stimulating agents	102 (82.9%)
Statins	54 (43.9%)
Renin angiotensin system inhibitors	41 (33.35)
b-blockers	42 (34.1%)
Ca-antagonists	65 (52.8%)
P-binders	90 (73.2%)
Active vitamin D_3	102 (82.9%)

Data are expressed as the means±SD.

Discussion

In the present study, we investigated the relationship between serum lipid and plasma fatty acid composition and the history of CVD in patients undergoing maintenance HD due to DM.

Comparing patient's backgrounds, the proportion of males was significantly higher and the proportion of patients using ESAs and RAS inhibitors in the CVD group was lower than those in the non-CVD group. The reason for this may be that CVD is originally known to be more prevalent in men, and therefore the proportion of males in the CVD group was higher. In addition, since both ESAs and RAS inhibitors are known to have cardio-protective effects (8, 9), the proportion of these drugs in the CVD group may have been lower.

The biochemical tests showed that serum levels of albumin, creatinine, T-C, and TG in the CVD group were significantly lower compared with those in the non-CVD group. This might reflect the poorer nutritional status of the CVD group. In addition, serum levels of T-C and TG in HD patients were generally low (10) and might not be considered to be at significant risk for CVD.

Fatty acid composition analysis revealed significantly lower levels of ALA and DPA in the CVD group compared with those in the non-CVD group. Elevated blood ALA has been reported to be associated with a decreased risk of CVD, and the low blood ALA levels in CVD group in the present study are considered to be consistent with this finding (11).

On the other hand, DPA is the n-3 fatty acid located in the middle of the metabolic pathway between EPA and DHA, and its inhibitory effect on platelet aggregation is stronger than that of EPA and DHA (12). This may be why DPA was low in the CVD group in the present study.

Table II. *Background data in the cardiovascular disease (CVD) and non-CVD groups.*

	CVD group	Non-CVD group
Patients' number	53	70
Male	43 (81.1%)*	43 (61.4%)
Dialysis duration (months)	70.5±54.4	58.8±51.6
Erythropoiesis stimulating agents	38 (71.7%)*	64 (91.4)
Statins	28 (52.8%)	26 (37.1%)
Renin angiotensin system inhibitors	11 (20.8%)*	30 (42.9%)
b-blockers	23 (43.4%)	19 (27.1%)
Ca-antagonists	27 (50.9%)	38 (54.3%)
P-binders	36 (67.9%)	54 (77.1%)
Active vitamin D_3	45 (84.9%)	57 (81.4%)

Data are expressed as the means±SD. Comparison of the dialysis duration was analyzed by unpaired t-test and comparison of the other data was performed by chi-square test between the CVD and non-CVD group. *CVD group *vs*. non-CVD group, $p<0.05$.

Table III. *Biochemical results in the cardiovascular disease (CVD) and non-CVD groups.*

	CVD group	Non-CVD group
Albumin (g/dl)	3.5±0.4*	3.7±0.3
Blood urea nitrogen (mg/dl)	61.6±17.7	61.0±14.7
Creatinine (mg/dl)	9.7±2.6*	10.7±2.8
C-reactive protein (mg/dl)	0.69±1.51	0.35±0.60
Calcium (mg/dl)	8.4±0.4*	8.6±0.5
Albumin-corrected calcium (mg/dl)	8.9±0.5	9.0±0.5
Inorganic phosphorous (mg/dl)	5.7±1.7	6.0±1.7
Intact-parathyroid hormone (pg/ml)	159.0±134.7	128.7±69.6
Total cholesterol (mg/dl)	147.7±36.9*	159.2±35.6
LDL-cholesterol (mg/dl)	82.7±29.3	86.7±28.8
HDL-cholesterol (mg/dl)	45.9±14.2	48.1±15.4
Triglyceride (mg/dl)	120.2±65.7*	143.8±124.4

Data are expressed as the means±SD and analyzed by unpaired *t*-test between the CVD and non-CVD groups. *CVD group *vs*. non-CVD group, $p<0.05$.

DPA has recently been reported to have various effects on atherosclerosis and CVD, and low levels of DPA are known to be a risk factor for CVD (13-16); it is thought that DPA itself is metabolized to an anti-inflammatory substance, which then exhibits anti-atherosclerotic effects (17, 18).

We have previously examined plasma fatty acid composition of HD patients in detail and reported that the levels of n-3 polyunsaturated fatty acids gradually decreased from normal renal function to chronic kidney disease and hemodialysis patients (19). Therefore, it has been suggested that arteriosclerosis in HD patients is associated with a decrease in n-3 fatty acids, a result that is almost consistent with the results in the present study.

Table IV. *Plasma fatty acid composition (wt%) in the cardiovascular disease (CVD) and non-CVD groups.*

	CVD group	Non-CVD group
16:0	22.62±1.51	22.81±1.81
18:0	6.70±0.76	6.85±0.77
18:1n-9	23.18±3.51	22.00±3.75
18:2n-6	28.21±3.44	27.52±4.18
18:3n-6	0.25±0.16	0.25±0.14
20:3n-3	0.97±0.33	0.91±0.28
20:4n-6 (Arachidonic acid)	5.35±1.08	5.35±1.50
22:4n-6	3.66±1.72	3.97±1.91
18:3n-3 (Alpha-linolenic acid)	0.74±0.26*	0.84±0.31
20:5n-3 (Eicosapentaenoic acid)	2.26±1.44	2.26±1.78
22:5n-3 (Docosapentaenoic acid)	0.61±0.21*	0.70±0.30
22:6n-3 (Docosahexaenoic acid)	3.29±1.22	3.40±1.14

Data are expressed as the means±SD and analyzed by unpaired t-test between the CVD and non-CVD group. *CVD group *vs*. non-CVD group, $p<0.05$.

Table V. *EPA/AA, (EPA+DHA)/AA, n-6/n-3 in the cardiovascular disease (CVD) and non-CVD groups.*

	CVD group	Non-CVD group
EPA/AA	0.45±0.33	0.48±0.47
(EPA+DHA)/AA	1.10±0.60	1.16±0.64
n-6/n-3	6.31±2.69	5.78±2.37

Data are expressed as the means±SD. AA: Arachidonic acid; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid.

In conclusion, we compared serum lipid and plasma fatty acid composition in HD patients due to DM with and without CVD, and found that the levels of T-C, TG, ALA, and DPA were lower in the group with a history of CVD. This suggests that CVD is associated with low nutrition and low levels of ALA and DPA in HD patients with DM.

Conflicts of Interest

The Authors declare that there are no conflicts of interest associated with the manuscript.

Authors' Contributions

N.N. and H.O. came up with this study. H.O., C.T., H.S, and T.S. were also responsible for patient entry and carried out the present study. D.N., M.N., I.N., T.F., R.M., and M.S. performed the analytic calculations and oversaw data collection and analysis. H.T., and T.S. helped supervise the project. Finally, N.N. prepared this manuscript. All Authors approved the final manuscript.

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