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The association between fatal vascular events and risk factors for carotid atherosclerosis in patients on maintenance hemodialysis: Plaque number of dialytic atherosclerosis study

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ABSTRACT

Atherosclerotic vascular diseases are a major cause of morbidity and mortality for end-stage renal disease patients. We followed prospectively 226 hemodialysis patients by carotid ultrasonography to determine if ultrasonographic markers are predictive of the prognosis of these patients. The end-point was death or completion of the five-year follow-up period. Fatal cerebrovascular and cardiovascular events were the most common cause of death. By multivariate analysis, diabetes mellitus (DM) ($P = 0.005$), plaque number (PN) by ultrasonography ($P = 0.023$), age ($P = 0.001$), calcium–phosphate product ($P = 0.049$), and serum albumin ($P = 0.009$) were extracted as independent risk factors. The five-year increase of PN was significantly greater for DM patients than for non-DM patients. Moreover, PN was an independent marker of a fatal event, irrespective of DM status. Our results suggest that PN may be a useful predictor of the long-term prognosis of hemodialysis patients.

1. Introduction

Atherosclerotic vascular diseases are a major cause of morbidity and mortality for end-stage renal disease patients [1]. The traditional risk factors for atherosclerotic disease, such as hypertension, dyslipidemia, diabetes mellitus (DM), and smoking, are well known for the general population. Our previous study revealed that the prevalence of carotid atherosclerosis by ultrasonography was significantly higher in hemodialysis patients than in the general population [2]. Other authors have reported non-traditional risk factors such as inflammation [3,4] and the hemodialysis procedure itself [5–8].

Diabetic nephropathy has become increasingly common among patients on maintenance hemodialysis in Japan [1]. The number of patients with DM undergoing hemodialysis was about 41.3% of all patients to who were newly introduced hemodialysis in 2004, and has exceeded the number of patients with chronic renal failure since 1998. The number of patients with diabetic nephropathy on hemodialysis each year is about 14,000 in Japan [1]. DM patients undergoing hemodialysis have more advanced carotid artery lesions than non-DM patients [2].

High-resolution B-mode ultrasonography has made possible the noninvasive evaluation of common carotid artery intima-media thickness (CCA-IMT). CCA-IMT has become widely accepted as a marker of generalized atherosclerosis [9–12] and an association has been made with the occurrence of future vascular events.

The aim of this five-year prospective study was to reconfirm the role of the traditional risk factors for atherosclerosis by ultrasonographic measurement of the number of plaques (plaque number: PN), CCA-IMT, and plaque score (PS) [12] as predictors of long-term risk. We also hoped to clarify the relationship between the putative risk factors and the progression of carotid atherosclerosis in Japanese hemodialysis patients, which is important for more precise assessment of the prognosis.

2. Methods

2.1. Study design

This prospective study was done to evaluate the five-year follow-up of 226 hemodialysis patients. Throughout this study, all

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hemodialysis patients received the best medical and surgical care available at the time.

2.2. Recruitment and follow-up

The profile of the patients in 2000 is described in our previous report [2]. Each patient was on regular dialysis (4–5 h three times per week) at baseline of the study (duration: 108.4 ± 82.7 months, range: 1–348 months). The dialysate contained 140 mEq/l of sodium, 2.0 mEq/l of potassium, 3.0 mEq/l of calcium, 1.0 mEq/l of magnesium, 110 mEq/l chloride, 30 mEq/l of bicarbonate, and 100 mg/dl of glucose. The lost to follow-up, deceased, and surviving patients are summarized in Fig. 1. The 226 hemodialysis patients (124 male and 102 female; mean age 60.4 ± 13.2 years, range: 22–86 years) were assessed at two dialysis units in Fukuoka Prefecture. Of the 226 hemodialysis patients, 30 were unavailable for follow-up, including 23 who were transferred to other hospitals and 7 who underwent kidney transplantation after the day of examination by carotid ultrasonography. Of the 124 male patients, 28 (22.6%) had DM, 112 (90.3%) had hypertension, 12 (9.6%) had hyperlipidemia, and 50 (40.3%) had a history of a vascular event. Of the 102 female patients, 23 (22.5%) had DM, 83 (81.4%) had hypertension, 12 (11.8%) had hyperlipidemia, and 32 (31.4%) had a history of a vascular event. Hyperlipidemia was seen in 24 (10.6%) patients including 12 (4 male, 8 female) who were untreated, and 12 (8 male, 4 female) who were treated with a statin based antihyperlipidemia drug.

Over the course of the study, 73 of the 226 patients (32.3%) died within the five-year period, with a mean follow-up of 2.29 (range: 0.03–4.98 years) and 167.2 person-years. The 123 surviving patients have a follow-up of five-year period, and 614.9 person-years of follow-up. The 30 lost to follow-up had a mean follow-up of 4.70 (range: 0.50–5.00 years) and 102.8 person-years of follow-up. There were 884.9 person-years of follow-up in this study, and a mean survival period of 3.92 years. All patients were Japanese and informed consent was obtained. The study was done in accordance with the principles of the Declaration of Helsinki.

2.3. End-points

Briefly, the first end-points of the study were a fatal event (vascular event including cerebrovascular and cardiovascular events, infection, malignancy, cardiac failure, or another illness as the main cause of death). Of the 73 who had died, 20 patients (27.4%) died of a vascular event (15 of cerebrovascular and 5 of cardiovascular events) which were defined as the second end point, 15 (20.5%) of infectious disease (8 of pneumonia, 4 of sepsis, 2 of shunt infection, one of cerebral abscess), 8 (11.0%) of malignancy (4 of digestive cancer, 2 of leukemia, one of spine cancer, one of kidney cancer), 7 (9.6%) of sudden death, and 23 (31.5%) of other causes (6 of cardiac failure, 4 of electrolyte abnormality, 2 of ileus, 2 of gastrointestinal bleeding, one of hepatic failure, one of thrombosis, one of acute pancreatitis, 4 patients who changed hospitals for whom the cause of death was unknown, and 2 of accidents).

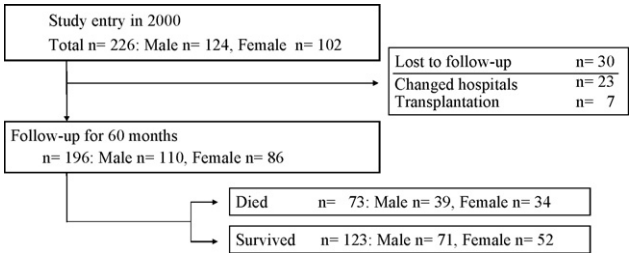

Fig. 1. Flow chart of 226 hemodialysis patients. Thirty patients were unable to be followed. The main causes of death among the 73 patients who suffered a fatal event were vascular events, infection, heart failure, and malignancy.

2.4. Medical history and lifestyle

Data were compiled from medical records and a questionnaire that included personal medical history, family history, and lifestyle habits. Pre-dialysis and post-dialysis blood pressure was measured three times per week at rest for five weeks in 2000, after which the mean blood pressure was calculated for each patient. Hypertension was defined as mean systolic pressure ≥140 mmHg, mean diastolic pressure ≥90 mmHg, or treatment with antihypertensive medications. Hyperlipidemia was defined as either total cholesterol ≥220 mg/dl or receiving lipid-lowering therapy. DM was defined as treatment with anti-diabetic agents or insulin or a past history of DM. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in square meters. A 12-lead electrocardiogram was recorded, and evidence of left ventricular hypertrophy (LVH) was assessed using the Sokolow–Lyon criteria.

2.5. Laboratory parameters

All blood samples were obtained immediately before hemodialysis and stored at −20 °C until analysis. Total cholesterol, triglycerides, and creatinine (enzymatic method), high-density lipoprotein cholesterol (homogeneous assay method), albumin (bromcresol green method), phosphorus (Fiske-Subbarow method), magnesium (xylidyl blue method), intact parathyroid hormone (immunoradiometric assay), Qualitative C-reactive protein (CRP) (turbidimetric immunoassay), and the hemoglobin, hematocrit, and white blood cell count (autoanalyzer) were measured by a commercial laboratory (CRC, Fukuoka, Japan). Qualitative CRP ≥0.5 mg/dl was defined as positive. Low-density lipoprotein cholesterol was calculated according to the Friedewald formula. All assays were done blinded to clinical data and the results of ultrasound examination.

2.6. Carotid ultrasound

Of the 123 surviving patients, 10 declined to undergo carotid ultrasonography in 2005, so data from these patients were only used for comparison of characteristics at baseline and for drawing the survival curve.

Thus, the study included 113 patients who had carotid ultrasonography between 2000 and 2005. Carotid artery lesions were assessed by high resolution B-mode ultrasonography with a 7.5 MHz linear array probe (SSD-1700, Aloka, Tokyo, Japan), as described previously. All examinations of the carotid arteries were done by the leading author, a well trained physician, without any knowledge of patient history or risk factor profile. Each subject was examined in the supine position in a semi-dark room. Both longitudinal and transverse images of the right and left carotid arteries were obtained in the anterior oblique, lateral, and posterior oblique planes. CCA-IMT was defined as the distance between the lumen–intima interface and the media–adventitia interface on B-mode images. Using the probe at an antero-oblique angle, the far wall of the carotid artery was visualized bilaterally in the common carotid artery (CCA-IMT: 20–50 mm proximal to the bifurcation of blood flow), the carotid bulb (0–20 mm proximal to the bifurcation of flow), and the internal and external carotid arteries (ICA and ECA: 0–20 mm distal to the bifurcation).

CCA-IMT was measured at 20, 25, and 30 mm proximal to the bifurcation of flow at the far wall of the right and left common

carotid arteries at end-diastole, and CCA-IMT was calculated as the mean value for each subject. We defined a plaque as a focal CCA-IMT thickening with advanced fibrofatty lesions but significant calcification and/or thrombosis, a scan area with CCA-IMT ≥1.1 mm, and plaque was detected in the internal or external carotid artery-IMT, or CCA-IMT on the right and left side. The PN was calculated by counting the number of plaques in the bilateral carotid arteries in the scanned area. The PS was calculated by totaling the maximal thickness values of all plaques in the scanned area, and categorized as normal (PS < 1.1), mild (PS = 1.1 to <5), moderate (PS = 5 to <10), and severe (PS ≥ 10) [12]. The increase in plaque over the five-years was defined as ΔPN, and percentage change of IMT progression was calculated by the following formula: progression rate = (value at five-year − baseline value) × 100/baseline value.

2.7. Statistical analysis

The survival time for each participant was calculated from the date of initial ultrasonography to the date of death or the end of follow-up for 60 months, whichever came first. The first end-point was defined as all cause death including the second end-point which defined vascular death as cerebro- and cardiovascular death. Two categorical variable comparisons were done by the Fisher's exact test. The mean values of numerical variables were compared by the unpaired *t*-test or the Mann–Whitney *U*-test, the paired *t*-test, or the Wilcoxon-test. The predictors of a fatal event included in multivariate analysis are as follows; age, sex, hypertension, hyperlipidemia, DM, dialysis duration, BMI, PN, CCA-IMT, PS (0/1: normal and mild/moderate and severe), serum albumin, serum total protein, serum qualitative CRP, serum

Table 1
Characteristics.

	Deceased patients (n = 73) mean ± S.D.		Surviving patients (n = 123) mean ± S.D		P-value[#]	Patients lost to follow-up (n = 30) mean ± S.D	
Physical condition							
Male, n (%)	39	53.4	71	57.7	0.558	14	46.7
Age (years)		67.9 ± 9.0		66.8 ± 12.9	<0.001		56.4 ± 15.1
Smoker, n (%)	34	46.6	52	42.3	0.558	12	40.0
Alcohol cosumption, n (%)	16	21.9	40	32.5	0.112	7	23.3
BMI (kg/m^2)		19.9 ± 2.6		20.2 ± 2.5	0.409		20.7 ± 3.6
Blood pressure (mmHg)							
Systlic		159.4 ± 25.6		150.2 ± 21.5	<0.001		147.1 ± 19.4
Diastolic		78.9 ± 12.6		78.8 ± 11.7	0.950		81.1 ± 8.7
Dialysis duration (month)		103.7 ± 75.9		114.1 ± 89.2	0.387		96.6 ± 70.2
LVH, n (%)	28	38.4	31	25.2	0.052	5	16.7
Present history							
Diabetes mellitus, n (%)	27	37.0	19	15.4	0.001	5	16.7
Hypertension, n (%)	67	91.8	103	83.7	<0.001	25	83.3
Hyperlipidemia, n (%)	4	5.5	12	9.8	0.290	8	26.7
Past history							
Cardiovascular events, n (%)	14	19.2	10	8.1	0.023	5	16.7
Cerebrovascular events, n (%)	24	32.9	23	18.7	0.025	6	20.0
Blood sample data							
Total cholesterol (mg/dl)		156.6 ± 32.8		159.5 ± 30.4	0.535		182.5 ± 35.3
HDL-C (mg/dl)		46.8 ± 15.6		45.8 ± 12.3	0.632		50.3 ± 15.3
LDL-C (mg/dl)		88.5 ± 26.4		90.2 ± 23.9	0.644		106.2 ± 28.0
Triglycerides (mg/dl)		106.2 ± 63.4		117.0 ± 59.1	0.232		130.0 ± 80.2
Total protein (g/dl)		7.0 ± 0.5		7.0 ± 0.5	0.932		7.1 ± 0.4
Albumin (g/dl)		3.8 ± 0.3		3.9 ± 0.3	<0.001		3.9 ± 0.3
Creatinine (mg/dl)		8.91 ± 2.12		11.06 ± 2.14	<0.001		10.69 ± 2.35
Uric acid (mg/dl)		8.8 ± 9.2		8.1 ± 1.3	0.376		8.2 ± 1.4
Calcium (mg/dl)		9.5 ± 0.9		9.5 ± 0.9	0.961		9.8 ± 1.3
Phosphorus (mg/dl)		5.6 ± 1.5		5.6 ± 1.3	0.997		5.3 ± 1.4
Magnesium (mg/dl)		2.7 ± 0.5		2.7 ± 0.4	0.482		2.9 ± 0.4
Calcium–phosphate product (mg/dl)^2		54.3 ± 16.2		53.3 ± 14.7	0.666		51.8 ± 14.8
Intact parathyroid hormone (pg/dl)		178.7 ± 212.2		166.8 ± 180.4	0.677		152.2 ± 157.8
Hemoglobin (g/dl)		9.8 ± 1.2		9.9 ± 1.1	0.662		10.0 ± 0.9
Hematocrit (%)		30.7 ± 3.4		30.9 ± 3.1	0.630		31.1 ± 2.8
White blood cell ($\times 10^3$/1)		5788 ± 1678		5818 ± 1687	0.903		5967 ± 1269
CRP (>0.5 mg/dl), n (%)	9	12.3	10	8.1	0.337	4	13.3
Ultrasonographic findings							
Prevalence of plaque, n (%)	72	98.6	103	83.7	0.001	24	80.0
Calcification plaque, n (%)	69	94.5	87	70.7	<0.001	23	76.7
PN		4.63 ± 3.18		2.54 ± 2.07	<0.001		2.97 ± 2.48
CCA-IMT(mm)		0.97 ± 0.16		0.86 ± 0.16	<0.001		0.87 ± 0.16
PS (nomal, mild/moderate, severe)		23/50		75/48			18/12
PS (moderate, severe; %)	50	68.5	48	39.0	<0.001	12	40.0

Values presented as mean value ± S.D. and number followed by (%).
Patients lost to follow-up were 23 who changed hospitals and 7 who received kidney transplantation.
BMI: body mass index, LVH: left ventricular hypertrophy, HDL-C: High density lipoprotein-cholesterol.
LDL-C: Low density lipoprotein-cholesterol, CRP: C-reactive protein.
CCA-IMT: common carotid artery intima-media thickness, PN: plaque number,
PS: plaque score; PS < 1.1 mm: normal, 1.1 ≤ PS < 5.0 mm: mild, 5 ≤ PS < 10 mm: moderate, PS ≥ 10.0 mm: severe.
[#] Comparing deceased patients and surviving patients.

calcium–phosphate product, serum intact parathyroid hormone, serum uric acid, history of cerebrovascular and cardiovascular disease, prevalence of LVH. Mortality was compared by Kaplan–Meier analysis and log rank statistics, with 95% confidence intervals (95% CI). The explanatory variables for DM, PN, age, calcium–phosphate product, and albumin were extracted using the Cox regression analysis. The relative risks and their 95% CI were calculated using the estimated regression coefficients and standard errors. In addition, time-to-fatal event curves were compared by the log–rank test and were used to estimate the absolute risk over five years for each of the ultrasound values. Adjustment variables were chosen for the multiple regression model based on the possibility that the covariate of interest may be associated with the risk of mortality. All statistical calculations were done with the Biomedical Computer Programs-P (BMDP) Statistical Software (Release 7.1, SUN/UNIX). A probability (P) value <0.05 was considered statistically significant.

3. Results

3.1. The characteristics of 73 deceased, 123 surviving, and 30 patients lost to follow-up (Table 1)

The prevalence of a history of DM (37.0%), hypertension (91.8%), and past history of a cardiovascular (19.2%), or cerebrovascular event (32.9%) at baseline were significantly higher in the deceased than in surviving patients (15.4%, 83.7%, 8.1%, and 18.7%, respectively). Additionally, the mean systolic blood pressure (159.4 mmHg) at baseline was significantly higher in the deceased than in the surviving patients (150.2 mmHg). However, the mean serum albumin (3.8 mg/dl) and the mean creatinine (8.91 mg/dl) were significantly lower in the deceased than in the surviving patients (3.9 mg/dl and 11.06 mg/dl, respectively). In carotid ultrasonographic findings, the mean PN (4.63), the mean CCA-IMT (0.97 mm), the prevalence of moderate and severe groups of PS (68.5%), plaque (98.6%), and calcification (94.5%) were significantly higher in the deceased than in the surviving patients (2.54, 0.86 mm, 39.0%, 83.7%, and 70.7%, respectively). There were no significant differences between the deceased patients in relation to smoking, alcohol consumption, sex, BMI, LVH, duration of hemodialysis, serum total cholesterol, high density lipoprotein, triglycerides, uric acid, intact PTH, qualitative CRP, mineral, or hematological values.

3.2. Multivariate analysis for the development of a fatal event

The Cox regression analysis with backward stepwise regression of 226 hemodialysis patients showed the significantly independent risk factors at baseline for all cause death to be a history of DM (P = 0.005), PN (P = 0.023), age (P = 0.001), calcium–phosphate product (P = 0.049), and serum albumin (P = 0.009) (Table 2).

The five-year survival rate was compared for four groups, classified by the PN by ultrasonography (0–1, 2, 3–4, and ≥5) and by DM status, and was adjusted for independent factors such as age, serum calcium–phosphate product, albumin, and related covariates. The highest group of PN ≥5 had a significantly lower survival rate than the other groups (log–rank test, P < 0.001) (Fig. 2). The survival rate of DM patients was significantly lower than that of non-DM patients (log–rank test, P < 0.001) (Fig. 3). To clarify the effect of PN and DM on survival, the combined risk factors for PN and DM were divided into four groups: PN <5 and non-DM (group A, n = 141), PN <5 and DM (group B, n = 33), PN ≥5 and non-DM (group C, n = 34), PN ≥5 and DM (group D, n = 18). The five-year survival rate by all cause mortality (Fig. 4a) and the five-year survival rate by vascular mortality (Fig. 4b) were adjusted for independent markers such as age, dialysis duration, albumin, and uric acid (Table 3). The five-year survival rate of group A was higher than that of the other groups (all $P \leq 0.001$). Moreover, the all cause and vascular mortality of group

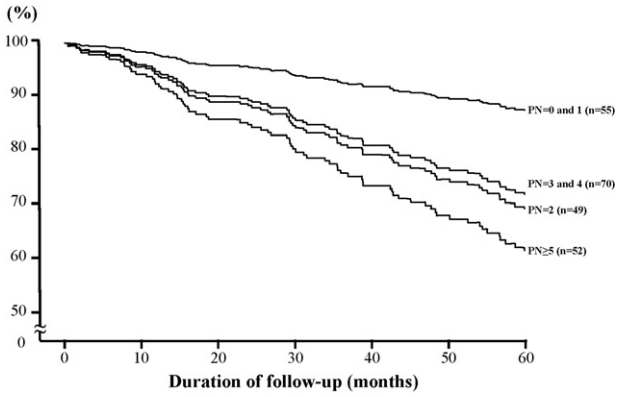

Fig. 2. The five-year survival rates of hemodialysis patients grouped by plaque number (PN). The five-year survival rate of patients with PN ≥5 was significantly lower than that of the other three patient groups (log–rank test: P < 0.001).

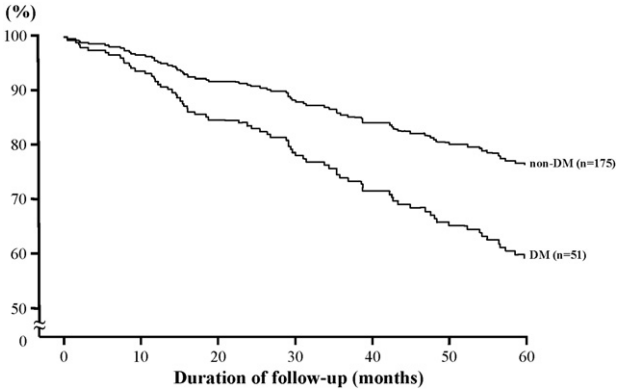

Fig. 3. The five-year survival rates of hemodialysis patients with and without diabetes mellitus (DM). The five-year survival rates of patients with DM (n = 51) was a significantly lower than that of non-DM patients (n = 175) (log–rank test: P < 0.001).

Table 2
Cox regression analysis with backward stepwise regression of the risk factors for a fatal event in 226 hemodialysis patients.

Parameters		β	Relative risk	95% CI		P-value
				Lower	Upper	
Diabetes mellitus	Yes	0.707	2.029	1.242	3.313	0.005
Plaque number	1	0.100	1.105	1.014	1.205	0.023
Age	1 y.o.	0.041	1.042	1.017	1.068	0.001
Ca × P	1 $(mg/dl)^2$	0.014	1.014	1.000	1.029	0.049
Abumin	1 g/dl	−1.165	0.312	0.131	0.745	0.009

95% CI: 95% confidence intervals.
Ca × P: serum calcium–phosphate product.

Table 3
Cox regression analysis with backward stepwise regression for all cause and vascular mortality according to significant risk markers and the combined plaque number (PN) and diabetes mellitus (DM) status.

Parameters		All cause mortality					Vascular mortality				
		β	Relative risk	95% CI		P-value	β	Relative risk	95% CI		P-value
				Lower	Upper				Lower	Upper	
Age	1 y.o.	0.048	1.05	1.02	1.08	<0.001					
Dialysis duration	1 month	0.004	1.00	1.00	1.01	0.029					
Albumin	1 g/dl	−0.978	0.38	0.16	0.89	0.025					
Uric acid	1 mg/dl	0.030	1.03	1.00	1.06	0.031					
group A vs. group B		1.280	3.60	1.78	7.28	<0.001	2.069	7.92	2.23	28.14	0.001
group A vs. group C		0.941	2.56	1.31	5.03	0.006	2.212	9.13	2.57	32.52	0.001
group A vs. group D		1.183	3.27	1.52	7.03	0.003	2.242	9.42	2.35	37.74	0.002

95% CI: 95% confidence intervals. Group A (n = 141), PN<5 and Non-DM; group B (n = 33), PN <5 and DM; group C (n = 34), PN >5 and Non-DM; group D (n = 18), PN >5 and DM.

C patients were not significantly different than those of group B and D patients (vs. group B, P = 0.336 and P = 0.802, respectively; vs. group D, P = 0.783 and P = 0.944, respectively). Therefore, PN was an important marker for the survival of hemodialysis patients, irrespective of DM status.

Table 3 shows significant risk parameters of the combined PN and DM for all cause and vascular mortality by Cox regression analysis with backward stepwise regression. The relative risk (RR) of significant parameters for all cause mortality were age (RR: 1.05), dialysis duration (RR: 1.00), serum albumin (RR: 0.38), serum uric acid (RR: 1.03), and group A vs. group B (RR: 3.60), group C (RR: 2.56), group D (RR: 3.27). The RR of significant parameters for vascular mortality were group A vs. group B (RR: 7.92), group C (RR: 9.13), and group D (RR: 9.42). Therefore, these findings suggest that PN ≥5 and DM were related to all cause and vascular mortality.

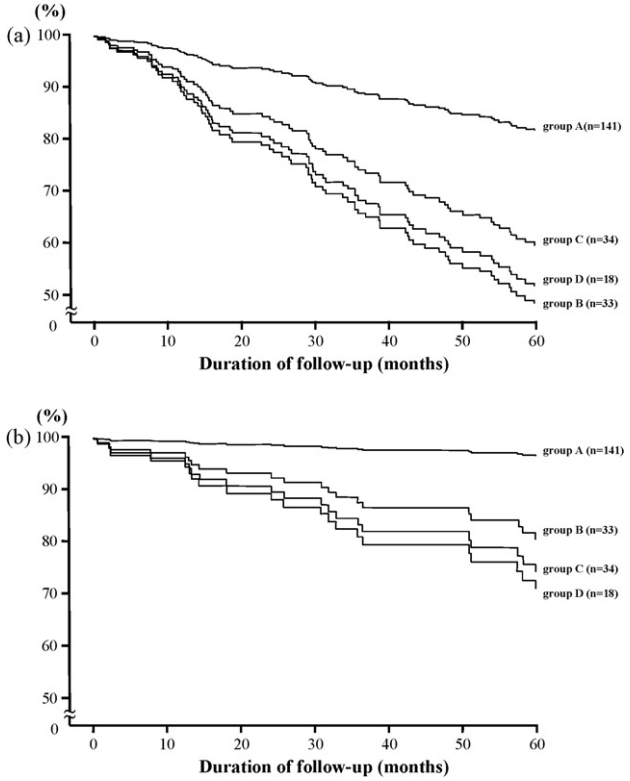

Fig. 4. The survival rate after adjustment for all cause mortality (a) and for vascular mortality (b) adjusted for age, calcium–phosphate product, and albumin. The five-year survival rates of hemodialysis patients grouped by plaque number (PN) and diabetes mellitus (DM) status (group A: n = 141, DM and PN <5; group B: n = 33, DM and PN ≥5; group C: n = 34, non-DM and PN <5; group D: n = 18, non-DM and PN ≥5). The survival rate after adjustment for all cause and vascular death in group A was significantly higher than that of the other three groups (log–rank test: both $P \leq 0.001$). Moreover, the all cause and vascular mortality of group C patients were not significantly different than those of group B and D patients (vs. group B, P = 0.336 and P = 0.802, respectively; vs. group D, P = 0.783 and P = 0.944, respectively).

3.3. Change of carotid atherosclerosis from baseline to follow-up for the 113 surviving patients (Table 4)

The mean PN and CCA-IMT levels were adjusted for independent factors such as age, calcium–phosphate product, and albumin by Cox regression analysis with backward stepwise regression. The mean PN in 2005 (at follow-up) of both DM and non-DM patients were significantly higher than those in 2000 (at baseline) (both $P \leq 0.001$). Notably, the mean PN of DM patients was significantly higher than that of non-DM patients at both baseline and follow-up (P = 0.019 and $P \leq 0.001$, respectively). Moreover, the increase of PN (ΔPN) during the follow-up period was significantly higher (4.81 ± 0.55) in DM patients than in non-DM patients (2.83 ± 0.23) ($P \leq 0.001$).

In the case of DM patients, the mean CCA-IMT was also significantly higher (1.14 ± 0.05 mm) at follow-up than at baseline (0.94 ± 0.03 mm) (P = 0.017). The mean CCA-IMT of DM patients was significantly higher than that of non-DM patients at both baseline and follow-up (P = 0.010 and $P \leq 0.001$, respectively), and the mean progression rate of CCA-IMT of DM patients was significantly greater ($22.4 \pm 4.9\%$) than that of non-DM patients ($1.7 \pm 2.0\%$) ($P \leq 0.001$). However, there was no statistically significant increase of the mean CCA-IMT of the 96 non-DM patients between baseline and follow-up (0.84 ± 0.01 mm and 0.82 ± 0.02 mm, P = 0.090). DM patients had significantly higher frequency of PS severity of moderate/severe than that non-DM at baseline (P = 0.00). Additionally, all 5 DM patients who had normal or mild PS at baseline changed to moderate or severe PS at follow-up, and 37 of 67 (55.2%) of non-DM patients who had normal or mild PS changed to moderate or severe PS.

4. Discussion

The present study of three ultrasonographic parameters, PN, CCA-IMT, and PS, revealed new information that may be useful for the evaluation of carotid atherosclerotic risk factors related to a fatal event, including all cause and vascular death, and the prognosis of Japanese hemodialysis patients. We found that the follow-up PN was significantly increased in comparison with the baseline PN, but that the CCA-IMT of non-DM patients was unchanged, CCA-IMT and PS were not independent risk markers in a multivariate analysis. We also found the predictive risk markers for all cause and vascular death by ultrasonography to be associated with PN parameters,

Table 4
Changes of carotid atherosclerosis.

	DM (n= 17)		non-DM (n= 96)		*p - value*
PN (mean ± S D)					
2000	3.46 ± 0.45	< 0.001[a]	2.33 ± 0.18	< 0.001[b]	0.019[c]
2005	8.18 ± 0.61		5.17 ± 0.25		< 0.001[d]
ΔPN	4.81 ± 0.55		2.83 ± 0.23		< 0.001[e]
CCA-IMT (mm, mean ± S D)					
2000	0.94 ± 0.03	0.017[a]	0.84 ± 0.01	0.090[b]	0.010[c]
2005	1.14 ± 0.05		0.82 ± 0.02		< 0.001[d]
Progression rate (%)	22.4 ± 4.9		1.7 ± 2.0		< 0.001[e]

PN: plaque number, CCA-IMT: common carotid artery-intima-median thickness. The increase in plaque over the five-years was defined as ΔPN. percentage change of IMT progression was calculated by the following formula: progression rate = (value at five-year − baseline value) × 100/baseline value. [a]Comparing atherosclerotic change of DM patients in 2000 and 2005. [b]Comparing atherosclerotic change of non-DM patients in 2000 and 2005. [c]Comparing DM and non-DM in 2000. [d]Comparing DM and non-DM in 2005. [e]Comparing five-year changes of DM and non-DM.

irrespective of DM status. Therefore, PN was an important marker for the survival of hemodialysis patients.

Benedetto et al. [16] reported that mean-IMT was an independent predictor of cardiovascular death among end-stage renal failure patients. However, our study documented no relation between CCA-IMT and mortality. This is because we more strictly defined vascular death as stroke and myocardial infarction excluding sudden death, heart failure, embolism, and aortic aneurysm. Although we used a 6 point average of CCA-IMT as in Benedetto et al., the following two points differed between our study and theirs. Firstly, the percentage of the studied patients with DM in our study (22.6%) was higher than in Benedetto et al. (6.5%). Secondly, the methodology of our study was classified according to DM status, and Benedetto's study included DM status and both hemodialysis and continuous ambulatory peritoneal dialysis. Therefore, we believe our study adds useful data for comparison with that of the previous report.

Some studies have shown that the rate of vascular events of hemodialysis patients is substantially higher than that of the general population (2.4–18.0%) [11,21], moreover, hemodialysis patients are characterized by an exceptionally high mortality rate by such diseases [7–12]. Of 226 hemodialysis patients, 73 (32.3%) in this study died within the five-year period, and 20 of the deceased patients (27.4%) had had a fatal vascular event, similar to that of studies from other laboratories, which found rates of 16–42% [7,18].

Complication with DM is a reproducible, traditional risk factor associated with the progress of atherosclerosis [9,18–19,22]. Some previous studies have shown that DM and/or hypertension are significantly involved in such fatal events [5,9,10,21], and that patients with both DM and ESRD have significantly higher CCA-IMT values than those with either DM or ERSD alone [9]. DM was also found to be strongly associated with a fatal event in this study. Many previous studies have used ultrasonography to assess risk factors for the progression of carotid atherosclerosis in the general population [2,13–15] and hemodialysis patients [2,5,7–12,16,17].

Our study demonstrated that PN was clearly correlated with all cause mortality. Moreover, PN was strongly associated with vascular mortality, irrespective of DM status, and the relative risk of non-DM patients with PN ≥5 was the same risk of DM for all cause and cardiovascular death, by multivariate analysis. These results suggest that PN is one of the most important markers for the prognosis of hemodialysis patients. None of the other ultrasonographic parameters were predictive in this study.

The mechanisms for the accelerated atherosclerosis of hemodialysis patients may be inflammation associated with dialysis-related causes [3,4,6,20,23] and/or the hemodialysis procedure itself [5–8]. One study reported that the dialysis procedure causes progressive endothelial cell injury that leads to both macro- and micro-vascular disease [13]. However, the reason for the increase of the PN in hemodialysis patients is not clear.

There are several limitations to this study. First, we were not able to classify the cause of death of 11 (15.1%) of the 73 deceased patients (7 sudden deaths and 4 for whom cause of death was unknown because of a change of hospitals), and we could not do ultrasonographic follow-up of 10 of the 123 surviving patients (8.1%) in 2005. Second, there were only two dialysis units, so the results would have only internal validity. A future, large-scale study with long-term observation will be necessary to fully clarify the risk factors of the fatal events of hemodialysis patients.

The present study revealed that PN by ultrasonography was an important marker for the survival of hemodialysis patients.

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