Kidney International, Vol. 64 (2003), pp. 1472–1479

DIALYSIS–TRANSPLANTATION

Impact of carotid atherosclerosis on long-term mortality in chronic hemodialysis patients

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Impact of carotid atherosclerosis on long-term mortality in chronic hemodialysis patients.

Background. Cardiovascular event is the major cause of mortality in patients on maintenance hemodialysis. We prospectively tested the predictive values of atherosclerotic parameters for all-cause and cardiovascular outcomes in 219 hemodialysis patients (age, 58 ± 13 years; time on hemodialysis, 13 ± 7 years; male/female, 144/75).

Methods. We measured blood homocysteine (Hcy), ultrasound carotid artery intima media thickness (IMT) and % aortic wall calcification at L2/3 region [% of calcification index in the abdominal aortic wall (%ACI)] by computed tomography (CT) scan, and followed all patients for 5 years.

Results. During the follow-up periods, 54 patients (25%) died, 40 (74%) of them of cardiovascular causes. IMT was significantly higher in patients who expired (0.75 ± 0.02 mm) than in those who survived (0.62 ± 0.01 mm). IMT was significantly correlated with age ($r = 0.47$, $P < 0.01$) and %ACI ($r = 0.27$, $P < 0.01$). The survival rate during the observation was significantly lower in the final IMT third (58%) than in the first (90%) and the middle IMT third (80%) ($P < 0.01$). Multivariate Cox proportional hazards analysis revealed that diabetes and IMT became independent determinants of all-cause and cardiovascular death. Adjusted hazards ratios of all-cause and cardiovascular mortality for an increase of 0.1 mm in IMT were 1.31 (95% CI, 1.07 to 1.59) and 1.41 (95% CI, 1.12 to 1.76). In contrast, %ACI at abdominal aorta and blood Hcy did not affect their 5-year mortality.

Conclusion. These findings suggested that measurement of carotid artery IMT is useful for predicting long-term mortality in patients receiving maintenance hemodialysis.

Atherosclerotic cardiovascular disease is the major cause of mortality and morbidity in hemodialysis patients. B-mode ultrasound imaging is a useful and noninvasive tool to directly quantitate the atherosclerotic burden [1, 2]. Hemodialysis patients are known to have an advanced carotid artery intima medial thickness (IMT) compared with age- and gender-matched normal subjects [3]. Calcified plaque is also common in carotid arteries of hemodialysis subjects without clinical vascular disease [4]. Recently, a marked increment of carotid artery IMT is noted in predialysis renal failure patients [5, 6]. End-stage renal failure itself, but not classical cardiovascular risk, is demonstrated as an independent predictor of arterial IMT [6]. Increased IMT, arterial stiffness, and coronary artery calcification are also noted in young adults on regular hemodialysis [7–9]. These findings suggest that uremia and/or metabolic disorder due to end-stage renal failure may be to a greater extent associated with accelerated atherosclerosis in dialysis subjects.

There still is a debate, however, as to whether IMT reflects local atherosclerosis or rather simple arteriosclerosis. IMT consists mainly of media and a small amount of intima, whereas atherosclerosis is an intimal process. Epidemiologic studies have shown that increases in carotid artery IMT are associated with risk of myocardial infarction and stroke in general subjects [1, 10]. In contrast, other studies rather demonstrate a better correlation of plaque diameter measurement than IMT with atherosclerotic events [11, 12]. Thus, it remains unclear as to whether carotid artery IMT is much useful for predicting long-term cardiovascular outcomes.

The main aim of the present study is to ascertain the clinical relevance of carotid artery IMT for cardiovascular and all-cause mortality in patients receiving regular hemodialysis. We cross-sectionally measured ultrasound IMT and vascular plaque of bilateral common carotid arteries. We also assessed abdominal aortic wall calcification by computed tomography (CT) scan, which has been validated as a predictor of cardiovascular morbidity and mortality in general population. After determining these parameters, we followed the patients for next 5 years.

Key words: IMT, %ACI, homocysteine, albumin, hemodialysis.

Received for publication January 8, 2003
and in revised form March 10, 2003, and May 4, 2003
Accepted for publication May 16, 2003

METHODS

Study population

We selected stable 219 out of 348 patients from a single dialysis unit (Maruyama Hospital, Hamamatsu, Japan) at August 1997. We excluded outpatients who denied participating in this study because of their time limitations ($N = 98$). Hospitalized subjects who complicated by acute infection, congestive heart failure (CHF), severe dialysis-related amyloidosis, and malignancies were not enrolled ($N = 28$). We also excluded subjects who had active collagen vascular diseases such as rheumatoid arthritis ($N = 3$). The patients comprised 144 males and 75 females with a mean age of 58 ± 13 years (range, 25 to 96 years). The mean time on hemodialysis was 13 ± 7 years (range, 1 to 28 years). There were 35 diabetic patients (16%). Eleven persons had a history of cardiovascular events such as cerebral infarction, CHF, angina, and acute myocardial infarction (AMI) at the assessment. The lifelong dose of smoking was calculated as Brickman index (BI), a product of years of smoking history and daily number of cigarettes.

Hemodialysis-related factors

All patients had been subjected to regular hemodialysis for 4 to 5 hours three times per week at a blood flow rate of 180 to 220 mL/min. All patients used bicarbonate dialysate (30 mEq/L) (Kindaly AF-2P, Fuso, Osaka, Japan) at a flow rate of 500 mL/min. All hemodialysis treatments were performed using one of the following dialyzer membranes: low-flux ultrafiltration rate (UFR) (<20 mL/min · hour), modified regenerated cellulose hollow-fiber (MRC) (AM-BC, Asahi Medical, Tokyo, Japan, or CL-EE, Terumo, Tokyo, Japan), medium-flux UFR (20 to 40 mL/min · hour), cellulose triacetate hollow-fiber (CTA) (FB-U, Nipro Medical, Osaka, Japan or TFW, Teijin-Gambro, Tokyo, Japan), and high-flux UFR (>40 mL/min · hour) polysulfone synthetic hollow-fiber (BS-U, Toray Medical, Tokyo, Japan or APA, Asahi Medical, Tokyo, Japan). There was no patient who reused the dialyzer membrane. Neither bacteria nor pyrogen was detected in the dialysate prepared from water obtained by reverse osmosis. Blood samples were drawn from the arterial site of the arteriovenous fistula at the beginning and the end of the hemodialysis unit. Serum or plasma was transferred into plastic tubes and stored until –82°C until the measurement. Serum urea nitrogen, creatinine, total protein, albumin, total cholesterol, high-density lipoprotein (HDL) cholesterol and hemoglobin were measured by standard laboratory techniques using automatic analyzer. Intact parathyroid hormone (PTH) was determined using immunoradiometric assay. C-reactive protein (CRP) was determined by laser nephrometer. Plasma total homocysteine (Hcy) was determined by a high-pressure liquid chromatography based on a derivative of SBD-F fluorescence. The efficiency of hemodialysis was assessed based on the delivered dose of dialysis (Kt/V_{urea}) using a single-pool urea kinetic model.

Evaluation of atherosclerotic changes

The right and left carotid arteries were examined using a 7.5 Hz linear array transducer with high-resolution B-mode echography (Aloka, Tokyo, Japan) as described previously [13]. This device can measure the arterial wall thickness by 0.1 mm. The subjects were in the supine position with the head slightly turned from echography at the measurement. All scannings were performed by the same investigator. The wall of the common carotid artery, 0.5 to 1.0 cm proximal to the beginning of the carotid bulb, was used for the measurement of the IMT and lumen diameter. The IMT was defined as the distance between the leading edge of the lumen intima echo of the near wall and the leading edge of the media adventitia echo. The lumen diameter was defined as the distance between the leading edge of the intima lumen echo of the near wall and the leading edge of the lumen intima echo of the far wall. To enhance the reproducibility of carotid measures, standardized interrogation angles were used. The mean values of the IMT and lumen diameter were calculated from at least two measurements for each artery. IMT measurements were always performed in plaque-free arterial segments. The intraobserver coefficient of variation in all of the patients was 6.0% (mean difference, 0.02 mm). We also measured carotid artery IMTs in six portions from healthy subjects by a blind observer, and found 9.2% of coefficient of variation (mean difference 0.03 mm). The existence of carotid plaque, which is defined as the intima media thickening of more than 1 mm, was screened for in the common, internal, and external carotid arteries. We measured the maximal diameter of carotid plaque along the artery wall.

Electrocardiogram (ECG) was recorded just before the starting of dialysis. The presence of abnormal Q or inverted T wave in extremity leads was defined as ischemic ECG changes. The percentile of calcification index in the abdominal aortic wall (%ACI) was measured at the horizontal CT slice between the second and third lumbar vertebrae, since calcific deposit was most remarkable in this region [14].

The predialysis mean blood pressure (MBP) was determined as MBP = diastolic + (systolic – diastolic)/3. Atherosclerotic index (AI) was calculated as AI = (total cholesterol – HDL cholesterol)/HDL cholesterol [15]. Low-density lipoprotein (LDL) cholesterol was calculated from modified Friedewald's formula for Japanese population (total cholesterol – HDL cholesterol – triglyceride/4) [16].

5-Year follow-up study

After the determination of initial laboratory and atherogenic parameters, we followed all patients for 5 years

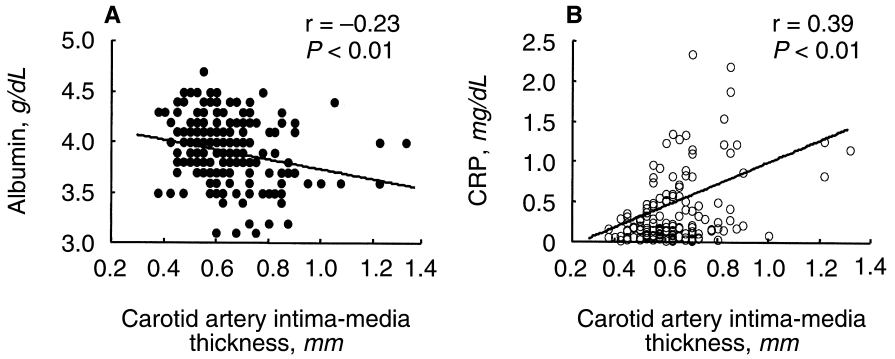

Fig. 1. Association between carotid artery intima media thickness (IMT) and blood albumin and C-reactive protein (CRP) in hemodialysis patients. A significant relationship was found between carotid artery IMT and albumin ($r = -0.23$, $P < 0.01$) (*A*) and CRP ($r = 0.39$, $P < 0.01$) (*B*).

until August 2002. No patient was lost to follow-up. Each death was reviewed and assigned an underlying cause by three physicians. Cardiovascular mortality included death from stroke, AMI, and CHF. We divided all subjects into surviving and expired groups and evaluated the influence of these parameters on mortality.

Statistical analysis

Each value was expressed as the mean ± SD. Differences between two groups were analyzed by an unpaired Student *t* test following the analysis of variance (ANOVA) method. *P* values less than 0.05 were considered statistically significant. Kaplan-Meier estimates of IMT and intact PTH were calculated for the time of death during follow-up. The *P* values for comparison of survival curves were determined by the log-rank test. The relative risk of different parameters was estimated using the Cox proportional hazards model. Relative risks (RR) and their 95% confidence intervals (95% CI) were calculated using the estimated regression coefficients and their standard error in the Cox regression analysis. We evaluated 17 parameters: age, gender, time on hemodialysis, diabetes mellitus, serum albumin, hemoglobin, the product of calcium and phosphate, total cholesterol, AI, Hcy, BI, Kt/V_{urea}, intact PTH, CRP, carotid artery IMT, plaque, and %ACI as a univariate model. In addition, chi-square statistics were obtained. The independent effect of each explanatory variable on log carotid artery IMT was assessed using forward stepwise multiple regression analysis with five associated variables, including age, albumin, total cholesterol, log CRP and BI. Since IMT and CRP were nonnormally distributed, we normalized these data by log transformation, and examined their correlations. All statistical calculations were performed with the StatView 5J software (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Clinical data and atherogenic parameters

There was a significant and positive relationship between age and carotid artery IMT ($r = 0.47$, $P < 0.01$) and %ACI at L2/3 region ($r = 0.41$, $P < 0.01$). In contrast, gender, seropositivity of antihepatitis C antibody, and time on hemodialysis were not associated with these two parameters. No significant difference was found in carotid artery IMT between diabetic (0.71 ± 0.18 mm) and nondiabetic patients (0.64 ± 0.15 mm). However, the prevalence of carotid artery plaque was significantly higher in diabetic subjects (54% vs. 33%, $P = 0.02$). Diabetic patients also had a significantly higher %ACI than nondiabetic patients (50.4 ± 29.3% vs. 22.7 ± 22.7%, $P < 0.01$).

Blood albumin was significantly and inversely correlated with carotid artery IMT ($r = -0.23$, $P < 0.01$, Fig. 1), but not with %ACI. Albumin was also significantly associated with log-transferred IMT ($r = -0.25$, $P < 0.01$). Similarly, IMT was positively correlated with CRP ($r = 0.39$, $P < 0.01$, Fig. 1). A significant and positive relationship between IMT and CRP was also observed following log transformation ($r = 0.32$, $P < 0.01$). There was a weak but significant and positive relationship between log IMT and BI in habitual smoking subjects ($r = 0.21$, $P < 0.05$, $N = 96$). Total cholesterol was also significantly and inversely correlated with log IMT ($r = -0.17$, $P < 0.02$). In contrast, plasma Hcy, LDL cholesterol, and blood pressure were not associated with carotid artery IMT or %ACI. Dialyzer membrane also did not influence mean IMT. There was no association between %ACI and the product of calcium and phosphate, blood pressure, or intact PTH in this study. A stepwise multiple regression analysis revealed that age and total cholesterol became significant determinants of IMT.

A significant increase in carotid artery IMT was found in hemodialysis patients possessing ischemic ECG changes (0.70 ± 0.18 mm, $N = 96$) compared with those without ischemic ECG changes (0.61 ± 0.12 mm, $N = 116$) ($P < 0.01$). The prevalence of carotid plaque was also higher in patients having ischemic ECG changes (47% vs. 29%, $P < 0.01$). A weak but significant and positive relationship was found between IMT and %ACI ($r = 0.27$, $P < 0.01$).

Table 1. Initial clinical parameters in surviving and expired hemodialysis patients

	Alive	Dead	*P* value
Number	165	54	
Age *years*	56 ± 11 [26–87]	65 ± 14 [25–96]	<0.01
Male/female	112/53	32/22	0.25
Time on hemodialysis treatment *years*	13 ± 7 [1–28]	12 ± 8 [3–25]	0.47
Prevalence of diabetes %	9.7	35.2	<0.01
HCV infection %	27.6	25.0	0.85
Dialysis-related factors			
Calcium *mEq/L*	4.6 ± 0.4	4.5 ± 0.5	0.36
Phosphate *mg/dL*	6.0 ± 1.6	5.5 ± 1.9	0.06
Product of calcium and phosphate	27.7 ± 8.0	24.9 ± 9.5	<0.05
Intact PTH *pg/mL*	207 ± 254	367 ± 1011	0.06
Hemoglobin *g/dL*	10.0 ± 1.1	9.9 ± 1.2	0.49
Kt/V_{urea}	1.25 ± 0.24	1.33 ± 0.19	0.34
PS membrane %	44.6	32.2	0.16
Nutrition-related factors			
Albumin *g/dL*	4.0 ± 0.3	3.8 ± 0.4	<0.01
Triglyceride *mg/mL*	134 ± 74	119 ± 97	0.27
Total cholesterol *mg/dL*	155 ± 33	144 ± 27	<0.05
BMI kg/m^2	21.3 ± 2.7	20.8 ± 1.8	0.68
CRP *mg/dL*	0.35 ± 0.42	0.46 ± 0.57	0.45
Atherosclerotic risk factors			
Blood pressure *mm Hg*			
Systolic	140 ± 22	148 ± 21	0.06
Diastolic	75 ± 13	74 ± 14	0.84
Mean	108 ± 16	111 ± 17	0.23
Smoking %	47.8	68.2	0.87
Brickman index in smokers	440 ± 348	630 ± 641	0.08
HDL cholesterol *mg/dL*	35 ± 10	33 ± 10	0.41
LDL cholesterol *mg/dL*	87 ± 29	82 ± 26	0.26
Atherogenic index	4.0 ± 0.3	3.8 ± 0.4	0.64
Homocysteine *μmol/L*	37.4 ± 24.3	34.0 ± 19.5	0.36
Atherosclerotic parameters			
Carotid artery IMT *mm*	0.62 ± 0.14	0.75 ± 0.18	<0.01
Prevalence of plaque %	32.1	50.0	<0.02
Maximal plaque diameter *mm*	3.2 ± 1.6	3.4 ± 1.9	0.71
% ACI at L2/3	24.4 ± 24.4	33.2 ± 28.1	0.09
Ischemic ECG change %	35.8	76.0	<0.01

Abbreviations are: HCV, hepatitis C virus; PTH, parathyroid hormone; PS, polysulfone; BMI, body mass index; CRP, C-reactive protein; %ACI, % aortic calcification index; ECG, electrocardiogram. Data are expressed as mean ± SD.

Table 2. Atherogenic parameters in the dead patients by cardiovascular or noncardiovascular events

	Cardiovascular	Noncardiovascular	*P* value
Number	37	14	
Age *years*	63 ± 15	73 ± 11	<0.02
Male %	54.1	71.4	NS
Time on hemodialysis treatment *years*	10 ± 7	13 ± 8	NS
Prevalence of diabetes %	27.3	27.8	NS
Albumin *g/dL*	3.8 ± 0.4	3.6 ± 0.3	NS
Total cholesterol *mg/dL*	148 ± 28	138 ± 25	NS
Hemoglobin *g/dL*	10.0 ± 1.1	9.5 ± 1.1	NS
Intact PTH *pg/mL*	471 ± 1202	135 ± 162	NS
LDL cholesterol *mg/dL*	83 ± 29	81 ± 20	NS
Atherogenic index	4.2 ± 1.8	2.8 ± 0.9	<0.02
Homocysteine *μmol/L*	33.1 ± 18.1	37.0 ± 24.9	NS
Carotid artery IMT *mm*	0.75 ± 0.17	0.75 ± 0.21	NS
Prevalence of plaque %	56.8	28.6	NS
%ACI at L2/3	38.2 ± 26.5	37.0 ± 24.9	NS
Ischemic ECG change %	75.0	63.6	NS

Abbreviations are: PTH, parathyroid hormone; %ACI, % aortic calcification index; ECG, electrocardiogram; NS, not significant. Data are expressed as mean ± SD.

Clinical parameters and the 5-year mortality

Fifty-four patients (25%) died during the 5-year follow-up (male/female, 32/22). The causes of death were cardiovascular events in 40 (74%), pulmonary infection in eight (15%), gastrointestinal bleeding in two (4%), and other causes in four patients (7%). Cardiovascular fatal events consisted of CHF in 23, AMI in 11, and stroke in six deaths. Dead patients were significantly older than surviving subjects ($P < 0.01$), but there was no difference in time on hemodialysis between two groups (Table 1). The prevalence of diabetes was significantly higher in the expired group ($P < 0.01$). In contrast, the prevalence of male and polyfulfone synthetic hollow-fiber membrane was identical between both groups.

In expired patients, a significant lower serum albumin ($P < 0.01$) and total cholesterol ($P < 0.05$) was found compared with living patients. The product of calcium and phosphate was significantly rather lower in the dead group ($P < 0.05$). CRP and hemoglobin did not differ between both groups (Table 1).

Mean carotid artery IMT was significantly larger in the dead group compared with that in the survival group (Table 1). A significant increase in IMT in the expired group was also evident both in nondiabetic subjects (0.61 ± 0.13 mm vs. 0.74 ± 0.19 mm, $P < 0.01$, $N = 184$) and in non-smokers (0.62 ± 0.14 mm vs. 0.74 ± 0.16 mm, $P < 0.01$, $N = 123$). The prevalence of carotid artery plaque ($P < 0.02$) and ischemic ECG changes ($P < 0.01$) was significantly higher in expired patients. In nondiabetic subjects, however, no significant difference was found in the prevalence of carotid artery plaque in the expired group ($N = 35$) compared with that in the surviving group ($N = 149$) (42.9% vs. 30.9%, $P =$ NS). In addition, there was no difference in maximal plaque diameter between both groups (Table 1). A significantly higher prevalence of ischemic ECG changes in the dead group was also evident in non-diabetic (67.7% vs. 34.0%, $P < 0.01$) and in nonsmokers (80.0% vs. 34.8%, $P < 0.01$), respectively.

There was no significant difference in %ACI between alive and dead subjects (Table 1). In nonsmokers, dead patients tended to have a higher %ACI compared with alive patients (38.6 ± 30.8% vs. 25.9 ± 25.7%, $P = 0.07$). However, in nondiabetic subjects, there was no difference in %ACI between both groups (22.9 ± 23.2% vs. 21.8 ± 20.8%, $P =$ NS). There was also no significant difference in the prevalence of blood Hcy, LDL cholesterol, blood pressure, and AI between two groups (Table 1).

In the dead group, expired patients by fatal cardiovascular events were significantly younger than those by noncardiovascular causes ($P < 0.02$) (Table 2). No differ-

Table 3. Univariate and multivariate Cox proportional hazards analysis for all-cause and cardiovascular mortality during the follow-up

Variable	Unit	Univariate			Multivariate		
		RR	95% CI	*P* value	RR	95% CI	*P* value
All-cause mortality							
Age	1 year	1.06	1.04–1.09	<0.01	—	—	—
Diabetes	Referent, nondiabetes	3.49	1.99–6.12	<0.01	2.88	1.46–5.61	<0.01
Albumin	1 g/dL	0.14	0.05–0.40	<0.01	0.22	0.06–0.73	0.01
Calcium x phosphate		0.96	0.93–0.99	<0.05	—	—	—
IMT	0.1 mm	1.44	1.27–1.64	<0.01	1.31	1.07–1.59	<0.01
Plaque	Referent, nonplaque	2.03	1.18–3.48	0.01	—	—	—
Cardiovascular mortality							
Age	1 year	1.05	1.02–1.07	<0.01	—	—	—
Diabetes	Referent, nondiabetes	3.55	1.84–6.85	<0.01	2.84	1.27–6.35	0.01
Albumin	1 g/dL	0.29	0.09–0.96	<0.05	—	—	—
Intact PTH	100 pg/mL	1.03	1.00–1.06	<0.03	1.05	1.02–1.08	<0.01
IMT	0.1 mm	1.45	1.25–1.68	<0.01	1.41	1.12–1.78	<0.01

Abbreviations are: IMT, intima media thickness; PTH, parathyroid hormone.

ence was found in the prevalence of diabetes and time on hemodialysis between two groups. AI was higher in patients with cardiovascular death than those without vascular accidents ($P < 0.02$). However, there was no difference in carotid artery IMT between both groups. No significant difference was also found in carotid artery plaque, %ACI, and ischemic ECG changes between two groups (Table 2).

Impact of carotid artery IMT on 5-year survival

Univariate Cox proportional regression analysis revealed that various factors such as age, diabetes, the product of calcium and phosphorus, albumin, carotid artery plaque, and IMT were associated with all-cause mortality (Table 3). Similarly, age, DM, intact PTH, albumin, and IMT were significantly related to 5-year cardiovascular death (Table 3). In contrast, %ACI was not related to all-cause (RR 1.01, 95% CI 1.00 to 1.02, $P = 0.08$) and cardiovascular mortality (RR 1.01, 95% CI 1.00 to 1.03, $P = 0.09$). Plasma Hcy was also not associated with all-cause (RR 0.99, 95% CI 0.98 to 1.01, P = NS) and cardiovascular mortality (RR 0.99, 95% CI 0.97 to 1.01, P = NS).

Multivariate regression analysis demonstrated that diabetes mellitus, albumin, and carotid artery IMT became significant independent predictors of all-cause mortality. IMT, intact PTH, and diabetes were also indicators of cardiovascular mortality. Adjusted hazards ratios of all-cause and cardiovascular mortality for an increase of 0.1 mm in IMT were 1.31 (95% CI, 1.07 to 1.59) and 1.41 (95% CI, 1.12 to 1.77), respectively ($P < 0.01$) (Table 3). A 0.1 mm increment of IMT also increased the risk of cardiovascular mortality by 39% (95% CI, 1.11 to 1.75) in patients without a history of cardiovascular accidents ($N = 208$).

When the patients were divided into three tertiles in relationship to IMT, Kaplan-Meier analysis revealed that the all survival rate during 5 years was significantly lower in the third tertile (58%, IMT $\geq$ 0.70 mm, $N = 74$) compared with that in the middle (80%, $0.55 <$ IMT < 0.70, $N = 74$), or in the first tertile (90%, IMT ≤ 0.55 mm, $N = 71$) ($P < 0.01$) (Fig. 2). Similarly, cardiovascular mortality rate was significantly higher in the final tertile (Fig. 2). In nondiabetic patients, significantly higher rates of all-cause and cardiovascular death were also observed in the final tertile compared to that in the first and in the second tertile ($P < 0.01$) (Fig. 3).

DISCUSSION

Recently, increased IMT is reported as an independent predictor of cardiovascular events and mortality in dialysis patients [17, 18]. Benedetto et al [17] first showed that carotid artery IMT was an independent predictor of 30-month mortality in end-stage renal failure patients on hemodialysis or peritoneal dialysis. They demonstrated that a 0.1 mm increment of IMT predicted a 24% higher risk for cardiovascular mortality. Nishizawa et al [18] also recently reported that increased IMT became an independent predictor of 30-month cardiovascular death. In contrast, Blacher et al [19] noticed that carotid arterial stiffness rather than IMT is a superior predictor for cardiovascular mortality in regular hemodialysis patients. They also showed that calcification score at aorta, coronary, femoral and common carotid arteries can be predictable of cardiovascular and all-cause mortality more sensitively than IMT [20]. Thus, whether measurement of carotid artery IMT is superior for predicting mortality remains still controversy in patients with end-stage renal failure. Since these studies followed the subjects for up to 30 months [17,18], we reexamined the impact of carotid artery wall changes on mortality during 60 months. We confirmed that carotid artery IMT became an independent predictor of all-cause and cardiovascular mortality. We also found that expired subjects had an increased carotid artery IMT in nondiabetes mellitus or nonsmok-

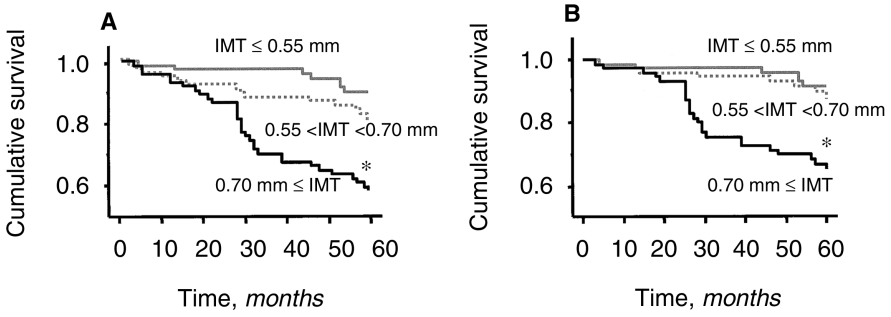

Fig. 2. Survival curves for all-cause (*A*) and cardiovascular mortality (*B*) for 5 years. Patients were divided in relationship to the tertiles of intima media thickness (IMT) (IMT ≤ 0.55 mm, 0.55 < IMT < 0.70 mm, IMT ≥ 0.70 mm). A significantly lower survival rate was found in the final tertile ($P < 0.01$).

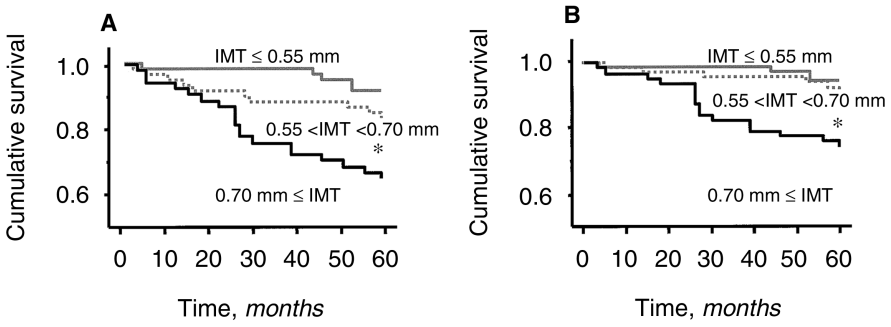

Fig. 3. The 5-year survival rates in nondiabetic subjects. Patients were divided in relationship to the tertiles of intima media thickness (IMT) (IMT ≤ 0.55 mm, 0.55 < IMT < 0.70 mm, IMT ≥ 0.70 mm). Significantly lower all-cause (*A*) and cardiovascular mortality (*B*) rates were found in the first and second tertiles compared with those in the last tertile ($P < 0.01$).

ing patients. In addition, increased IMT was associated with poor prognosis in nondiabetic subjects. These findings convincingly suggested that assessment of carotid artery IMT is useful in predicting for future mortality in uremic persons.

Arterial calcification is known to be another independent predictor for incidental cardiovascular events in general population [21–23]. In the Framingham Heart Study, abdominal aortic calcific deposits are associated with increased risks for congestive heart failure [22], and vascular morbidity and mortality [23]. Calcification of the aortic arch is also related to future coronary heart disease, stroke, and peripheral vascular disease [24]. In hemodialysis patients, the presence and extent of arterial calcifications at large arteries are demonstrated as a predictor of cardiovascular mortality [20]. The product of calcium and phosphate, an important factor associated with calcification of the abdominal aorta [25], is also an independent risk factor for cardiovascular death [26]. In the present study, however, univariate regression analysis failed to show any significant association between aortic wall calcification and mortality. The reasons for this minor contribution of aortic calcific deposit are unknown, but may be partly due to our shorter observation time and analytic methods. In Framingham Heart Study [23], the impact of increased abdominal aortic calcification on cardiovascular death became obvious over 12-year follow-up. Furthermore, heritable factors play a role in the presence and extension of abdominal aortic calcification in general subjects [27]. Interestingly, increased aortic pulse wave velocity (PWV), a marker of aortic stiffening, is shown as an independent predictor of mortality in hemodialysis patients [28, 29]. Insensitivity of PWV in response to decreases in blood pressure is also an independent predictor of mortality in dialysis subjects [30]. Because PWV is associated with the extent of elastic-type arterial calcification [28, 31], comeasurement of aortic PWV will more clarify a possible role of aortic wall calcification for future death in hemodialysis subjects. In addition, recently available higher-resolution axial CT would be expected to provide more reproducible and quantitative estimates of aortic calcific deposits.

Hyperhomocysteinemia is frequently found in dialysis subjects and has demonstrated as a potent indicator of mortality in the previous studies [18, 32, 33]. In this study, however, we did not find any association between plasma total Hcy and cardiovascular and all-cause mortality. The reasons for this minor role of Hcy remain unknown, but may be partly due to well nutritional status in our patients. Median serum albumin was 4.0 g/dL, and only 25 patients (11.4%) had a lower serum albumin below 3.5 g/dL in this study. Serum albumin is the main carrier of circulating Hcy. Blood total Hcy level is strongly related to serum albumin, nutritional status, and dietary protein intake in hemodialysis subjects [34], indicating that well-preserved nutritional status may influence the impact of Hcy on mortality. In addition, our study may not have enough population to demonstrate the effect of Hcy on mortality.

Long-standing inflammation, malnutrition, and oxida-

tive stress are known to be associated with accelerated atherosclerosis in patients with end-stage renal failure [35, 36]. Age, systemic blood pressure, and smoking were correlated independently with carotid artery IMT [33]. However, in this study, only normal aging became a determinant of IMT among traditional risk factors. In contrast, blood albumin, total cholesterol and CRP were significantly correlated with log IMT. We found that low cholesterolemia was an indicator of IMT, confirming a possible role of malnutrition and/or inflammation for accelerated arterial thickening in hemodialysis patients [13].

We found that elevated intact PTH became another independent predictor of cardiovascular mortality in our patients. IMT tended to be higher in the dead group compared with that in the alive group ($P = 0.06$) (Table 1). Intact PTH is reported to be associated with carotid artery IMT in patients with primary and secondary hyperparathyroidism [37, 38]. However, in this study, intact PTH was not related to IMT and %ACI, indicating that elevations in PTH was not associated with arterial thickening and calcification in large-sized vessels. Additional studies will be needed to examine that increased PTH may affect small-sized arterial vascular tone and/or cardiac function via an increase in the intracellular calcium concentration.

In this study, IMT became a significant predictor of overall death, a similar finding with a previous study [19]. In addition, atherogenic parameters did not differ between patients who died of cardiovascular causes and those who did not have fatal cardiovascular events, probably due to older population in the noncardiovascular fatal group (mean age, 63 years vs. 73 years). We confirmed a significant increase in carotid artery IMT in age-matched subjects with cardiovascular death (mean age, 74 years, $N = 14$) compared to those without cardiovascular death ($N = 14$) (0.90 ± 0.13 mm vs. 0.75 ± 0.21 mm, $P < 0.04$).

There are some limitations in this study. First, we did not measure carotid arterial stiffening. Second, we semiquantitatively evaluated vascular calcification only at abdominal aorta, since assessment of coronary artery calcification was inaccurate by CT scan. Recently, electron beam tomography (EBT) is used as a noninvasive method directly to measure coronary calcium content. A high calcium score at coronary arteries on EBT imaging is indicative for myocardial infarction and coronary death in middle-aged general subjects [39]. Thus, EBT measurement will clarify the prognostic values of coronary plaque calcification in dialysis patients. Finally, we could not define abnormal IMT and %ACI in this study, since we did not examine these parameters in age- and gender-matched healthy population. Different imaging protocols and/or races also failed to take referred control values from literature [3–9].

Although it became clear that carotid artery IMT is a good predictor of subsequent mortality in hemodialysis persons, differing imaging protocols were used in the various trials, making comparison of the results unnecessarily confusing in dialysis subjects. For example, we focused mainly on the near wall of common carotid artery, and calculated its mean value, while another study [5] included bulb, internal and external arteries, and used their greatest IMTs for analysis. Furthermore, focal plaque is commonly found in internal carotid artery but seldom in common carotid artery [1]. Thus, further trials will be needed to establish a standardized protocol and consensus to facilitate comparison of results among the many studies using this technique.

CONCLUSION

We showed that increased carotid artery IMT portends a significantly higher risk of all-cause and cardiovascular death in hemodialysis patients. A 0.1 mm increment of carotid artery IMT was associated with 31% and 41% increased risks for all-cause and cardiovascular 5-year mortality, respectively. Recently, clinical trials by calcium antagonists [40] and antibiotics [41] are reported to regress progression of carotid artery IMT in general subjects. Thus, additional studies will be needed to ascertain that slowing incremental value of carotid artery IMT by pharmacologic agents may be a predictor of survival in dialysis subjects.

ACKNOWLEDGMENTS

We thank for Dr. Mitsuyoshi Furuhashi and clinical laboratory stuffs in Maruyama Hospital (Hamamatsu, Japan) for their kind supports in this study.

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