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ORIGINAL ARTICLE

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Impact of high coronary artery calcification score (CACS) on survival in patients on chronic hemodialysis

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Abstract
Background. Electron-beam computed tomography (EBCT) is a noninvasive measure of coronary artery calcification and, therefore, could be a marker of developing cardiovascular disease. Whether the coronary artery calcification score (CACS) is a prognostic marker in chronic dialysis patients is not known.
Methods. In the present study, the mortality rate was observed in relation to the baseline CACS. EBCT was performed in 104 chronic hemodialysis patients (62 men and 42 women) in one dialysis unit. The mean (SD) duration of hemodialysis was 48.7 (62.6) months at the time of EBCT. The mean (SD) age at EBCT was 55.9 (13.6) years, ranging from 23 to 88 years. The duration of follow-up was 43.8 (19.3) months after the EBCT. Cox proportional hazard analysis was performed to examine the impact of CACS on survival after adjusting for age, sex, duration of dialysis, diabetes mellitus, hypertension, serum albumin, and dyslipidemia.
Results. The CACS was distributed from zero to 5896, with a median of 200. During the study period, 24 patients (15 men and 9 women) died, 7 in the low CACS group (<200) and 17 in the high CACS group (≥ 200). The 5-year cumulative survival rate was 84.2% in the low CACS group and 67.9% in the high CACS group. The adjusted relative risk (95% confidence interval) of death was 1.001 (1.000–1.002); $P = 0.0003$, for the absolute value of CACS.
Conclusions. The present study suggested that CACS was an independent predictor of death in patients on chronic hemodialysis. Patients with a high CACS should be carefully monitored and evaluated for reversible prognostic factors such as dyslipidemia and, probably, hyperphosphatemia and a high value for the calcium × phosphate product.

Key words Coronary artery calcification score (CACS) · Hemodialysis · Mortality

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Introduction

Coronary artery disease (CAD) carries an enhanced risk of mortality in hemodialysis patients compared to that in the general population.[1,2] Therefore, the early detection and treatment of CAD could improve the survival rate of chronic hemodialysis patients. However, coronary angiography, which is the gold standard to diagnose CAD, is too invasive to recommend for all dialysis patients. On the other hand, vascular calcification, including coronary artery calcification, is quite common in these patients. A recent study showed that noninvasive tests for CAD, such as electrocardiogram, echocardiography, and dipyridamole thallium 201 scintigraphy, which are used commonly in nondialysis patients, were of limited value in hemodialysis patients because of their low sensitivity.[3]

Electron-beam computed tomography (EBCT) is a noninvasive measure of coronary artery calcification and is a possible marker of coronary artery disease.[4] Whether the coronary artery calcification score (CACS) is a prognostic marker in chronic hemodialysis patients is not known. The present study aimed to examine the prognosis of chronic hemodialysis patients in relation to consecutively obtained CACS in patients in one dialysis unit.

Patients and methods

Patients

All patients who agreed to undergo an EBCT study and who were receiving hemodialysis at Okinawa Chubu Tokushukai Hospital were studied. We invited every hemo-

dialysis patient to have EBCT unless they were unable to hold the breath during the EBCT study. Informed consent was obtained from each patient. A total of 104 patients, 62 men and 42 women, were enrolled in the present study during the period July 1996 to March 2001, and they were followed-up to May 1, 2003. Chronic hemodialysis patients who are resident in Okinawa and who survive for at least 1 month on scheduled dialysis are registered with the Okinawa Dialysis Study (OKIDS) registry. Details of this registry have been reported previously.[5] The dialysis regimen in Okinawa is similar to that used in other parts of Japan.[6] The present study was performed in one of the institutions in which patients were registered with the OKIDS registry. In our registry, more than 83% of the patients underwent dialysis three times per week. The dialysis period per session was 3.0 to 3.5 h in 5.2%, 3.5 to 4.0 h in 57.0%, 4.0 to 5.0 h in 10.0%, and more than 5.0 h in 27.8%. Bicarbonate solution was used as the dialysate at all units. Dialyzer reuse is rare in Japan. The laboratory values were obtained before routine hemodialysis was begun and within 6 months before the EBCT study was begun. Hypertension was defined as systolic blood pressure of 140 mmHg or more and diastolic blood pressure of 90 mmHg or more, or the current use of antihypertensive medication. Dyslipidemia was defined as total cholesterol, 220 mg/dl or more, triglyceride level of 150 mg/dl or more, or high-density lipoprotein (HDL)-cholesterol of less than 40 mg/dl. Causes of death were noted as infection, dialysis withdrawal, cardiovascular, sudden death, cerebrovascular, and "others". Death due to withdrawal occurred in patients who had severe cachexia or malnutrition or who were hemodynamically unstable and thus unable to undergo regular dialysis. Those who were symptomatic and showed a high CACS were examined by echocardiography, cardiac scintigraphy, or cardiac angiography to determine whether ischemic heart disease was present.

Details of the EBCT study have been reported previously.[7] EBCT was performed using an Imatron C 150 XL scanner (Imatron, South San Francisco, CA, USA) at an acquisition time of 100 msec, collimation of 3 mm, and gated to 80% of the eletrocardiographic RR interval. Single-slice breath-hold sections were acquired. Entire heart images were acquired in 28 continuous slices, beginning from the lower edge of the carina. Epicardial artery lesions were manually plainmetered by three experienced radiology technicians with the aid of Imatron software (version 12.43). The number of calcifications, surface area, and average and highest density values were measured in every instance. Coronary artery calcifications (CACs) were defined as plaque in at least three contiguous pixels (area, 1.02 mm^2) with a density value greater than 130 Housfield units, and the degree of CAC was calculated by using the method of Agatston et al.[8]

Statistical analysis

The unpaired *t*-test, Fisher's test, and the χ^2 test were used to compare discrete variables between groups. Survival rates were calculated by the Kaplan-Meier method. Cox proportional hazard analysis was done to examine the impact of the baseline levels of CACS on the mortality rate after adjusting for the confounding variables of age, sex, duration of hemodialysis, diabetes mellitus, hypertension, dyslipidemia, and serum albumin, using an SAS model (SAS Institute, Cary, NC, USA). The observation period was calculated from the time of EBCT to the last follow-up date and expressed per 1000 patient-years. Data values were expressed as means (SD). *P* values of less than 0.05 were considered statistically significant.

Results

The mean (SD) age at the time of EBCT was 55.9 (13.6) years, ranging from 23 to 88 years, and the duration of hemodialysis was 48.7 (62.6) months, ranging from 1 to 264 months. The mean (SD) duration of follow-up after the EBCT was 43.8 (19.3), ranging from 1 to 82 months. The baseline CACS was distributed from zero to 5896, and the median CACS was 200. The clinical background of the patients was summarized according to the baseline CACS, and groups below the median and above the median were compared (Table 1). The patients were classified into two groups according to the CACS, as low (<200), in 54 patients, and high (≧200), in 50 patients. Patients in the high CACS group were significantly older, had a longer duration of hemodialysis, and had a higher prevalence of dyslipidemia than those in the low CACS group. Mean (SD) levels of serum albumin and total cholesterol in the low CACS group were 3.7 (0.4) g/dl and 145.9 (36.5) mg/dl, and these levels were comparable to those in the high CACS group, at 3.6 (0.4) g/dl and 155.3 (37.0) mg/dl. Triglyceride levels were significantly different ($P < 0.01$) between the low CACS and the high CACS groups, at 122.0 (67.0) mg/dl and 168.8 (86.2) mg/dl, respectively.

During the study period, 24 patients died. The death rate was 63.2 per 1000 patient-years (high CACS group, 98.2 per 1000 patient-years; low CACS group, 33.9 per 1000 patient-years). Among the 104 patients studied, 19 patients (18.3%) had no evidence of CAC, and their baseline CACS was zero. None of these patients died of cardiovascular disease. In the low CACS group, the survival rate was 96.3% at 12 months, 94.4% at 24 months, 90.3% at 36 months, and 84.2% at 60 months, whereas that of the high CACS group was 92.0% at 12 months, 82.0% at 24 months, 73.5% at 36 months, and 67.9% at 60 months. The survival curves for the low CACS and high CACS patients were significantly different ($P = 0.015$ by log-rank) (Fig. 1). Cardiovascular events both cardiac and cerebrovascular, and infection were frequent in the high CACS group (Table 2). On multivariate analysis, the adjusted relative risk (95% confidence interval) of death was 1.001 (1.000–1.002), $P = 0.0003$, for the absolute value of CACS, but for the groups according to CACS category, there was no significant difference in relative risk (Table 3).

Table 1. Clinical background of the patients according to the baseline coronary artery calcification score (CACS)

	Total (n = 104)	CACS < 200 (n = 54)	CACS ≥ 200 (n = 50)
Men (%)	62 (59.6)	31 (57)	31 (62)
Age, years	55.9 (13.6)	52.3 (13.2)	59.7 (13.1)*
HD duration, months	48.7 (62.6)	30.3 (43.7)	68.6 (73.4)*
Body mass index, kg/m^2	22.8 (3.6)	22.5 (3.8)	23.0 (3.4)
Diabetes (%)	40 (38)	17 (31.5)	23 (46)
SBP, mmHg	154.2 (18.3)	152.8 (17.2)	155.6 (19.5)
DBP, mmHg	81.2 (12.2)	82.2 (11.5)	80.1 (13.0)
Hypertension (%)	88 (84.6)	46 (85.2)	42 (84)
Dyslipidemia (%)	47 (45.2)	17 (31.5)	30 (60)*
PTH, pg/ml	205 (303)	158 (153)	257 (405)
Serum Ca, mg/dl	9.3 (0.85)	9.23 (0.89)	9.40 (0.80)
Serum Pi, mg/dl	6.0 (1.45)	5.93 (1.43)	6.15 (1.49)
Ca, Pi product	56.2 (14.7)	55.0 (15.6)	57.6 (13.8)
Use of $CaCO_3$	88.0%	86.8%	89.4%
Vitamin D use	51.9%	55.6%	48.0%
Vitamin D pulse	9.6%	7.4%	12.0%
Smoker	19.2%	24.1%	14.0%

* $P < 0.01$ (CACS < 200 vs CACS ≥ 200)
Data values are means (SD)
HD, hemodialysis; SBP, systolic blood pressure; DBP, diastolic blood pressure. Dyslipidemia: total cholesterol ≥220 mg/dl, triglyceride ≥150 mg/dl, or high-density lipoprotein (HDL)-cholesterol <40 mg/dl; hypertension: SBP ≥140 mmHg, DBP ≥90 mmHg, or on antihypertensive medication

Table 2. Number of patients with ischemic heart disease, number of deaths, death rates, and causes of death according to the baseline coronary artery calcification score (CACS)

	CACS < 200 (n = 54)	CACS ≥ 200 (n = 50)
Ischemic heart disease	1 (4.3%)	20 (57.1%)
Number of deaths	7	17
Death rate, %	13.0%	34.0%
Causes of death		
Cardiac	1	5
Stroke	3	2
Infection	2	6
Other	1	4

Evidence of ischemic heart disease was examined in 58 patients (55.8% of the total, 23 for CACS <200 and 35 for CACS ≥200). The study period was from July 1996 to May 2003

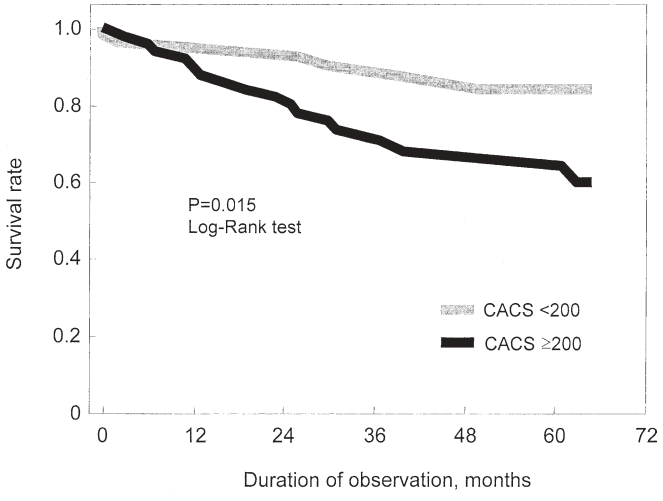

Fig. 1. Survival curves, calculated by the Kaplan Meier method, based on the baseline coronary artery calcification score (*CACS*). The study period was from July 1996 to May 2003

Discussion

Cardiovascular disease remains a major cause of death in chronic dialysis patients. In particular, the prognosis after acute myocardial infarction is very poor.[1,2] In the present study, the overall death rate in the high CACS group was higher than that in the low CACS group. To perform EBCT, one may need patients who can hold their breath for a while. Obviously, this process results in selection bias.

The present study may support the notion that coronary EBCT predicts future atherosclerotic cardiovascular events in asymptomatic subjects.[9] Five patients died of cardiac disease in the high CACS group, whereas there were one death due to cardiac disease in the low CACS group. Poor phosphorus control is associated with an increased mortality risk, particularly for cardiac death.[10] Elevations in serum phosphorus and the calcium-phosphorus product lead to metastatic calcification, including that of cardiovascular tissue.[10] However, arterial calcification in uremic patients can be different from that in the general population. In the general population, intimal wall calcification occurs frequently in atherosclerosis,[11] whereas, in contrast, medial wall calcification is more common in chronic dialysis patients.[11] A high CACS obtained by EBCT may suggest the existence of arterial calcification of either the intima, the media, or both.

Mechanisms of vascular calcification could be multifactorial. However, phosphorus control is the most important

Table 3. Cox proportional hazard analyses, both univariate and multivariate, were done to evaluate factors associated with patients' survival

Variables	Univariate		Multivariate	
	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Absolute value of CACS	1.000 (1.000–1.001)	<0.0001	1.001 (1.000–1.002)	0.0003
CACS category (<200, ≥200)	2.851 (1.182–6.877)	0.0197	2.687 (0.873–8.267)	0.0847

Multivariate analyses were done with other variables i.e., age, sex, duration of dialysis, diabetes mellitus, serum albumin, hypertension, and dyslipidemia. The study period was from July 1996 to May 2003
RR, relative risk; CI, confidence interval

means of preventing secondary hyperparathyroidism,[12] and may be helpful in preventing coronary artery calcification. Other than the secondary hyperparathyroidism, in a previous study, we showed the significant impact of dyslipidemia on CACS progression in chronic hemodialysis patients.[7] Uremic lipoprotein abnormalities may be an important factor in accelerated atherosclerosis in dialysis patients.[13] Reports have shown that calcium-phosphorus homeostasis and hyperparathyroidism affect uremic dyslipidemia by suppressing lipoprotein-regulating enzymes.[14] Recently, the role of malnutrition and chronic inflammation in atherosclerosis has been increasingly recognized.[15] Actually, we confirmed that high C-reactive protein (CRP)[16] and hypoalbuminemia[17] were significant predictors of mortality in chronic hemodialysis patients. Unfortunately, CRP levels were not available in this study.

There are several limitations of the present study. First, we recognize that our sample size was small and from a single center, and that the observation period was short. The overall mortality rate was not so different from that of the whole Okinawa area. However, the mortality rate was quite different between the low and high CACS groups (Table 2). Actually, we found no deaths due to cardiovascular disease in those patients who had no evidence of CAC, in whom the baseline CACS was zero. The gold standard for the diagnosis of coronary artery disease is the coronary angiogram, but this may be too invasive for patients on chronic hemodialysis. Therefore, firstly, we recommend that only symptomatic patients who show a high CACS should have a coronary angiogram for further examination. Second, it is possible that dialysis modalities may affect the prevalence of high CACS and cardiac valve calcification.[18] In Japan, most of our end-stage renal disease patients are maintained by hemodialysis and the number of renal transplantations is quite small,[19] as in the present study. Third, whether the high CACS in our cohort was directly related to mortality was not certain. A high CACS may suggest the existence of severe atherosclerosis and calcification in other organs. Pulmonary calcification may result in right ventricular dysfunction and respiratory distress.[20] Further studies of the association between cardiovascular disease and high CACS are needed. Fourth, we showed previously that the mean increase in CACS was as high as 220 during a mean follow-up of 17 months in patients on hemodialysis.[7] Whether the increase in CACS was proportional to the baseline CACS remained to be confirmed. Finally, although "zero" CACS is normal, most of the patients in the present study had some evidence of CAC. Nineteen of the 104 patients (18.3%) showed "zero" CACS in our present study. Their duration of dialysis was significantly shorter (28.2 months) than that in the patients with a CACS of more than zero (53.9 months). Otherwise, there were no differences in other parameters between these groups. The cutoff value of CACS is not certain yet. In this study, we used a CACS of 200, as it was the median value and the numbers of subjects were almost equal. In each dialysis patients, every effort should be made to reduce CACS. Sevelamer, which was shown to attenuate the progression of CACS,[21] was not available in Japan at the time of writing this article.

In summary, the present study showed that the CACS was an independent predictor of overall mortality in chronic hemodialysis patients. Thus, patients with a high CACS should be carefully monitored and evaluated for reversible prognostic factors such as dyslipidemia and, probably, hyperphosphatemia and a high value for the calcium × phosphate product.

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References

1. Herzog CA, Ma JZ, Collins AJ. Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. N Engl J Med 1998; 339:799–805.
2. Iseki K, Fukiyama K, for the Okinawa Dialysis Study Group. Long-term prognosis and incidence of acute myocardial infarction in patients on chronic hemodialysis. Am J Kidney Dis 2000; 36:820–5.
3. Schmidt A, Stefenelli T, Schuster E, Mayer G. Informational contribution of noninvasive screening tests for coronary artery disease in patients on chronic renal replacement therapy. Am J Kidney Dis 2001; 37:56–63.
4. Simons DB, Schwartz RS, Edwards WD, Sheedy PF, Breen JF, Rumberger JA. Noninvasive definition of anatomic coronary artery disease by ultrafast computed tomographic scanning. J Am Coll Cardiol 1992; 20:1118–26.

5. Iseki K, Kawazoe N, Osawa A, Fukiyama K. Survival analysis of dialysis patients in Okinawa, Japan (1971–1990). Kidney Int 1993; 43:404–9.
6. Hidai H. Need for an incentive-based reimbursement policy toward quality care for dialysis patient's management. Kidney Int 2000; 58:363–73.
7. Tamashiro M, Iseki K, Sunagawa O, Inoue T, Higa S, Afuso H, et al. Significant association between the progression of coronary artery calcification and dyslipidemia in patients on chronic hemodialysis. Am J Kidney Dis 2001; 38:64–9.
8. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultra fast computed tomography. J Am Coll Cardiol 1990; 15:827–32.
9. Arad Y, Spadaro LA, Goodman K, Lledo-Perez A, Sherman S, Lerner G, et al. Predictive value of electron beam computed tomography of the coronary arteries: 19-months follow-up of 1173 asymptomatic subjects. Circulation 1996; 93:1951–3.
10. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium × phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis 1998; 31:607–17.
11. Schwarz U, Buzello M, Ritz E, Stein G, Raabe G, Wiest G, et al. Morphology of coronary atherosclerotic lesions in patients with end-stage renal failure. Nephrol Dial Transplant 2000; 15:218–23.
12. Hsu CH. Are we mismanaging calcium and phosphate metabolism in renal failure? Am J Kidney Dis 1997; 29:641–9.
13. Shoji T, Nishizawa Y, Kawagishi T, Tanaka M, Kawasaki K, Tabata T, et al. Atherogenic lipoprotein changes in the absence of hyperlipidemia in patients with chronic renal failure treated by hemodialysis. Atherosclerosis 1997; 131:229–36.
14. Shoji T, Nishizawa Y, Nishitani H, Yamakawa M, Morii H. Impaired metabolism of high density lipoprotein in uremic patients. Kidney Int 1992; 41:1653–61.
15. Bergstrom J, Lindholm B. Malnutrition, cardiac disease, and mortality: an integrated point of view. Am J Kidney Dis 1998; 32:834–41.
16. Iseki K, Tozawa M, Yoshi S, Fukiyama K. Serum C-reactive protein (CRP) and risk of death in chronic dialysis patients. Nephrol Dial Transplant 1999; 14:1956–60.
17. Iseki K, Miyasato F, Tokuyama K, Nishime K, Uehara H, Shiohira Y, et al. Low diastolic blood pressure, hypoalbuminemia, and risk of death in a cohort of chronic hemodialysis patients. Kidney Int 1997; 51:1212–17.
18. Wang AYM, Woo J, Wang M, Sea MMM, Ip R, Li PKT, et al. Association of inflammation and malnutrition with cardiac valve calcification in continuous ambulatory peritoneal dialysis patients. J Am Soc Nephrol 2001; 12:1927–36.
19. Iseki K, Tozawa M, Iseki C, Takishita S, Ogawa Y. Demographic trends in the Okinawa Dialysis Study (OKIDS) registry (1971–2000). Kidney Int 2002; 61:668–75.
20. Akmal M, Barndt RR, Ansari AN, Mohler JG, Massry SG. Excess PTH in CRF induces pulmonary calcification, pulmonary hypertension and right ventricular hypertrophy. Kidney Int 1995; 47:158–63.
21. Chertow GM, Burke SK, Raggi P, for the Treat to Goal Working Group. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int 2002; 62: 245–52.