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The association between mortality and abdominal aortic calcification and relation between its progression and serum calcium concentration in chronic hemodialysis patients

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Abstract

Background: The composite summary score (range, 0–24) of abdominal aortic calcification (AAC) devised by Kauppila et al is a simple method of assessing AAC severity. However, few studies have been conducted to determine an optimal AAC cutoff score for the prediction of mortality or to investigate the relation between mineral metabolism and AAC progression using the scoring system.

Methods: The medical records of 112 patients on hemodialysis who had undergone simple lateral lumbar radiography every 6 months from August 2009 were reviewed. Patients were followed until November 2012, and the relationship between the degree of AAC at baseline and mortality was evaluated. In addition, the relationship between the progression of AAC and serum concentrations of calcium and phosphate was evaluated in the 75 patients who were successfully followed until November 2012.

Results: The mean AAC score at baseline was 5.5 ± 4.8, and the cutoff calcification score for the prediction of mortality was 7.75 (sensitivity=61%, specificity=81%). Patients were allocated to Group A (baseline total calcification score ≤ 8.0, $n=85$) or Group B (baseline total calcification score > 8.0, $n=27$), and multivariate analysis showed that Group B was an independent risk factor of all-cause mortality and cardiovascular events. Of the 75 patients successfully followed, 51 showed AAC progression (Group 1) and 24 showed no change or improvement (Group 2). Group 1 was found to have significantly higher mean serum corrected calcium levels during the 2nd year and 3rd year of follow-up than Group 2. Furthermore, repeated-measures analysis of variance showed higher monthly corrected calcium concentrations ($P=0.099$) and mean corrected calcium levels during the 1st year, 2nd year, and 3rd year of follow-up ($P=0.062$) in Group 1, but without statistical significance. The cutoff values of mean corrected calcium of the 2nd year and 3rd year for the prediction of AAC progression during follow-up years were 8.96 mg/dL and 9.45 mg/dL, respectively. Serum phosphate levels and corrected calcium × phosphate values were similar in Groups 1 and 2.

Conclusion: Patients with an AAC score of > 8 at baseline seem to be at higher risk of mortality during follow-up. Of the serum variables examined, such as corrected calcium, phosphate, and corrected calcium × phosphate, corrected calcium was

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found to be marginally associated with AAC progression. However, a larger-scale prospective study is required to confirm our findings.

Introduction

Arterial calcification, including aortic calcification, is highly prevalent in end-stage renal disease (ESRD) patients, and the extent of arterial calcification has been shown to be predictive of subsequent cardiovascular disease (CVD) and mortality in these patients [1–5].

Animal experiments suggest that disturbances in mineral metabolism play a major role in the initiation and progression of medial wall calcification [6,7]. Human studies have shown that, in addition to traditional risk factors, several clinical factors—such as hypercalcemia, hyperphosphatemia, elevated calcium (Ca) × phosphate (P) product, hyperparathyroidism, chronic inflammation, Ca overload (induced by the use of Ca-based P binders and vitamin D analogues), higher dialysate Ca concentration, adynamic bone disease, and old age—are associated with the progression of arterial calcification in ESRD patients on dialysis [1,8–11].

Hyperphosphatemia is being increasingly recognized as a major stimulus of vascular calcification [12]; however, studies have produced inconsistent results about associations between hyperphosphatemia and the extent and progression of vascular calcification [2]. Furthermore, in one report, it was suggested that arterial calcification may be a bystander, rather than the cause of changes in cardiac structure and function [13,14]. In addition, patients without evidence of arterial calcification at presentation are unlikely to develop arterial calcification *de novo*, at least in the short term [15,16].

The composite summary score (range 0–24) of abdominal aortic calcification (AAC) devised by Kauppila et al [17] provides a simple, low-cost means of assessing subclinical vascular disease, and has been shown to be highly predictive of subsequent cardiovascular morbidity and mortality in the general population and hemodialysis (HD) patients [4,5,18]. However, few studies have sought to determine optimal AAC score cutoff values for the prediction of mortality or the relation between mineral metabolism and AAC progression using the scoring system.

Accordingly, the aims of this study were to evaluate the relationship between baseline AAC score and mortality and to identify an optimum AAC cutoff score for the prediction of mortality in ESRD patients on HD. In addition, the serum levels of Ca, P, and Ca × P products were monitored during follow-up, and their relationships with AAC progression were analyzed.

Methods

Participants

This retrospective study was performed on ESRD patients on HD who had been followed up at the outpatient HD clinic of Inha University Hospital (Incheon, Republic of Korea). A total of 112 ESRD patients on HD at study commencement in September 2009 were included. Patients were followed up until death, kidney transplantation, transfer to other hospital, or until November 2011. Demographic, clinical, and biochemical data were collected from medical records. Comorbidities were assessed using modified Charlson comorbidity index (CCI) score [19,20].

HD was performed for 4 hours per session, three times per week, using a polysulfone dialyzer (F6HPS; Fresenius Medical Care, Bad Homburg, Germany) and a Fresenius Medical Care 5008 machine. Dialyzers were not reused. Dialysate concentrations of sodium, potassium, bicarbonate and calcium were 138 mEq/L, 2.5 mEq/L, 30 mEq/L, and 3.5 mEq/L, respectively, for nondiabetics, and 140 mEq/L, 2.0 mEq/L, 25 mEq/L, and 2.5 mEq/L, respectively, for diabetics. Blood flow rates were between 250 mL/minute and 300 mL/minute, depending on arteriovenous fistula status. The dialysate flow rate was 500 mL/min and Kt/Vurea was calculated using the Daugirdas second-generation equation [21].

The study protocol was approved by the Institutional Review Board of Inha University Hospital and complied with the Declaration of Helsinki. Written consent forms were not required because of the retrospective nature of the study. All data used were obtained routinely for patient management purposes.

Evaluation of abdominal aortic calcification

Between September 2009 and November 2011, radiographs of the left lumbar spine were acquired in the standing position every 6 months. The severity of AAC was graded using the scoring system devised by Kauppila et al [17].

Calcific deposits in the abdominal aorta adjacent to each lumbar vertebra from the first lumbar vertebrae to the fourth lumbar vertebrae were assessed separately at baseline for the anterior and posterior aortic walls. Lesions were graded as follows: 0, no aortic calcific deposits; 1, small scattered calcific deposits occupying less than one-third of the longitudinal wall of the aorta; 2, calcific deposits occupying one-third or more, but less than two-thirds of the longitudinal wall of the aorta; and 3, calcific deposits occupying two-thirds or more of the longitudinal wall of the aorta. Individual level-specific severity scores were summarized to yield anterior wall (ScAnt; range 0–12), posterior wall (ScPost; range 0–12), and sum (ScSum; range 0–24) AAC scores.

AAC scoring was performed using radiographs taken at baseline and after 3 years by three physicians (HYK, OHL, and MJK) who were completely unaware of the patient data. Prior to scoring, the three assessors were trained by a radiologist on how to perform the scoring until similar scores were achieved. When the scores of the three assessors differed, mean scores were used.

To decide whether AAC had progressed over the 3-year study period, the three assessors compared baseline and final X radiographs. Progression of AAC was defined as the occurrence of new calcifications or as enlargements of the calcified area present at baseline. Patients were assigned to Group 1 (exhibit progression; $n=51$) or Group 2 (showed no change or an improvement; $n=24$) based on the assessors' opinions.

When opinions differed, patients were allocated according to the opinions of two agreeing assessors. The percentage of agreement for progression by three assessors was 84.0%, and the κ value was 0.749.

Determination of coronary arterial calcification scores

The following equation developed by Huybrechts et al [22], which is based on electron-beam tomography findings, was used to determine coronary artery calcification scores (eCoronary score):

$$\begin{aligned}\text{Log}_e(\text{eCoronary score}) &= \text{Age} \times 0.02 + \text{ESRD duration} \\ &\quad (>36\ \text{months} = 1;\ \leq 36\ \text{months} = -1) \times 0.35 \\ &\quad + \text{corrected Ca} \times 1.42 + \text{P} \times 0.39 \\ &\quad + \text{total cholesterol} \times (-0.16) \\ &\quad + \text{high density lipoprotein (HDL) cholesterol} \times (-0.54) \\ &\quad + \text{CVD history}\ (1 = \text{no},\ -1 = \text{yes}) \times (-0.70) \\ &\quad + \text{CVD history}\ (1 = \text{no},\ -1 = \text{yes}) \times \text{age} \times 0.01\end{aligned}$$

To use this equation, corrected Ca, P, total cholesterol, and HDL cholesterol concentrations were converted into SI units.

Biochemical assays

Routine blood tests were performed monthly. Triglyceride, HDL cholesterol, low density lipoprotein (LDL) cholesterol, C-reactive protein (CRP), and intact parathyroid hormone (iPTH) were measured every 3 months. Corrected Ca (cCa) levels were calculated using the following formula [23]:

$$\text{cCa} = \text{Ca} + 0.8 \times (4 - \text{serum albumin}).$$

Monthly cCa, P, and cCa $\times$ P product values during follow-up period were subjected to analysis.

Statistical analysis

Results are presented as mean $\pm$ standard deviation (SD) or as medians and ranges. Differences between group means and median values were evaluated using the unpaired Student *t* test and the Mann–Whitney *U* test. In case of continuous variables (e.g., Ca, P, iPTH) measured repeatedly during the follow-up, differences between the groups were analyzed by repeated-measures analysis of variance. Group categorical data were compared using the Chi-square test. Receiver operating characteristic (ROC) curve analysis was used to define the best baseline AAC score cutoff value for mortality based on considerations of sensitivity and specificity—that is, as the value that maximized the sum of sensitivity and specificity.

Patients were divided into Group A (baseline AAC score $\leq$ cutoff value; $n=85$) or Group B (baseline AAC score $>$ cutoff value; $n=27$). Overall patient survival was estimated using the Kaplan–Meier method, and outcomes were compared using the log rank test. The data of patients who underwent kidney transplantation or were transferred to other hospitals were censored for patient survival analysis. The primary outcome was all-cause mortality, and the secondary outcome was CVD events (fatal and nonfatal). CVD events were defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, therapeutic coronary procedure (coronary artery bypass graft, percutaneous transluminal coronary angioplasty, and/or stenting), therapeutic carotid procedure (endarterectomy and/or stenting), vascular intervention (revascularization, percutaneous transluminal angioplasty, and/or stenting), or amputation. Patients who stopped receiving HD at our hospital due to kidney transplantation or moved to another hospital were not followed to determine primary or secondary outcomes, which were analyzed using Cox's multivariate proportional hazard models that included all significant variables identified by univariate analysis.

Patients who completed the study period were allocated based on AAC progression to Group 1 or Group 2 as described above. These two groups were compared with respect to baseline characteristics, serum Ca, P, and cCa $\times$ P product levels during the follow-up. A p value of <0.05 was considered significant.

Results

Abdominal aortic calcification at baseline and mortality

Table 1 lists the baseline characteristics of the 112 participants. The mean overall patient age was 59 ± 12 years, and the male/female ratio was 1:1.3. Fifty-three patients (47.3%) were diabetics. Previous mean durations of ESRD and HD were 6.0 ± 4.0 years and 4.4 ± 3.6 years, respectively. The mean age-adjusted CCI (aCCI) score at baseline was 3.5 ± 1.2, the mean BMI was 22.4 ± 3.3 kg/m^2, and the mean eCoronary score was 138.0 ± 167.1 (median value 104.3). Mean hemoglobin, blood urea nitrogen, serum creatinine, albumin, total cholesterol, triglyceride, LDL cholesterol, HDL cholesterol, lipoprotein (a), Ca, cCa, P, cCa $\times$ P, and iPTH concentrations were 10.0 ± 1.2 g/dL, 69.0 ± 18.3 mg/dL, 10.6 ± 2.7 mg/dL, 3.7 ± 0.4 g/dL, 149 ± 33 mg/dL, 130 ± 86 mg/dL, 86 ± 25 mg/dL, 39 ± 12 mg/dL, 28.1 ± 25.3 mg/dL, 9.2 ± 0.9 mg/dL, 9.4 ± 0.9 mg/dL, 5.1 ± 1.7 mg/dL, 48.1 ± 16.2 mg^2/dL^2, and 141.6 ± 187.5 pg/mL, respectively. The mean Kt/Vurea was 1.4 ± 0.2, the mean ScSum AAC score was

Table 1. Baseline patient characteristics

Characteristic	Value
n	112
Sex (M/F)	1:1.3
DM (%)	53 (47.3)
Age (y)	59 ± 12
HD duration (y)	4.4 ± 3.6
ESRD duration (y)	6.0 ± 4.0
aCCI score	3.5 ± 1.2
BMI (kg/m^2)	22.4 ± 3.3
AAC score (25th, 50th, 75th percentile)	5.5 ± 4.8 (1.5, 4.5, 8.0)
eCoronary score (median)	138.0 ± 167.1 (104.3)
BUN (mg/dL)	69.0 ± 18.3
Creatinine (mg/dL)	10.6 ± 2.7
Albumin (g/dL)	3.7 ± 0.4
Hb (g/dL)	10.0 ± 1.2
Total cholesterol (mg/dL)	149 ± 33
Triglyceride (mg/dL)	130 ± 86
LDL cholesterol (mg/dL)	86 ± 25
Ca (mg/dL)	9.2 ± 0.9
P (mg/dL)	5.1 ± 1.7
cCa (mg/dL)	9.4 ± 0.9
cCa $\times$ P (mg^2/dL^2)	48.1 ± 16.2
iPTH (pg/mL)	141.6 ± 187.5
Lipoprotein (a) (mg/dL) (median)	28.1 ± 25.3 (17.9)
CRP (mg/dL) (median)	0.46 ± 0.97 (0.14)
Kt/Vurea	1.4 ± 0.2

AAC, abdominal aortic calcification; aCCI, age-adjusted Charlson comorbidity index; BMI, body mass index; BUN, blood urea nitrogen; Ca, calcium; cCa, corrected calcium; CRP, C-reactive protein; DM, diabetes mellitus; eCoronary score, estimated coronary calcification score; ESRD, end-stage renal disease; Hb, hemoglobin; HD, hemodialysis; iPTH, intact parathyroid hormone; LDL, low density lipoprotein; P, phosphate.

5.5 ± 4.8, and the 25th percentile, 50th percentile, and 75th percentile values of ScSum AAC score were 1.5, 4.5 and 8.0, respectively.

The mean follow-up duration was 32.8 ± 12.2 months (range 3–46 months). During the follow-up period, 18 (16.1%) patients died (5 of cardiovascular causes). Twenty-one patients experienced nonfatal CVD events. Sixteen patients were transferred to other hospitals. Three patients underwent kidney transplantation, and two patients were lost during follow-up. The 3-year survival rate was 84.0%.

The ROC curve analysis of baseline AAC score, with respect to mortality, revealed an area under the ROC curve of 0.681 [95% confidence interval (CI), 0.517–0.845; $P=0.015$]. The optimal cutoff value of ScSum AAC score was 7.75 (sensitivity = 61%, specificity = 81%; Fig. 1). When an AAC score 5 was used as a cutoff value, the area under the ROC curve was 0.374 ($P=0.092$). Patients were allocated to one of two groups using a cutoff value of 8; Group A (baseline ScSum AAC score ≤ 8.0, $n=85$) or Group B (baseline ScSum AAC score > 8.0, $n=27$). Age, ESRD duration, HD duration, proportion of patients with diabetes, aCCI score, eCoronary score, cCa, CRP, LDL cholesterol, and iPTH concentrations were all significantly higher in Group B (Table 2).

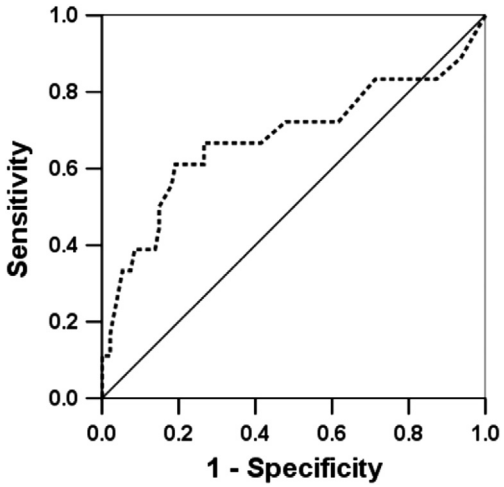

Figure 1. Receiver operating characteristic (ROC) curve analysis of baseline abdominal aortic calcification (AAC) score for the mortality. Area under the ROC curve is 0.681 (95% confidence interval, 0.517–0.845, $P=0.015$). The cutoff value of AAC score is 7.75 (sensitivity = 61%, specificity = 81%).

Kaplan–Meier analysis revealed that all-cause mortality was significantly higher in Group B (Fig. 2A; $P=0.001$). Group B also had a significantly higher proportion of fatal and nonfatal CVD events than Group A (Fig. 2B; $P=0.037$). According to multivariate analysis, adjusted for aCCI score, ESRD and HD durations, eCoronary score, CRP, cCa, LDL cholesterol, and iPTH, Group B was an independent risk factor of all-cause mortality [hazard ratio (HR), 4.205; 95% CI, 1.658–10.669] (Table 3). Furthermore, Group B (HR, 1.801; 95% CI 1.281–2.531), eCoronary score (HR, 1.002; 95% CI, 1.001–1.004), and LDL cholesterol (HR, 1.018; 95% CI, 0.999–1.037) were found to be independent risk factors of fatal and nonfatal CVD events.

Progression of abdominal aortic calcification

Of the 112 patients, 75 (67.0%) completed the follow-up X-ray for 3 years and 37 did not. The causes of incomplete follow-up were as follows: death (18 patients), kidney transplantation (3 patients), transfer to other hospitals (16 patients), follow-up loss (2 patients), and failure to undergo a follow-up X-ray at 3 years (1 patient). No differences in baseline clinical and laboratory characteristics were evident between the patients who did and did not complete follow-up, with the exception of age (56 ± 11 vs. 66 ± 12 years, $P < 0.001$). Fifty-one of the 75 patients (68.0%) who completed

Table 2. Comparison of characteristics between two groups according to AAC score

	Group A AAC score ≤ 8 ($n=85$)	Group B AAC score > 8 ($n=27$)	*P*
Age (y)	57 ± 13	66 ± 9	0.020
Male (%)	33 (38.8)	15 (55.6)	0.126
DM (%)	33 (38.8)	20 (74.1)	0.001
HD duration (y)	3.9 ± 3.4	6.0 ± 4.1	0.007
ESRD duration (y)	5.4 ± 3.9	7.6 ± 4.1	0.013
BMI (kg/m^2)	22.4 ± 3.4	22.5 ± 3.0	0.857
aCCI score (median)	3.4 ± 2.4 (2.5)	12.5 ± 3.3 (11.5)	<0.001
eCoronary score (median)	111.8 ± 1.2 (95.1)	220.5 ± 305.7 (143.2)	0.001
BUN (mg/dL)	70.2 ± 18.4	65.3 ± 17.8	0.229
Creatinine (mg/dL)	10.8 ± 2.8	10.2 ± 2.4	0.312
Kt/Vurea	1.4 ± 0.2	1.4 ± 0.2	0.542
Albumin (g/dL)	3.8 ± 0.4	3.7 ± 0.4	0.253
Hb (g/dL)	10.0 ± 1.3	10.0 ± 1.1	0.791
CRP (mg/dL)	0.36 ± 0.59	0.75 ± 1.65	0.058
cCa (mg/dL)	9.3 ± 0.9	9.7 ± 0.8	0.046
P (mg/dL)	5.3 ± 1.7	4.7 ± 1.5	0.139
cCa × P (mg^2/dL^2)	48.9 ± 16.2	45.8 ± 16.4	0.399
iPTH (pg/mL) (median)	165.8 ± 207.1 (82.4)	65.6 ± 60.0 (43.6)	0.001
Total cholesterol (mg/dL)	150 ± 32	144 ± 37	0.414
Triglyceride (mg/dL)	132 ± 92	125 ± 67	0.704
LDL cholesterol (mg/dL)	84 ± 25	93 ± 23	0.070
HDL cholesterol (mg/dL)	39 ± 12	38 ± 13	0.698
Lipoprotein (a)	26.2 ± 21.1	34.3 ± 35.4	0.268

aCCI, aged-adjusted Charlson comorbidity index; BMI, body mass index; BUN, blood urea nitrogen; cCa, corrected calcium; CRP, C-reactive protein; DM, diabetes mellitus; ESRD, end-stage renal disease; Hb, hemoglobin; HD, hemodialysis; HDL, high density lipoprotein; iPTH, intact parathyroid hormone; LDL, low density lipoprotein; P, phosphate.

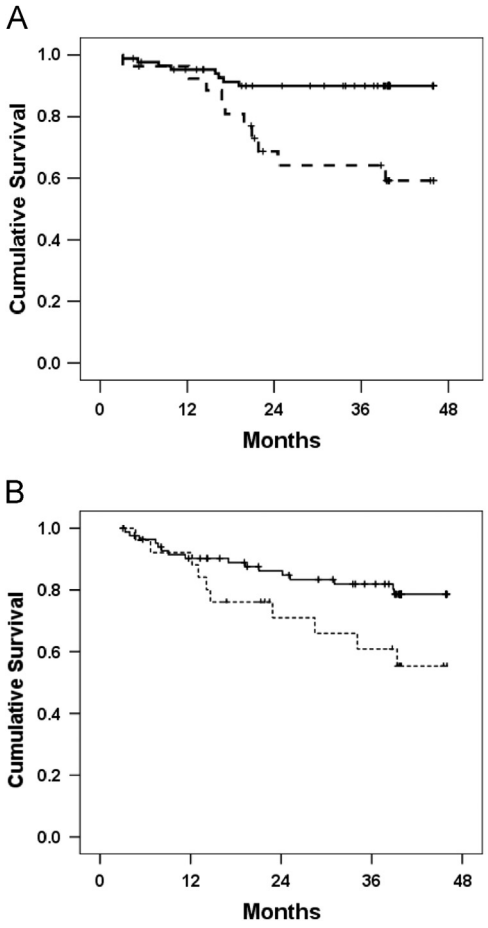

Figure 2. Kaplan–Meier curves for (A) all-cause mortality and (B) fatal and nonfatal events. The linear line denotes patients with baseline abdominal aortic calcification (AAC) score ≤ 8 and the broken line denotes patients with baseline AAC score > 8.

Table 3. Risk factors for all-cause mortality and fatal and nonfatal cardiovascular events

	HR	95% CI		*P*
		Lower	Upper	
All-cause mortality*				
AAC score > 8.0†	4.205	1.658	10.669	0.002
Fatal and nonfatal cardiovascular events‡				
AAC score > 8.0†	1.801	1.281	2.531	0.001
eCoronary score	1.002	1.001	1.004	0.007
LDL cholesterol	1.018	0.999	1.037	0.057

* Adjusted for duration of ESRD and HD, aCCI, eCoronary score, CRP, cCalcium, iPTH, and LDL cholesterol.
† The reference is patients with AAC score ≤ 8.0.
‡ Adjusted for duration of ESRD and HD, aCCI, CRP, cCalcium, and iPTH.
Results shown as HR and 95% CI from Cox proportional hazard models. AAC, abdominal aortic calcification; aCCI, age-adjusted Charlson comorbidity index; cCalcium, corrected calcium; CI, confidence interval; CRP, C-reactive protein; eCoronary score, estimated coronary calcification score; ESRD, end-stage renal disease; HD, hemodialysis; HR, hazard ratio; iPTH, intact parathyroid hormone; LDL, low density lipoprotein.

follow-up showed progression of ScSum AAC scores (Group 1) and 24 showed no change or improvement (Group 2). Age, sex ratio, proportions with diabetes, and durations of ESRD and HD were not different in these two groups. Furthermore, no intergroup differences were observed in Hb, total cholesterol, LDL cholesterol, albumin, P, cCa × P, and iPTH during follow-up. cCa concentrations remained constant from baseline to Month 14 (Fig. 3). However, from 15 months, cCa concentrations were significantly higher in Group 1 and remained so until the end of the follow-up period. Mean cCa concentrations were similar during the 1st year in Groups 1 and 2. During the 2nd year and 3rd year, Group 1 had significantly higher mean cCa concentrations (Table 4). However, repeated-measures analysis of variance showed that monthly cCa concentrations ($P=0.099$) and mean cCa concentrations during the 1st year, 2nd year, and 3rd year ($P=0.062$) were not significantly higher in Group 1.

In addition, the ROC curve analysis of mean cCa concentrations versus the progression of AAC revealed areas of 0.583 (95% CI, 0.439–0.727; $P=0.247$), 0.690 (95% CI, 0.558–0.822; $P=0.008$), and 0.710 (95% CI, 0.584–0.836; $P=0.004$) for mean values during the 1st year, 2nd year, and 3rd year, respectively. The cutoff values of mean cCa concentrations during the 2nd year and 3rd year were 8.96 mg/dL (sensitivity = 68.6%, specificity = 70.8%) and 9.45 mg/dL (sensitivity = 49.0%, specificity = 87.5%), respectively.

In addition, the ROC curve analysis of baseline ScAnt, ScPost, and ScSum AAC scores for the progression of AAC revealed areas of 0.643 (95% CI, 0.506–0.780; $P=0.018$), 0.679 (95% CI, 0.536–0.823; $P=0.013$), and 0.670 (95% CI, 0.532–0.808; $P=0.018$), respectively. The cutoff values of baseline ScAnt, ScPost, and ScSum scores were 0.75 (sensitivity = 88.2%, specificity = 33.3%), 1.25 (sensitivity = 72.5%, specificity = 66.7%), and 2.25 (sensitivity = 74.5%, specificity = 58.3%), respectively.

Discussion

In this study, baseline degree of AAC was found to be associated with all-cause mortality and fatal and nonfatal CVD events in ESRD patients on HD. The optimum AAC cutoff score for predicting mortality was found to be 7.75. AAC progression was found in 68% of patients who had successfully completed follow-up. Furthermore, patients showing AAC progression tended to have higher serum cCa concentrations.

As atherosclerosis advances, microcalcifications of subintimal plaque form and increase in size to become visible on routine radiographs of the thorax and abdomen [18,24], and thus, provide a means of quantitatively evaluating disease severity by simple radiography. In a previous study, AAC assessed by simple lateral abdomen radiography was found to be highly predictive of subsequent cardiovascular morbidity

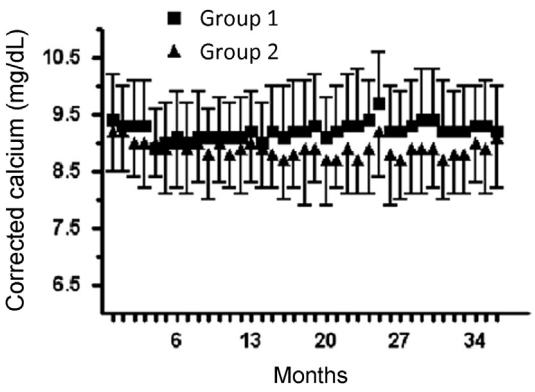

Figure 3. Comparison of mean values of corrected calcium concentrations of 3 years between Groups 1 and 2.

Table 4. Comparison of mean values of cCa, P, and cCa × P at 1st, 2nd, and 3rd years between Groups 1 and 2*

	Group 1 ($n=51$)	Group 2 ($n=24$)	*P*
cCa (mg/dL)			
1st year	9.1 ± 0.6	9.0 ± 0.7	0.302
2nd year	9.2 ± 0.7	8.8 ± 0.6	0.015
3rd year	9.3 ± 0.7	8.9 ± 0.7	0.018
P (mg/dL)			
1st year	5.1 ± 0.9	5.0 ± 1.1	0.609
2nd year	5.2 ± 0.9	4.9 ± 1.1	0.347
3rd year	5.2 ± 1.2	5.0 ± 1.2	0.709
cCa × P (mg^2/dL^2)			
1st year	47.0 ± 9.1	45.1 ± 11.7	0.437
2nd year	47.7 ± 11.8	43.2 ± 10.4	0.113
3rd year	48.2 ± 13.6	44.8 ± 11.7	0.296

* Group 1, progression of AAC score; Group 2, no progression of AAC score.
cCa, corrected calcium; P, phosphate.

and mortality [18]. Vascular calcification, including aortic calcification, is highly prevalent in dialysis patients [25,26], and CVD is the leading cause of death among ESRD patients [27]. Furthermore, several studies have indicated that arterial calcifications contribute to the high incidence of cardiovascular events and mortalities observed in ESRD patients [2,3,26,28–30]. The results of these studies demonstrate that scoring based on simple lateral abdominal radiographic findings can be used to evaluate AAC and that patients with higher AAC scores exhibit significantly higher mortality and fatal and nonfatal CVD events. A small number of studies have attempted to determine optimal AAC score cutoff values for the prediction of mortality. However, in these previous studies, patients were classified based on the presence or absence of AAC or using tertile of total AAC score [4,5]. The latter study showed that an AAC score of 5 (lower tertile value of total score 24) indicated a higher risk of mortality [5], and another study produced a similar result [31]. In the present study, we found that the optimum AAC cutoff score for predicting mortality was 7.75 and that its sensitivity and specificity were 61% and 81%, respectively. By contrast, an AAC score of 5 was not found to be statistically significant. We are not able to speculate convincingly as to why an AAC score of 8 is superior to a score of 5 because of the small-scale and retrospective nature of the present study. Nevertheless, this cutoff value of 8 could be valuable in clinical practice because it provides a straightforward means of identifying patients at high risk of mortality or CVD events.

It is known that, in addition to traditional risk factors, several clinical factors—such as hypercalcemia, hyperphosphatemia, an elevated Ca × P product, hyperparathyroidism, chronic inflammation, Ca overload induced by the use of Ca-based P binders and vitamin D analogues, a high dialysate Ca concentration, adynamic bone disease, and old age—are associated with the progression of arterial calcification in ESRD patients on dialysis [1,2,8–11]. Of these, hyperphosphatemia is increasingly being mentioned as a major stimulus for vascular calcification [12]. However, hypercalcemia and hyperphosphatemia both appear to have important roles in this context. Ca accelerates the mineralization of vascular smooth muscle cell by activating Pit-1 (a type III sodium-dependent P co-transporter) and by increasing the cellular influx of phosphate [7,32]. Chertow et al [1] reported that Ca-based P binders are associated with progressive coronary artery and aortic calcification, and suggested that Ca might directly or indirectly adversely influence the balance of skeletal and extraskeletal calcification in HD patients. Yamada et al [33] reported that an increase in serum Ca after HD was related to the rate of progression of aortic calcification, and Noordzij et al [2] reported that a baseline plasma Ca level of > 9.5 mg/dL was associated with the progression of AAC. In the present study, serum cCa concentration showed an association with the progression of vascular calcification rather than hyperphosphatemia or an elevated Ca × P product.

When we evaluated mean serum cCa concentrations during the 3-year study period, it was found that the cutoff value of mean cCa concentration during the 3rd year for the progression of AAC was 9.45 mg/dL, which is similar to the result obtained by Noordzij et al [2]. Furthermore, this cutoff value is similar to the serum level of cCa recommended by the Kidney Disease Outcomes Quality Initiative (K/DOQI) guideline for bone metabolism and disease in chronic kidney disease [34]. The observed importance of serum cCa concentration, rather than hyperphosphatemia and elevated Ca × P product in the present study, seems to be the result of relatively low serum iPTH concentrations in Groups 1 and 2. Interestingly, the cutoff values of ScAnt, ScPost, and ScSum AAC scores for the prediction of progression were very low—at 0.75, 1.25, and 2.25, respectively—which indicates that even the presence of slight AAC seems to progress in ESRD patients on HD, and suggests the importance of strict Ca and P control.

This study has several limitations. First, we only investigated the relations between serum cCa, P, and cCa × P product on AAC progression. Furthermore, the intergroup serum cCa concentration differences did not reach statistical significance. This prevents us from concluding that serum calcium concentration importantly contributes to AAC progression, but nevertheless suggests a possible association between serum cCa concentrations and AAC progression. Second, we did not evaluate relations between Ca load, serum vitamin D, and dialysate Ca concentrations and the progression of AAC. Therefore, the relation between arterial calcification and Ca overload due to the administration of excessive Ca-containing P binders remains controversial [1,8,35,36]. Third, the retrospective nature of and the fact that it was conducted at a single dialysis center introduces the possibility of selection bias with respect to the evaluation of AAC progression. Finally, the number of study participants was relatively small.

We conclude that AAC scores evaluated using simple abdomen radiographs appear to be associated with mortality and CVD events in ESRD patients on HD. An optimum AAC cutoff score of 8 can be used to predict mortality. Furthermore, our findings suggest that serum cCa concentration is associated with the progression of AAC. However, a further larger-scale study is required with a longer follow-up to confirm our findings.

Conflicts of interest

All authors declare no conflicts of interest.

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