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Risk factors for progression of aortic arch calcification in patients on maintenance hemodialysis and peritoneal dialysis

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Abstract

Vascular calcification is accelerated during dialysis and is known to be an important risk factor for cardiovascular disease. Progression of aortic arch calcification (AoAC) can be simply estimated with an AoAC score (AoACS) using plain chest radiography. The objective of this study was to evaluate risk factors for AoAC progression. The enrolled subjects were 125 newly treated hemodialysis patients and 59 peritoneal dialysis patients. In the patients who had undergone chest radiography before initial dialysis therapy and every year, we estimated AoACS and then divided the patients into two groups based on the presence or absence of AoAC progression. We also compared the baseline clinical and biochemical profiles in the two groups. Eighty-five (46.2%) were men (mean age, 58.6 ± 12.7 years). Seventy-six patients (41.3%) had AoAC before initial dialysis, with a mean AoACS of 13.0 ± 20.4%. The mean duration of follow-up was 2.7 ± 1.0 years. Half of the patients (50%) had progressive AoAC. Age >65 years ($p = 0.003$), dialysis duration ($p = 0.004$), diabetes ($p = 0.015$), and the presence of AoAC at baseline ($p = 0.001$) were related to AoAC progression. No significant association was found between AoAC progression and the baseline clinical parameters, including gender, obesity, hypertension, and dialysis modality. In a multivariate analysis, dialysis duration ($p = 0.003$) and the presence of AoAC at baseline ($p < 0.001$) were independent risk factors for AoAC progression in patients undergoing dialysis. The duration of dialysis and the presence of AoAC before initial dialysis were significantly related to the progression of AoAC in these patients. The results suggest that patients should be carefully managed from the predialysis stage to prevent AoAC progression and to reduce cardiovascular morbidity.

Key words: Aortic arch calcification, cardiovascular morbidity, chest radiography, dialysis

INTRODUCTION

Vascular calcification increases arterial stiffness and reduces vascular compliance, thereby increasing left ventricular (LV) afterload, LV hypertrophy, and LV oxygen consumption. The status of these parameters is related to the induction of cardiovascular disease events, which is the leading cause of death in patients undergoing dialysis.[1] The cardiovascular mortality rate among patients undergoing dialysis is as much as 20–30 times higher than that seen in the general population.[2] Aortic arch calcification (AoAC) could be used as a surrogate marker for the risk of cardiovascular complications in patients undergoing dialysis.[3] Recently, the progression of vascular calcification has been recognized as a more important risk factor than the presence of vascular calcification.[4–6] Therefore, we

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estimated AoAC progression using a follow-up of AoAC score (AoACS) on chest radiography. We suggest that the evaluation of AoACS on chest radiography is a simple and useful office-based index for assessing arteriosclerosis in patients. The objective of this study was to estimate the progression of AoAC during dialysis and to evaluate risk factors for the progression of AoACS in patients undergoing chronic dialysis.

MATERIALS AND METHODS

Study population

A total of 217 adult patients undergoing dialysis (125 on hemodialysis [HD] and 59 on peritoneal dialysis [PD]) who were newly treated at the dialysis unit of Uijeongbu St. Mary's Hospital during the 5-year period between January 1, 2004 and January 31, 2009 were included. We excluded patients with an episode of acute renal failure and patients who stopped dialysis or died within 1 year or who were followed up with chest radiography for <1 year after initial dialysis therapy. Out of the 217 patients, 184 patients who had undergone chest radiography for at least 1 year through January 31, 2010 were included in this study. This study was approved by the Institutional Review Board of Uijeongbu St. Mary's Hospital.

Progression of AOACS

All patients had undergone chest radiography before the initial dialysis therapy and at least once every year. Two radiologists independently reviewed all chest radiographs to detect AoAC. Radiographs were assessed for the presence of AoAC using the scale developed by Ogawa et al.[7] as shown in Figure 1. The scale, which divides the arch into 16 sections by circumference, was applied to the aortic arch on the chest radiography, and the number of calcified sectors was divided by 16. The AoACS was calculated after multiplying by 100 to express the results as a percentage. AoACS progression was defined when the relative change in the AoACS was more than 0% per year on repeated exams.

Evaluation of clinical and biochemical findings

We retrospectively reviewed medical records and evaluated clinical profiles before initial dialysis. The clinical risk factors considered were age >65 years, obesity (body mass index >25 kg/m^2), diabetes mellitus (DM), hypertension, dialysis duration, and dialysis modality. Blood was obtained before starting dialysis at admission to measure various markers, including hemoglobin, total cholesterol, triglyceride, calcium, phosphate, intact parathyroid hormone (iPTH), C-reactive protein (CRP), and albumin. Glycosylated hemoglobin (HbA1c) was measured in patients with DM. The biochemical risk factors considered were anemia, dyslipidemia, hypercalcemia, hyperphosphatemia, high calcium-phosphorus product level, high or low iPTH levels, and hypoalbuminemia. Anemia was defined as hemoglobin <11 g/dL, dyslipidemia was

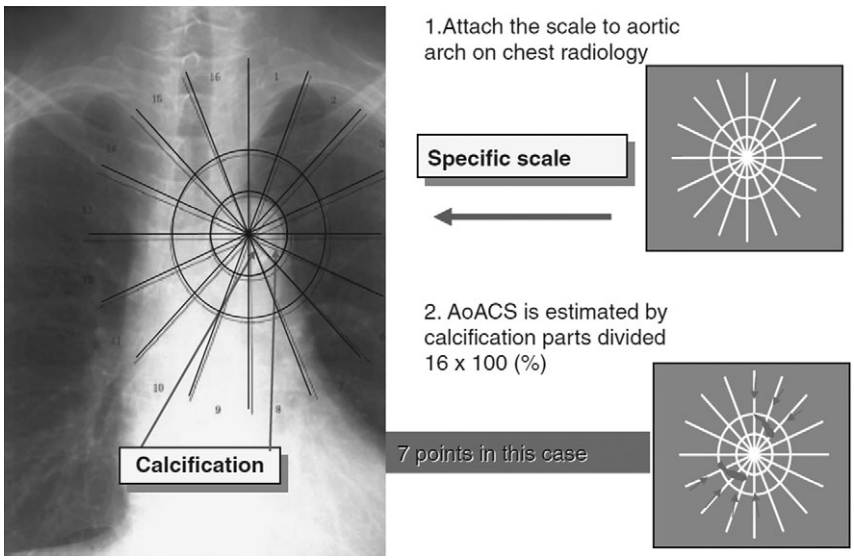

Figure 1 Measurement of the aortic arch calcification score (AoACS) by plain chest radiography in patients on maintenance dialysis (Material in Figure 1 is quoted from Tetsuya Ogawa's original article, which was published in *Hemodialysis International* in 2009).

defined as total cholesterol >200 mg/dL, triglycerides >150 mg/dL, or high-density lipoprotein cholesterol <40 mg/dL for male and <50 mg/dL for female after fasting for 12 hours, or use of lipid-lowering medication according to National Cholesterol Education Program (NCEP): Adult Treatment Panel (ATP III) 2001 guidelines. Hypercalcemia was defined as calcium >10.2 mg/dL, hyperphosphatemia as phosphate >5.5 mg/dL, high calcium-phosphorus product level as $Ca \times P > 55$ $(mg/dL)^2$, high iPTH as >300 pg/mL, low iPTH as <150 pg/mL, and hypoalbuminemia as <3.5 g/dL.

Comparison of clinical and biochemical risk factors according to AoACS progression

We divided the 184 patients into two groups based on the presence or absence of AoACS progression on follow-up chest radiographs during dialysis. We compared the baseline clinical and biochemical profiles in the two groups.

Statistical analysis

Continuous variables are reported as means and standard deviations, and categorical variables are described as counts and percentages. Two continuous variables were compared using Student's t test for normally distributed data, and the chi-square test or Fisher's exact test were used to compare categorical variables. Univariate analyses between AoACS progression and clinical or biochemical profiles were performed. A multivariate analysis of risk factors for AoACS progression in dialysis patients was performed with SPSS software (SPSS, Inc., Chicago, IL, USA). P values <0.05 were considered statistically significant.

RESULTS

Clinical and biochemical data

Eighty-five (46.2%) patients enrolled were men and 99 (53.8%) were women. Their mean age was 58.6 ± 12.7 years (range, 25–83 years). The mean duration of dialysis was 2.7 ± 1.0 years (range, 1–5 years). The underlying renal diseases were DM in 114 (62.0%) patients, hypertension in 42 (22.8%), chronic glomerulonephritis in 14 (7.6%), and others in 14 (7.6%). The enrolled study subjects were 125 patients undergoing HD and 59 patients undergoing PD.

The baseline clinical characteristics of the patients undergoing chronic dialysis before initial dialysis are shown in Table 1. The baseline biochemical profiles of the patients undergoing chronic dialysis are shown in Table 2. We compared the clinical (Table 3) and biochemical profiles (Table 4) according to the presence and absence of AoAC progression in patients undergoing dialysis.

Table 1 The baseline clinical profiles of the patients undergoing chronic dialysis before initial dialysis (n = 184)

Clinical variables	Mean ± SD or % (n)
Age (years)	58.6 ± 12.7
Old age (>65 y)	40.2% (74)
Height (cm) : Weight (kg)	160.1 ± 8.9 : 60.2 ± 10.9
BMI (kg/m^2)	23.4 ± 3.4
Obesity (BMI > 25)	25.0% (46)
DM	62.0% (114)
Hypertension	61.4% (113)
Dialysis duration (years)	2.7 ± 1.0 (1–5)
Dialysis modality (HD : PD)	67.9% : 32.1% (125 : 59)

BMI = body mass index; DM = diabetes mellitus; SD = standard deviation.

AoAC progression

Seventy-six patients (41.3%) had AoAC at baseline, with a mean AoACS of 13.0 ± 20.4%. One hundred eight patients (58.7%) had no AoAC at baseline. Ninety-two patients (50%) showed AoACS progression, and 92 patients (50%) showed no progression during dialysis. A total of 70 of 108 patients with a calcification score of 0 at baseline remained free of calcification throughout the study, and 38 showed progressive calcification. Fifty-four of 76 patients with a positive calcification score at baseline showed progression of AoAC throughout the study, and 22 showed no progression of calcification. Progressive

Table 2 The baseline biochemical profiles of the patients undergoing chronic dialysis before initial dialysis (n = 184)

Biochemical variables	Mean ± SD
Hemoglobin (g/dL)	8.4 ± 1.6
Total cholesterol (mg/dL)	169.3 ± 47.3
TG (mg/dL)	139.9 ± 65.8
HbA1c (%)	7.1 ± 1.8
Calcium (mg/dL)	7.8 ± 0.9
Phosphate (mg/dL)	5.6 ± 1.8
Calcium phosphorus product $(mg/dL)^2$	43.9 ± 12.9
iPTH (pg/mL)	221.1 ± 242.5
Albumin (g/dL)	3.2 ± 0.5

iPTH = intact-parathyroid hormone; SD = standard deviation; TG = triglyceride.

Table 3 Comparison of baseline clinical profiles according to the presence (n = 92) and absence (n = 92) of AoACS progression in patients undergoing dialysis

Clinical variables	AoACS progression (+) Mean ± SD or % (n)	AoACS progression (–) Mean ± SD or % (n)	P value
Age (years)	63.2 ± 10.4	54.1 ± 13.2	<0.001*
Old age (>65 years)	51.0% (47)	29.3% (27)	0.003*
Gender (male, %)	47.8% (44)	44.5% (41)	0.657
BMI (kg/m^2)	23.3 ± 2.8	23.5 ± 3.8	0.677
Obesity (BMI > 25)	26.0% (24)	23.9% (22)	0.733
DM	70.6% (65)	53.2% (49)	0.015*
Hypertension	61.9% (57)	60.8% (56)	0.880
Dialysis duration (years)	2.92 ± 1.14	2.57 ± 10.2	0.026*
Dialysis modality (HD, %)	70.6% (65)	65.2% (60)	0.430
Phosphate binder (%)			
Calcium containing	29.6% (27)	41.3% (38)	0.150
Non-calcium containing	0% (0)	4.3% (4)	0.150

*p < 0.05.
AoACS = aortic arch calcification score; BMI = body mass index; DM = diabetes mellitus; HD = hemodialysis; PD = peritoneal dialysis; SD = standard deviation.

Table 4 Comparison of baseline biochemical profiles according to the presence (n = 92) and absence (n = 92) of AoACS progression in patients undergoing dialysis

Biochemical variables	AoACS progression (+) Mean ± SD	AoACS progression (–) Mean ± SD	P value
Hemoglobin (g/dL)	8.6 ± 1.6	8.3 ± 1.6	0.212
T cholesterol (mg/dL)	166.6 ± 47.7	172.1 ± 46.9	0.450
TG (mg/dL)	133.3 ± 64.8	146.5 ± 66.5	0.189
HbA1c (%) (n = 85)	7.2 ± 1.8	7.1 ± 2.0	0.898
Calcium (mg/dL)	7.9 ± 0.9	7.7 ± 0.9	0.415
Phosphate (mg/dL)	5.5 ± 1.8	5.8 ± 1.8	0.310
CaP product $(mg/dL)^2$	43.3 ± 13.3	44.5 ± 12.5	0.527
iPTH (pg/mL)	192.7 ± 162.4	247.3 ± 296.7	0.164
CRP (mg/dL)	2.6 ± 2.3	2.3 ± 4.8	0.883
Albumin (g/dL)	3.2 ± 0.5	3.2 ± 0.6	0.262
Abnormal biochemical variables	**AoACS progression (+) % (n)**	**AoACS progression (–) % (n)**	**P value**
Anemia (Hb < 11 g/dL)	93.4% (86/92)	96.7% (89/92)	0.305
Dyslipidemia	51.1% (44/86)	53.4% (46/86)	0.760
Hyperphosphatemia (P > 5.5 mg/dL)	43.4% (40/92)	56.5% (52/92)	0.077
CaP Product (Ca × P > 55 $(mg/dL)^2$	17.3% (16/92)	15.2% (14/92)	0.690
iPTH < 150 pg/mL	56.7% (42/74)	48.7% (39/80)	0.320
iPTH > 300 pg/mL	22.9% (17/74)	22.5% (18/80)	0.944
Hypoalbuminemia (Albumin < 3.5 g/dL)	66.2% (55/83)	61.3% (54/88)	0.505

Numbers in parenthesis mean the number of subjects with results/the number of subjects involved in the analysis. We had no case of hypercalcemia.
AoACS = aortic arch calcification score; CaP product = calcium phosphorus product; CRP = C-reactive protein; iPTH = intact parathyroid hormone; SD = standard deviation; TG = triglyceride.

Table 5 Comparison of baseline AoACS and the presence of AoAC at baseline according to the presence (n = 92) and absence (n = 92) of AoACS progression in patients undergoing dialysis

	AoACS progression (+) Mean ± SD or % (n)	AoACS progression (−) Mean ± SD or % (n)	P value
Baseline AoACS (%)	18.0 ± 20.4	8.1 ± 19.2	0.001*
The presence of AoAC at baseline (%)	58.7% (54/76)	23.9% (22/76)	<0.001*

*$p < 0.05$. Numbers in parenthesis mean the number of subjects with results/the number of subjects involved in the analysis.
AoAC = aortic arch calcification; AoACS = aortic arch calcification score; SD = standard deviation.

AoAC correlated with baseline calcification. The mean progression rate of AoACS was 3.4 ± 4.9% per year.

Comparison of clinical and biochemical risk factors according to AoACS progression

As shown in Table 3, age ($p < 0.001$) was significantly higher in patients with AoACS progression than in patients without. Additionally, age >65 years ($p = 0.003$), dialysis duration ($p = 0.004$), and DM ($p = 0.015$) were significant risk factors for the progression of AoACS. No significant correlation was detected between the progression of AoACS and baseline clinical parameters, including male gender, body mass index, obesity, hypertension, and dialysis type.

As shown in Table 4, we found no association between AoACS progression and baseline biochemical profiles such as hemoglobin, total cholesterol, triglyceride, HbA1c, calcium, phosphate, calcium phosphate product, iPTH, CRP, or albumin. Furthermore, there was no association between AoACS progression and abnormal biochemical findings such as anemia, dyslipidemia, hyperphosphatemia, high calcium-phosphorus product, high or low iPTH levels, or hypoalbuminemia. No patients had hypercalcemia.

Baseline AoACS ($p = 0.001$) and baseline AoAC rate ($p < 0.001$) were significantly higher in patients with AoACS progression than in those without (Table 5). Univariate analyses were performed to identify risk factors associated with AoACS progression in HD and PD patients. DM, age >65 years, dialysis duration, and the presence of AoAC at baseline were possible risk factors in HD patients and age, dialysis duration, and the presence of AoAC at baseline in PD patients.

Evaluation of independent risk factors of AoACS

Multivariate analyses included factors with $p < 0.05$ on univariate analyses as possible risk factors to evaluate the independent risk factors for AoACS progression. Dialysis duration ($p = 0.003$) and the presence of AoAC at baseline ($p < 0.001$) were independent risk factors associated with AoACS progression in patients undergoing dialysis (Table 6). The presence of AoAC at baseline ($p = 0.001$) was an independent risk factor associated with AoACS progression in HD patients and the duration of dialysis ($p = 0.042$) in PD patients (Table 7).

DISCUSSION

AoAC is a known independent risk factor for cardiovascular disease in patients undergoing dialysis. Moreover, AoAC progression as shown by a radiological examination, is also significantly associated with increased cardiovascular mortality risk.[8] Numerous risk factors are related to vascular calcification; however, there are still no definite methods for reducing vascular calcification despite continued efforts. In this study, the extent and progression of AoAC was quantified with chest radiography using the ΔAoAC score (%) per year. Plain radiography is not sensitive for detecting early-stage vascular calcification. However, it may be a convenient screening test to evaluate AoAC progression and arteriosclerosis status in patients undergoing dialysis.

Vascular calcification is an actively regulated process and not a passive process resulting from simple precipita-

Table 6 Multivariate analysis of risk factors for AoACS progression in patients undergoing dialysis (n = 184)

	Beta	SE	P value
DM	0.135	0.073	0.059
Old age (>65 years)	0.103	0.076	0.165
Dialysis duration	0.205	0.032	0.003*
The presence of AoAC at baseline (%)	0.285	0.076	0.001*

*$p < 0.05$. $R^2 = 0.182$.
AoAC = aortic arch calcification; AoACS = aortic arch calcification score; Beta = standardized regression coefficient; DM = diabetes mellitus; SE = standard error.

Table 7 Multivariate analysis of risk factors for AoACS progression in patients with HD (n = 125) and PD (n = 59)

	Beta	SE	P value
In HD patients			
DM	0.108	0.089	0.224
Old age (>65 y)	0.105	0.089	0.238
Dialysis duration	0.004	0.003	0.105
The presence of AoAC at baseline (%)	0.309	0.091	0.001*
In PD patients			
Age	0.012	0.006	0.057
Dialysis duration	0.009	0.004	0.042*
The presence of AoAC at baseline (%)	0.115	0.151	0.452

*$p < 0.05$. $R^2 = 0.430$ in HD patients and $R^2 = 0.458$ in PD patients. AoAC = aortic arch calcification; AoACS = aortic arch calcification score; Beta = standardized regression coefficient; DM = diabetes mellitus; HD = hemodialysis; PD = peritoneal dialysis; SE = standard error.

tion of increased calcium-phosphate products. Traditionally, vascular calcification has been associated with risk factors such as hypertension, DM, aging, and dyslipidemia. However, these factors do not fully explain the progression of vascular calcification and the high frequency of cardiovascular disease.[3,6,9–12] Results of previous studies have shown that vascular smooth-muscle cells transform into osteoblast-like cells in the vessel wall and play a critical role in mineralization.[13] Several transcription factors including Msx 2, osterix, and RUNX2 promote osteogenesis. As a result, the simultaneous increases in inducers, such as hyperphosphatemia, hypercalcemia, uremic toxins, and oxidative stress, and the reduction in arterial osteochondrocytic program inhibitors, such as matrix G1a protein, osteopontin, osteoprotegerin, Fetuin-A, and pyrophosphate, lead to overt vascular calcification.[6,10,14,15]

Vascular calcification can be assessed using several radiological tools including computed tomography, ultrasonography, and simple X-rays. We evaluated the extent of AoAC with plain radiography, according to the method of Ogawa et al.[7] The AoACS on a chest X-ray reflects the magnitude of whole aortic calcification.[16] Many previous studies have shown that AoAC using simple imaging methods is related to cardiovascular morbidity and mortality in patients undergoing dialysis as well as in the general population. Therefore, we suggest that evaluating AoAC on plain chest radiography may be a simple and inexpensive method for predicting cardiovascular morbidity in patients with chronic kidney disease (CKD) and patients undergoing dialysis. This advantage may be applied equally for evaluating the progression of vascular calcification.

Vascular calcification is usually progressive.[5,10] Aging is the most consistent risk factor for progressive calcification, and dialysis is a known accelerator of vascular calcification.[7,17] A previous study demonstrated that dialysis increases vascular smooth-muscle cell apoptosis and osteocytic differentiation in children with CKD to have fewer proatherosclerotic risk factors.[17] Another study showed that patients with progressive coronary artery calcification were older and had been undergoing dialysis for a longer period. A study of patients between the ages of 20 to 30 years indicated that the AoACS nearly doubled over a 20-month period.[18] Patients with baseline vascular calcification had a tendency to show progressive calcification, whereas those without it remained free of calcification.[11] In our results, preexisting AoAC and the duration of dialysis were strong determinant factors for the progression of calcification, and the baseline AoAC was higher in patients with progressive AoAC than in those without.

Additional risk factors for vascular calcification include inflammation, malnutrition, and oxidative stress.[19] We found no association between CRP level or hypoalbuminemia and AoAC progression. It was a limitation of this study that no other important circulating markers of inflammation were measured. Vascular calcification is also known to correlate with the duration of CKD[20]; however, we could not determine the duration of renal failure in this patients because we had few cases of earlier stage of CKD followed up and we included only patients after start of dialysis in this study. In contrast to previous reports, we did not show the association between mineral metabolism and the progression of vascular calcification. Prolonged exposure to worsening mineral dysregulation during the dialysis could contribute to induce the progression of vascular calcification. Despite the difference in taking calcium-containing phosphate binder, there was no difference of serum calcium and phosphate levels between the two groups of AoACS progression and nonprogression. Also, the average serum mineral levels were almost within normal range, which may explain the lack of relationship between mineral metabolism and vascular calcification in our results. It is also important to know that calcification could progress even in patients with well-controlled mineral levels.[21]

Few data are available to compare the progression of vascular calcification based on the dialysis modality. Most recent vascular calcification studies have included patients undergoing HD, but limited data are available on the

clinical characteristics of vascular calcification in patients undergoing PD.[22] Sigrist et al. indicated that HD aggravates calcification more than PD dose. They stated that patients undergoing PD had higher residual kidney function.[5] Residual renal function is one of the most important phosphorus control factors and declines more rapidly in patients undergoing HD than in those undergoing PD. However, the reasons for this are unclear. We did not compare residual renal function in patients with HD and PD; however, dialysis modality was not related to AoAC progression. In a subgroup analysis of patients according to dialysis modality, there was a difference in risk factor for AoAC progression between HD and PD patients. The presence of AoAC at baseline was a more important risk factor for AoAC progression in HD patients, on the other hand, the duration of dialysis was a more important risk factor for AoAC progression in PD patients.

We identified the risk factors associated with AoAC progression in our patients undergoing dialysis. DM, age >65 years, dialysis duration, and the presence of AoAC at the start of the dialysis based on plain chest radiography were possible risk factors for AoAC progression, and duration of dialysis and the presence of AoAC at the start of the dialysis were independent risk factors for AoAC progression in patients undergoing chronic dialysis. In our opinion, additional assessments are needed to compare AoAC progression and useful surrogate markers for the risk of cardiovascular morbidity such as LV mass, carotid artery intima-media thickness, arterial stiffness, and endothelial dysfunction. The impact of AoAC progression on cardiovascular mortality during dialysis also needs to be investigated. In conclusion, we emphasize that it is important to prevent vascular calcification during the early stage of CKD to avoid progression of vascular calcification and to reduce cardiovascular morbidity in patients undergoing dialysis.

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