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Sex-specific relationship between vascular calcification and incident fracture in patients with end-stage renal disease

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Background: Vascular calcification (VC) is a major component of mineral bone disorders in patients with end-stage renal disease (ESRD). Bone metabolism is affected by various factors, including sex hormones. This study investigated whether there was a sex-specific relationship between VC and incident fracture in patients with ESRD.

Methods: This was a retrospective cohort study of dialysis patients from a single center. VC was assessed by the aortic calcification index (ACI) using abdominal computed tomography. Patients were grouped by sex and stratified into low or high ACI groups, according to the median ACI value. The association between ACI and incident fracture was analyzed.

Results: Data from 593 patients (male: n = 328, median ACI, 14.57; female: n = 265, median ACI, 19.44) were included. During a median follow-up of 36.7 months, 71 patients (12.0%) developed fractures. The fracture-free survival rate was significantly lower in the high ACI group versus the low ACI group, both in males (P = 0.021) and females (P = 0.001). In males, multivariate analysis showed that the high ACI group and ACI *per se* were not significant risks for fracture. However, in females, both the high ACI group (adjusted hazard ratio, 2.720; P = 0.003) and ACI *per se* (adjusted hazard ratio, 1.768; P = 0.035) were independently associated with fracture after adjustment for confounding variables.

Conclusion: VC was independently associated with incident fracture in female patients with ESRD. There may be a sex-specific relationship between VC and fracture in patients with ESRD.

Keywords: Bone fracture, Dialysis, Kidney failure, chronic, Sex, Vascular calcification

Introduction

Chronic kidney disease-mineral and bone disorder (CKD-MBD) is a clinical syndrome that describes a systemic disorder of mineral and bone metabolism caused by CKD. CKD-MBD includes biochemical abnormalities of calcium, phosphorus, parathyroid hormone (PTH), and vitamin D, bone disease, and vascular calcification (VC) [1]. The incidence of fracture increases as CKD progresses [2]. In the Dialysis Outcomes and Practice Patterns Study (DOPPS), across all countries studied the incidence of fracture was significantly higher in patients receiving maintenance dialysis compared with the gen-

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eral population [3]. The high risk of fracture results from both CKD-MBD-related factors and classical risk factors seen in the non-CKD population [4]. VC, a main component of CKD-MBD, is related to bone health in CKD. Previous studies have shown that VC was associated with bone histomorphometry, exhibiting low bone activity, and adynamic bone disease [5], as well as low bone volume in patients with end-stage renal disease (ESRD) [6,7]. VC has also been shown to be associated with a low trabecular bone score, a surrogate measure of the microarchitectural integrity of bone, in patients with ESRD [8]. Previous reports have demonstrated that ESRD patients with VC have a high risk for fracture [9,10].

Studies in the general population have demonstrated differences in fracture incidence and location according to sex. The fracture incidence at all sites was higher in males than females in the second and third decades, and thereafter females developed fractures more frequently than males. The incidence of fragility fractures in particular was greater in females after the age of 50 years [11]. The age-adjusted incidence of hip fracture was also reported to be higher in females than males in studies using nationwide data in the United States and South Korea [12,13]. This sex-specific pattern is related to differences in the structure [14], geometry, and mineralization of bone [15,16], and fall risk and behavioral and medical factors [17] that differ according to sex.

The predominance of fractures in females is also observed in patients with CKD, as the incidence of fracture is greater in female patients with CKD than male patients [2] across all ranges of estimated glomerular filtration rates [18]. In addition, female dialysis patients have been shown to be affected by hip fracture more frequently and at a younger age than male dialysis patients [19]. Female sex has also been identified as an independent predictor for fragility fractures in prevalent hemodialysis patients [10]. These findings suggest a sex-specific difference in the pathogenesis of fracture in patients with ESRD, although little is known about the sex-specific relationship between VC and incident fractures in these patients. This study investigated whether there was a sex-specific relationship between the degree of VC and incident fracture in ESRD patients starting dialysis.

Methods

Study population

This was a retrospective cohort study of ESRD patients that started maintenance dialysis (incident dialysis patients) between January 2006 and July 2017. In our center, we perform computed tomography (CT) of the abdomen at the initiation of dialysis to evaluate acquired cystic lesions in the kidney. Incident dialysis patients who had undergone abdomen CT scans were included. Subjects who were younger than 20 years, or currently undergoing treatment for malignancy or major surgery, or those who were followed-up for less than 1 month were not included in the cohort. In line with the principles of the Declaration of Helsinki, the study was approved by the Institutional Review Board of The Catholic University of Korea (OC19OISI0172). As it was a retrospective study using data obtained from medical records, informed consent was exempted by the Institutional Review Board.

Abdominal aortic calcification assessment

The abdominal aorta was examined based on consecutive, sequential, 8 mm-section, non-contrast CT scans. The aortic calcification index (ACI) was calculated as the proportion of the aortic circumference covered by the most extensive calcification, as previously described [20]. This method was used to quantify arteriosclerosis in the cross-section that showed the most extensive aortosclerosis before the bifurcation of the renal artery. The arithmetic mean values of three measurements were calculated and used for the analysis. The ACI was independently checked by two observers and reproducibility was absolute for the patients examined.

Data collection and definitions

Baseline demographics and clinical data (including age, sex, height, weight, co-morbidities, laboratory data, and treatment characteristics) were collected. Body mass index was calculated as kg/m^2. The residual kidney function (RKF) was calculated from the serum urea and creatinine concentrations using the equation proposed by Shafi et al [21]: RKF (mL/min/1.73 m^2) = 2.4 × blood urea nitrogen$^{0.984}$ × creatinine$^{-1.868}$. Cardiovascular disease

(CVD) was defined as coronary heart disease (angina pectoris and myocardial infarction), heart failure, cerebrovascular disease (transient ischemic attack, cerebral infarction, and cerebral hemorrhage), peripheral vascular disease, and pulmonary vascular disease. Patients were divided into two groups according to sex and stratified into two groups by median ACI value (low and high ACI groups) (Fig. 1).

Outcome measures

The data on fracture events was collected by reviewing medical records and radiographs performed in our center. The incident fracture was defined as the first development of fracture after the initiation of dialysis. Fractures were assessed at multiple sites, including the skull/face, vertebra, rib/thorax, clavicle/scapula, humerus/elbow, forearm/wrist, hand, pelvis, hip/femur, lower leg/ankle, and foot. Surgically-induced fractures or fractures attributed to metastatic bone disease were excluded.

Statistical analysis

Continuous data were expressed as the mean ± standard deviation or as the median with an interquartile range (25th–75th percentile) in cases of skewed distribution, and were compared using the Student's *t* test or the Mann–Whitney *U* test, as appropriate. Categorical data were expressed as number (%) and compared using the chi-squared test. Kaplan–Meier curves and log-rank tests were used to estimate cumulative event-free rates.

The Cox proportional hazards model was used in the whole group and in each sex group to estimate the hazard ratio (HR) and 95% confidence intervals (CIs) for the incident fracture over time according to the ACI groups and an increase in the ACI. Due to skewed distribution, ACI levels were logarithmically transformed in the Cox proportional regression analysis. The log-transformed ACI + 1 (log ACI) was used in the analysis by including ACI as a continuous variable. The HR of the high ACI group (categorical variable) was evaluated with consideration of the low ACI group as the reference. The confounders analyzed in the univariate model were variables associated with CKD-MBD and traditional factors related to fracture. A multivariate Cox proportional hazard model included the significant factors in univariate analysis (forward selection method). A P value < 0.05 was considered statistically significant. The statistical analyses were performed using PASW Statistics version 18.0 (SPSS Inc., Chicago, IL, USA).

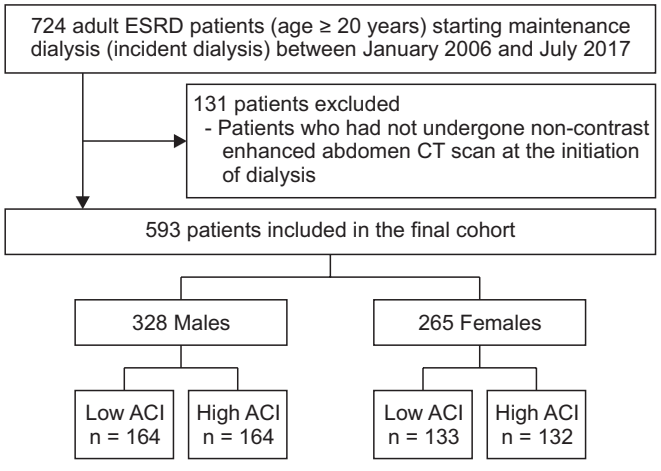

Figure 1. Study flow diagram.
ACI, aortic calcification index; CT, computed tomography; ESRD, end-stage renal disease.

Results

Patient characteristics

Among 724 adult ESRD patients who started maintenance dialysis, 131 patients who did not have non-contrast enhanced abdomen CT scan data were excluded (Fig. 1). A total of 593 patients were included (male, n = 328; female, n = 265). The characteristics of the study patients are described in Table 1. Smoking was more prevalent among male patients than in female patients, and RKF at initiation of dialysis, total cholesterol, high density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, and intact PTH levels were higher in females than males. The median ACI was also higher in female patients than males (19.44 and 14.57, respectively). Other demographic parameters and use of medications did not differ between male and female patients.

Table 2 shows a comparison of the characteristics of patients in the low and high ACI groups for each sex. In males, the age, percentage of patients who had diabetes mellitus and a history of CVD, and RKF at the initiation of dialysis were higher in the high ACI group than in the low ACI group. The calcium and phosphorous product and intact PTH level were significantly lower in the high ACI

Table 1. Comparison of baseline characteristics between males and females

Variable	Male (n = 328)	Female (n = 265)	*P* value
Age (yr)	59.3 ± 13.7	60.8 ± 14.7	0.213
BMI (kg/m^2)	23.6 ± 3.7	24.1 ± 4.4	0.162
Smoking	124 (37.8)	10 (3.8)	< 0.001
Diabetes mellitus	195 (59.5)	141 (53.2)	0.127
History of CVD	63 (19.2)	55 (20.8)	0.639
Cause of ESRD			
Diabetes mellitus	190 (57.9)	140 (52.8)	0.658
Hypertension	82 (25.0)	76 (28.7)	
Glomerulonephritis	20 (6.1)	17 (6.4)	
Others	36 (11.0)	32 (12.1)	
Hemodialysis	234 (71.3)	190 (71.7)	0.924
Peritoneal dialysis	94 (28.7)	75 (28.3)	
Previous fracture	1 (0.3)	6 (2.3)	0.049
RKF (mL/min/1.73 m^2)	5.7 ± 4.7	7.1 ± 4.9	< 0.001
Urea nitrogen (mg/dL)	82.9 ± 34.7	78.9 ± 33.4	0.159
Albumin (g/dL)	3.4 ± 0.6	3.4 ± 0.6	0.932
Alkaline phosphatase (U/L)	146.7 ± 107.8	163.8 ± 193.1	0.198
Calcium × Phosphorus product (mg^2/dL^2)	43.3 ± 14.1	43.6 ± 14.5	0.764
Hemoglobin (g/dL)	8.9 ± 1.9	9.0 ± 1.8	0.676
Total cholesterol (mg/dL)	162.3 ± 60.0	175.1 ± 55.8	0.009
Triglyceride (mg/dL)	128.5 (95.0–177.0)	135.0 (96.3–175.8)	0.771
HDL-cholesterol (mg/dL)	36.9 ± 13.3	41.3 ± 15.8	0.039
LDL-cholesterol (mg/dL)	102.7 ± 43.5	110.9 ± 42.9	< 0.001
Intact PTH (pg/mL)	265.3 ± 212.3	314.6 ± 305.9	0.035
hs-CRP (mg/L)	2.2 ± 4.1	2.8 ± 4.8	0.090
ACI	14.6 (0–26.7)	19.4 (0–34.9)	0.004
Parathyroidectomy	2 (0.6)	9 (3.4)	0.150
Ca-based P-binders	216 (65.9)	163 (61.5)	0.273
Non-Ca-based P-binders	75 (22.9)	56 (21.1)	0.613
Vitamin D analogues	92 (28.0)	81 (30.6)	0.503
Use of corticosteroids	133 (40.5)	111 (41.9)	0.742
Statins	175 (53.4)	133 (50.2)	0.443
RAAS blockers	236 (72.0)	186 (70.2)	0.638
Calcium channel-blockers	244 (74.4)	194 (73.2)	0.745
Beta-blockers	208 (63.4)	173 (65.3)	0.637

Data are presented as mean ± standard deviation, number (%), or median (range).

ACI, aortic calcification index; BMI, body mass index; Ca-based P-binder, calcium-based phosphate-binders; CVD, cardiovascular disease; ESRD, end stage renal disease; HDL, high-density lipoprotein; hs-CRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein; non-Ca-based P-binders, non-calcium-based phosphate-binders; PTH, parathyroid hormone; RAAS, renin-angiotensin-aldosterone system; RKF, residual kidney function.

group than in the low ACI group. In the high ACI group, fewer patients used calcium-based phosphate-binders (Ca-based P-binders), non-calcium-based phosphate-binders (non-Ca-based P-binders), and vitamin D analogues, whereas more patients used beta-blockers than those with low ACI.

Similarly, in female patients, the high ACI group was older and had a higher prevalence of diabetes mellitus and history of CVD than the low ACI group. The high ACI group had higher hemoglobin levels and lower intact PTH levels compared with the low ACI group. In the high ACI group, fewer patients used Ca-based P-binders and

Table 2. Comparison of baseline characteristics between low and high ACI group in each sex

Variable	Male		*P* value	Female		*P* value
	Low ACI (n = 164)	High ACI (n = 164)		Low ACI (n = 133)	High ACI (n = 132)	
Age (yr)	51.7 ± 12.3	67.0 ± 10.3	< 0.001	52.7 ± 13.5	68.9 ± 10.7	< 0.001
BMI (kg/m^2)	24.0 ± 4.0	23.2 ± 3.3	0.070	23.7 ± 4.3	24.5 ± 4.4	0.187
Smoking	66 (40.2)	58 (35.4)	0.318	7 (5.3)	3 (2.3)	0.215
Diabetes mellitus	85 (51.8)	110 (67.1)	0.005	59 (44.4)	82 (62.1)	0.004
History of CVD	20 (12.2)	43 (26.2))	0.001	17 (12.8)	38 (28.8)	0.001
Cause of ESRD						
Diabetes mellitus	83 (50.6)	107 (65.2)	0.050	58 (43.6)	82 (62.1)	< 0.001
Hypertension	46 (28.0)	36 (22.0)		36 (27.1)	40 (30.3)	
Glomerulonephritis	12 (7.3)	8 (4.9)		16 (12.0)	1 (0.8)	
Others	23 (14.0)	13 (7.9)		23 (17.3)	9 (6.8)	
Hemodialysis	110 (67.1)	124 (75.6)	0.087	90 (67.7)	100 (75.8)	0.144
Peritoneal dialysis	54 (32.9)	40 (24.4)		43 (32.3)	32 (24.2)	
Previous fracture	1 (0.6)	0 (0.0)	1.000	2 (1.5)	4 (3.0)	0.447
RKF (mL/min/1.73 m^2)	4.5 ± 3.9	6.8 ± 5.2	< 0.001	6.5 ± 5.3	7.6 ± 4.4	0.052
Urea nitrogen (mg/dL)	85.8 ± 35.7	80.0 ± 33.5	0.130	80.8 ± 37.3	77.0 ± 28.9	0.351
Albumin (g/dL)	3.4 ± 0.6	3.4 ± 0.6	0.910	3.5 ± 0.6.	3.3 ± 0.6	0.088
Alkaline phosphatase (U/L)	148.4 ± 115.1	144.9 ± 100.3	0.770	184.0 ± 250.2	143.4 ± 105.9	0.087
Calcium × Phosphorus product (mg^2/dL^2)	45.0 ± 15.3	41.5 ± 12.4	0.023	44.8 ± 15.6	42.4 ± 13.2	0.182
Hemoglobin (g/dL)	8.9 ± 2.0	8.8 ± 1.8	0.704	8.6 ± 2.0	9.3 ± 1.5	< 0.001
Total cholesterol (mg/dL)	167.8 ± 67.5	156.5 ± 50.7	0.093	178.5 ± 55.3	171.6 ± 56.3	0.324
Triglyceride (mg/dL)	133.0 (99.0–190)	124.0 (93.0–173.0)	0.086	128.5 (96.8–183.8)	135.0 (96.3–173.8)	0.944
HDL-cholesterol (mg/dL)	37.5 ± 14.3	36.4 ± 12.2	0.471	42.0 ± 14.8	40.6 ± 16.8	0.454
LDL-cholesterol (mg/dL)	106.6 ± 47.1	98.3 ± 38.7	0.124	112.8 ± 45.3	108.9 ± 40.5	0.508
Intact PTH (pg/mL)	312.7 ± 233.7	216.6 ± 175.6	< 0.001	351.3 ± 309.2	273.1 ± 298.1	0.048
hs-CRP (mg/L)	1.9 ± 3.6	2.5 ± 4.5	0.156	2.4 ± 4.6	3.3 ± 5.1	0.116
Parathyroidectomy	0 (0.0)	2 (1.2)	0.498	8 (6.0)	1 (0.8)	0.036
Ca-based P-binders	119 (72.6)	97 (59.1)	0.010	91 (68.4)	72 (54.5)	0.020
Non-Ca-based P-binders	52 (31.7)	23 (14.0)	< 0.001	36 (27.1)	20 (15.2)	0.018
Vitamin D analogues	54 (32.9)	38 (23.2)	0.049	48 (36.1)	33 (25.0)	0.050
Use of corticosteroids	67 (40.9)	66 (40.2)	0.910	52 (39.1)	59 (44.7)	0.356
Statins	86 (52.4)	89 (54.3)	0.740	65 (48.9)	68 (51.5)	0.667
RAAS blockers	123 (75.0)	113 (68.9)	0.219	93 (69.9)	93 (70.5)	0.925
Calcium channel-blockers	119 (72.6)	125 (76.2)	0.448	90 (67.7)	104 (78.8)	0.041
Beta-blockers	95 (57.9)	113 (68.9)	0.039	83 (62.4)	90 (68.2)	0.323

Data are presented as mean ± standard deviation, number (%), or median (range).

ACI, aortic calcification index; BMI, body mass index; Ca-based P-binder, calcium-based phosphate-binders; CVD, cardiovascular disease; ESRD, end stage renal disease; HDL, high-density lipoprotein; hs-CRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein; non-Ca-based P-binders, non-calcium-based phosphate-binders; PTH, parathyroid hormone; RAAS, renin-angiotensin-aldosterone system; RKF, residual kidney function.

non-Ca-based P-binders and underwent parathyroidectomy, while more patients used calcium-channel blockers when compared with those with low ACI.

Incidence, location, and age groups of fracture according to sex

During a median follow-up period of 36.7 months (range, 18.0–65.3 months), 71 patients (12.0%) developed fractures. Among them, eight patients developed a

fracture at multiple anatomical sites. Among a total number of 93 fractures, the fracture locations were as follows: hip/femur, n = 25 (26.9%); lower leg/ankle, n = 14 (15.1%); vertebra, n = 13 (14.0%); foot, n = 13 (14.0%); forearm/wrist, n = 7 (7.5%); pelvis, n = 6 (6.5%); humerus/elbow, n = 5 (5.4%); hand, n = 5 (5.4%); rib/thorax, n = 2 (2.2%); skull/face, n = 2 (2.2%); and clavicle/scapula, n = 1 (1.1%). The distribution of fracture location was not different between males and females (Table 3).

Fig. 2 shows the number of patients who developed fractures, according to sex and age groups. A trend for a higher proportion of female patients than male patients at age 60 to 79 was noted, however the distribution was not statistically different (P = 0.340).

The risk of fracture was compared, according to sex and menopausal status, using Kaplan-Meier curves. Fig. 3A shows fracture-free survival according to sex. Female patients had a significantly lower fracture-free survival rate compared with males (10 year fracture-free survival rates 41.0% versus 76.7%, P = 0.004). Among 265 female patients, 248 patients had records available for their menopausal status at the initiation of dialysis: 44 patients were premenopausal and 204 patients were postmenopausal. Fig. 3B shows the fracture-free survival of male patients,

Table 3. Fracture incidence at different locations according to sex

	Male (n=36)	Female (n=57)	*P* value
Skull/face	2 (5.6)	0 (0.0)	0.382
Vertebra	2 (5.6)	11 (19.3)	
Rib/thorax	1 (2.8)	1 (1.8)	
Clavicle/scapula	1 (2.8)	0 (0)	
Humerus/elbow	3 (8.3)	2 (3.5)	
Forearm/wrist	2 (5.6)	5 (8.8)	
Hand	2 (5.6)	3 (5.3)	
Pelvis	2 (5.6)	4 (7.0)	
Hip/femur	12 (33.3)	13 (22.8)	
Lower leg/ankle	4 (11.1)	10 (17.5)	
Foot	5 (13.9)	8 (14.0)	

Data are presented as number (%).

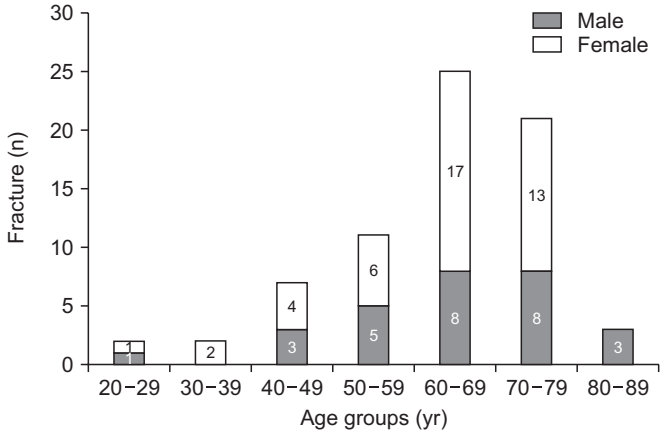

Figure 2. The number of patients who developed fractures according to sex and age groups. The distribution of patients with fractures according to age group was not statistically different between males and females (P = 0.340).

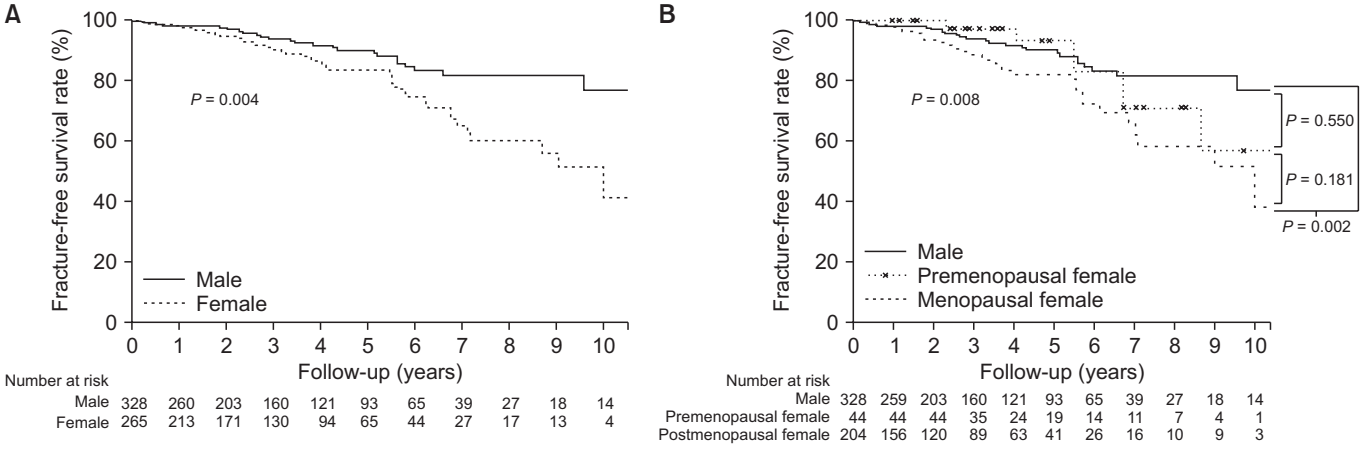

Figure 3. Fracture-free survival rates according to sex (Kaplan–Meier curves). (A) Female patients had a significantly lower fracture-free survival rate when compared with male patients (P = 0.004). (B) Fracture-free survival rates of male patients, premenopausal female patients, and postmenopausal female patients. The fracture-free survival rates were significantly different between three groups (P = 0.008). The fracture-free survival rate was significantly lower in postmenopausal females compared to males (P = 0.002). However the fracture-free survival rates were not different between males and premenopausal females (P = 0.550), and between premenopausal females and postmenopausal females (P = 0.181).

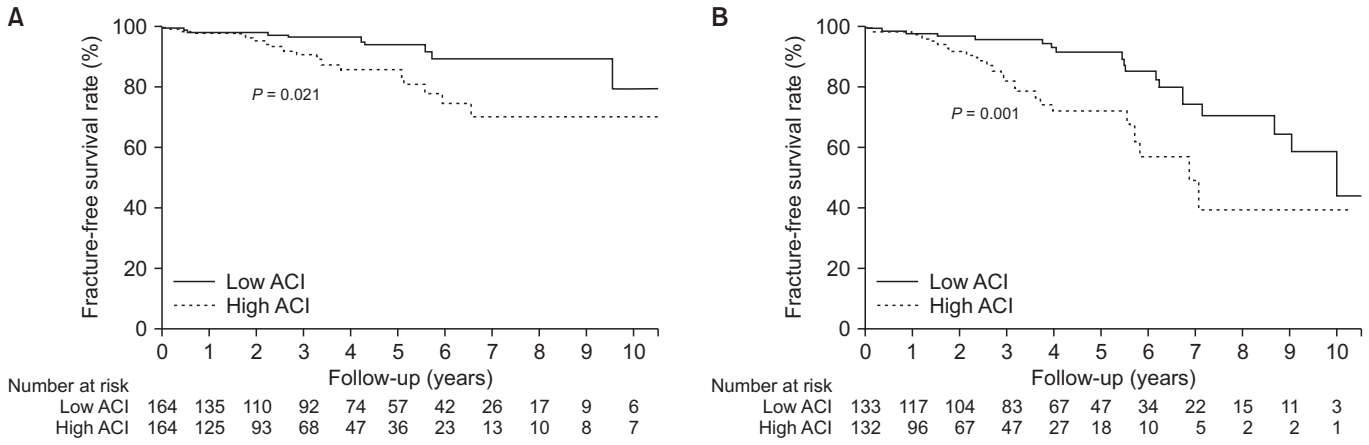

Figure 4. Fracture-free survival rates according to the aortic calcification index (ACI) in each sex (Kaplan-Meier curves). (A) In males, the high ACI group showed a lower fracture-free survival rate compared with the low ACI group (P = 0.021). (B) In females, the fracture-free survival rate was significantly lower in the high ACI group compared with the low ACI group (P = 0.001).

premenopausal female patients, and postmenopausal female patients and a significant difference was noted between the three groups (P = 0.008). The 10 year fracture-free survival rates for premenopausal females and postmenopausal females were 56.8% and 38.4%, respectively. The fracture-free survival rate was significantly lower in postmenopausal females compared to males (P = 0.002). However the fracture-free survival rates were not different between males and premenopausal females (P = 0.550), and between premenopausal females and postmenopausal females (P = 0.181).

Sex-specific relationships between VC and fracture

The risk of fracture was compared according to sex and ACI using Kaplan–Meier curves. Fig. 4 shows the fracture-free survival in the low and high ACI groups in each sex. In both male (Fig. 4A) and female (Fig. 4B) patients, the 10 year fracture-free survival rate was significantly lower in the high ACI group compared with the low ACI group (male, 70.1% versus 79.6%, respectively; P = 0.021; female, 39.4% versus 44.0%, respectively; P = 0.001).

Table 4 shows the Cox regression analysis conducted to evaluate the HR and 95% CI for incident fracture in the whole study group. In univariate analysis, both the log ACI (HR, 1.986; P < 0.001) and high ACI group (HR, 2.336; P = 0.001) showed a statistically significant association with fracture. In multivariate analysis that included ACI as a continuous variable (Model 1), the association of log ACI with fracture remained statistically significant (HR, 1.712; P = 0.011). In multivariate analysis that included ACI as a categorical variable (Model 2), the association of a high ACI group with fracture was not significant. There was a significant interaction between the log ACI and sex for incident fracture (P for interaction < 0.001). The interaction between the high ACI group and sex for fracture was also significant (P for interaction = 0.005).

Table 5 shows the Cox regression analysis for incident fracture in male patients. In univariate analysis, both the log ACI (HR, 1.857; P = 0.036) and high ACI group (HR, 2.432; P = 0.025) showed a statistically significant association with fracture. In multivariate analyses (Models 1and 2), the HRs of the log ACI and high ACI group were not significant.

Table 6 shows the Cox regression analysis for incident fracture in female patients. In univariate analysis, the HRs of the log ACI (HR, 2.017; P = 0.007) and high ACI group (HR, 2.645; P = 0.002) were statistically significant. In multivariate analyses (Models 1 and 2), the significant association remained robust (log ACI: HR, 1.768; P = 0.035; high ACI group: HR, 2.720; P = 0.003).

Discussion

This study shows that VC was significantly associated with incident fracture in female patients with ESRD after adjusting for multiple covariates, while this relationship was not robust in male patients. Although previous reports have shown that VC is a risk factor for fracture in ESRD patients [9,10], a sex-specific association had not

Table 4. Predictors for incident fracture in all patients

	Univariate		Multivariate (Model 1)		Multivariate (Model 2)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Female	1.995 (1.238–3.215)	0.005	2.134 (1.276–3.569)	0.004	2.180 (1.305–3.644)	0.003
Age (per 1 yr)	1.034 (1.014–1.055)	0.001	–	–	1.031 (1.009–1.054)	0.005
Diabetes mellitus	2.256 (1.353–3.762)	0.002	2.187 (1.240–3.856)	0.007	2.420 (1.391–4.210)	0.002
CVD	1.616 (0.909–2.875)	0.102				
Smoking	0.450 (0.229–0.883)	0.020	–	–	–	–
Previous fracture	0.049 (0.000–31901)	0.659				
BMI (per 1 kg/m^2)	1.028 (0.972–1.087)	0.330				
Parathyroidectomy	0.845 (0.261–2.734)	0.845				
RAAS blocker	0.826 (0.488–1.399)	0.826				
Ca-based P-binder	0.621 (0.389–0.991)	0.046	–	–	–	–
Non-Ca-based P-binders	0.526 (0.269–1.028)	0.060				
Vitamin D analogue	0.731 (0.423–1.265)	0.263				
Corticosteroid	0.704 (0.438–1.131)	0.704				
Hemoglobin (per 1 g/dL)	1.081 (0.949–1.232)	0.242				
Albumin (per 1 g/dL)	1.010 (0.670–1.524)	0.962				
Intact PTH (per 1 pg/mL)	0.998 (0.997–1.000)	0.018	–	–	–	–
Alkaline phosphatase (per 1 U/L)	1.001 (0.999–1.002)	0.287				
Calcium × Phosphorus product (per 1 mg^2/dL^2)	0.990 (0.973–1.008)	0.990				
hs-CRP (per 1 mg/L)	0.996 (0.987–1.005)	0.996				
RKF (per 1 mL/min/1.73 m^2)	1.036 (1.001–1.073)	0.042	–	–	–	–
Log ACI	1.986 (1.363–2.895)	< 0.001	1.712 (1.134–2.583)	0.011		
High ACI group	2.336 (1.448–3.768)	0.001			–	–

Dashes indicate that the variable did not enter the multivariate model.

ACI, aortic calcification index; BMI, body mass index; Ca-based P-binder, calcium-based phosphate-binders; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; non-Ca-based P-binders, non-calcium-based phosphate-binders; PTH, parathyroid hormone; RAAS, renin-angiotensin-aldosterone system; RKF, residual kidney function.

Model 1: including Log ACI and other variables with statistical significance in univariate analysis. Model 2: including High ACI group and other variables with statistical significance in univariate analysis.

been demonstrated. Therefore, these findings suggest that ACI, a marker of VC, may be a reliable marker for future fracture development in female patients with ESRD, although its role appears to be less valuable in male patients.

In this study, Kaplan–Meier analysis showed that both male and female patients with high ACI had lower fracture-free survival rates than those with low ACI. Previous studies have shown an association between VC and low bone mineral density (BMD) or bone mass in CKD patients [6,7,22]. Osteoporosis and VC are closely related because they share pathogenic factors, such as inflammation and vitamin D, vitamin K, and Klotho deficiencies [23]. Renal osteodystrophy, which is the bone component of CKD-MBD, affects bone quality as well as bone quantity [24]. We have previously reported that patients with ESRD have abnormal bone microarchitecture, as assessed by the trabecular bone score [25]. A recent report showed that VC was associated with a low trabecular bone score in ESRD patients [8]. In addition, in patients with ESRD, VC is associated with lower serum PTH levels and histomorphometric features of low bone activity and adynamic bone disease [5]. Similarly, the high ACI groups in the current study showed lower intact PTH levels than the low ACI groups in both sexes. Altogether, these findings suggest that ESRD patients with more severe VC have a higher risk of fracture as a result of abnormal bone quantity and bone quality.

In the current study, the association between a high ACI and fracture was significant in female patients with ESRD

Table 5. Predictors for incident fracture in male patients

	Univariate		Multivariate (Model 1)		Multivariate (Model 2)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (per 1 yr)	1.042 (1.009–1.076)	0.013	1.042 (1.009–1.076)	0.013	1.042 (1.009–1.076)	0.013
Diabetes mellitus	2.136 (0.939–4.860)	0.070				
CVD	2.670 (1.165–6.117)	0.020	–	–	–	–
Smoking	0.757 (0.345–1.664)	0.489				
Previous fracture	0.049 (0.000–3.310)	0.863				
BMI (per 1 kg/m^2)	1.005 (0.910–1.109)	0.927				
Parathyroidectomy	0.047 (0.000–10088)	0.625				
RAAS blocker	0.611 (0.275–1.353)	0.224				
Ca-based P-binder	0.898 (0.414–1.947)	0.785				
Non-Ca-based P-binders	0.771 (0.312–1.904)	0.573				
Vitamin D analogue	1.495 (0.699–3.199)	0.300				
Corticosteroid	0.840 (0.397–1.777)	0.646				
Hemoglobin (per 1 g/dL)	1.106 (0.910–1.344)	0.310				
Albumin (per 1 g/dL)	0.837 (0.438–1.599)	0.590				
Intact PTH (per 1 pg/mL)	1.000 (0.998–1.002)	0.824				
Alkaline phosphatase (per 1 U/L)	0.999 (0.995–1.003)	0.676				
Calcium × Phosphorus product (per 1 mg^2/dL^2)	0.972 (0.942–1.004)	0.089				
hs-CRP (per 1 mg/L)	0.984 (0.959–1.009)	0.210				
RKF (per 1 mL/min/1.73 m^2)	0.991 (0.917–1.071)	0.817				
Log ACI	1.857 (1.042–3.312)	0.036	–	–		
High ACI group	2.432 (1.118–5.289)	0.025			–	–

Dashes indicate that the variable did not enter the multivariate model.

ACI, aortic calcification index; BMI, body mass index; Ca-based P-binder, calcium-based phosphate-binders; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; non-Ca-based P-binders, non-calcium-based phosphate-binders; PTH, parathyroid hormone; RAAS, renin-angiotensin-aldosterone system; RKF, residual kidney function.

Model 1: including Log ACI and other variables with statistical significance in univariate analysis. Model 2: including High ACI group and other variables with statistical significance in univariate analysis.

after adjusting for multiple confounding factors. However, in male patients with ESRD, the ACI did not show a significant association with fracture in the multivariate analyses. Previous reports have shown the protective role of estrogens against VC [26]. The prevalence of subclinical and clinical CVD increases within the first decade after menopause [27], and early estrogen treatment reduces coronary artery calcification [28] and coronary heart disease risk in postmenopausal females [27]. Estrogen decreases proliferation of vascular smooth muscle cells in animal and human models [29]. Estrogen also prevents the development of atherosclerotic plaques, and inhibits VC via the vascular RANKL system, which is a common osteoporosis and VC mechanism [30]. In a longitudinal study of a Framingham Heart Study cohort, progression of abdominal aortic calcification was associated with greater bone loss in females, but not in male patients [31]. Similarly, in a population-based prospective cohort study of elderly male and female subjects (Rotterdam study), there was a significant association between the progression of coronary artery calcification and BMD in females, but not in males [32]. In a stratified analysis, the association between BMD loss and coronary artery calcification was particularly evident in female patients with lower estradiol levels. These findings implicate that the female-specific association between VC and osteoporosis is related to estrogen deficiency.

Estrogens are the main female sex steroids, and they also have a regulatory role in bone metabolism in patients with CKD [33]. Female hemodialysis patients have been reported to have lower BMD values than males, probably as a result of fluctuations in the menstrual cycle

Table 6. Predictors for incident fracture in female patients

	Univariate		Multivariate (Model 1)		Multivariate (Model 2)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (per 1 yr)	1.025 (1.004–1.055)	0.025	–	–	–	–
Diabetes mellitus	2.473 (1.283–4.767)	0.007	2.106 (1.043–4.251)	0.038		
CVD	1.009 (0.445–2.287)	0.983				
Smoking	0.047 (0.000–55.158)	0.396				
Previous fracture	0.048 (0.000–39587)	0.663				
BMI (per 1 kg/m^2)	1.037 (0.970–1.110)	0.285				
Parathyroidectomy	0.735 (0.221–2.448)	0.616				
RAAS blocker	1.074 (0.528–2.184)	0.844				
Ca-based P-binder	0.503 (0.275–0.919)	0.026	–	–	–	–
Non-Ca-based P-binders	0.418 (0.147–1.186)	0.101				
Vitamin D analogue	0.387 (0.162–0.925)	0.033	–	–	–	–
Corticosteroid	0.621 (0.335–1.152)	0.131				
Hemoglobin (per 1 g/dL)	1.087 (0.908–1.301)	0.366				
Albumin (per 1 g/dL)	1.101 (0.648–1.871)	0.721				
Intact PTH (per 1 pg/mL)	0.997 (0.995–0.999)	0.003	–	–	–	–
Alkaline phosphatase (per 1 U/L)	1.001 (0.999–1.002)	0.273				
Calcium × Phosphorus product (per 1 mg^2/dL^2)	1.001 (0.980–1.023)	0.908				
hs-CRP (per 1 mg/L)	1.000 (0.991–1.009)	0.970				
RKF (per 1 mL/min/1.73 m^2)	1.057 (1.008–1.108)	0.022	1.056 (1.001–1.114)	0.045	1.070 (1.017–1.126)	0.010
Menopause	1.744 (0.765–3.977)	0.186				
Log ACI	2.017 (1.216–3.345)	0.007	1.768 (1.041–3.005)	0.035		
High ACI group	2.645 (1.426–4.906)	0.002			2.720 (1.419–5.214)	0.003

Dashes indicate that the variable did not enter the multivariate model.

ACI, aortic calcification index; BMI, body mass index; Ca-based P-binder, calcium-based phosphate-binders; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; non-Ca-based P-binders, non-calcium-based phosphate-binders; PTH, parathyroid hormone; RAAS, renin-angiotensin-aldosterone system; RKF, residual kidney function.

Model 1: including Log ACI and other variables with statistical significance in univariate analysis. Model 2: including High ACI group and other variables with statistical significance in univariate analysis.

[34,35]. In female ESRD patients, the skeletal sensitivity to PTH was increased compared with male patients [36]. The bone microarchitecture deteriorated to a greater extent in female ESRD patients than in males, and the reduction in trabecular parameters correlated with the severity of hyperparathyroidism only in females [37]. Therefore, the estrogen deficiency in CKD may have a greater effect on the bone health in females than in males because of the interaction with the PTH.

In males, androgens are converted to estrogens by the aromatase enzyme, and the skeletal health is affected by both estrogens and androgens. However, the role of estrogen on VC in males has not yet been reported, and the estrogen signaling pathway and expression of estrogen receptor genes in males differ from those in females. Androgens have important actions on peak bone mass acquisition and skeletal maintenance. Androgens also exert anti-fracture effects via extraskeletal factors such as muscle mass/strength and risk of falls [38]. Currently, the results on the association between androgens and VC are conflicting; some studies have reported that androgen (testosterone) causes VC, while others reported that androgen had an inhibitory effect on VC [39]. Therefore, in males, androgen may be a confounding factor for VC and fracture. Overall, early menopause and estrogen deficiency in female ESRD patients may have affected VC and bone health more severely than in male patients, and poor treatment for osteoporosis, because of the limited use of anti-osteoporotic drugs in patients with CKD, may have accelerated the occurrence of fractures [19]. This re-

lationship may be reflected as a female-specific association between ACI and fracture in the current study.

There are some limitations to the current study. First, it was a retrospective analysis of data from a single center that was conducted by reviewing medical records. Therefore, center-specific effects cannot be excluded and there may be a bias. A larger scale study is required to generalize the results. Second, the effect of dialysis adequacy could not be assessed, as we did not assess dialysis adequacy at the initiation of dialysis. Third, BMD data were not included in the analysis as this parameter was not routinely evaluated. Fourth, data on the use of estrogen treatment in females and sex hormone levels were limited and were therefore not included in the analysis. Finally, the pathophysiologic mechanism of the sex-specific association between VC and fracture was not demonstrated.

In conclusion, the results of this study support the link between VC and fracture in female ESRD patients. The significant association in females, but not in males, after controlling for various factors suggests that the association between VC and fracture may be sex-specific in patients with ESRD. Further population-based, longitudinal studies are required to generalize these results.

Conflicts of interest

All authors have no conflicts of interest to declare.

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Authors' contributions

Yun Jung Nam participated in the data collection and wrote the manuscript. So Yeon Hwang, Da Won Kim, and Dongryul Kim participated in the data collection. Seok Joon Shin provided technical support. Hye Eun Yoon participated in the study design, conception, and interpretation of data, performed the statistical analysis, and helped to draft the manuscript. All authors read and approved the final manuscript.

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