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Original Article

Cardiovascular

Coronary artery calcification in Korean patients with incident dialysis

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Abstract

Introduction: Patients with chronic kidney disease have an extremely high risk of developing cardiovascular disease (CVD). In patients with end-stage renal disease (ESRD), coronary artery calcification (CAC) is associated with increased mortality from CVD.

Methods: The present study aimed to investigate the risk factors for CAC in Korean patients with incident dialysis. Data on 423 patients with ESRD who started dialysis therapy between December 2012 and March 2014 were obtained from 10 university-affiliated hospitals. CAC was identified by using noncontrast-enhanced cardiac multidetector computed tomography. The CAC score was calculated according to the Agatston score, with CAC-positive subjects defined by an Agatston score >0.

Findings: Patients' mean age was 55.6 ± 14.6 years, and 64.1% were men. The CAC-positive rate was 63.8% (270 of 423). Results of univariate analyses showed significant differences in age, sex, etiology of ESRD and comorbid conditions according to the CAC score. However, results of multiple regression analysis showed that only a higher age was significantly associated with the CAC score. Receiver operating characteristic curves showed that the sensitivity and specificity of L-spine radiography for diagnosing CAC were 56% and 91%, respectively, for diagnosing CAC (area under the curve, 0.735).

Discussion: CAC was frequent in patients with incident dialysis, and multiple regression analysis showed that only age was significantly associated with the CAC score. In addition, L-spine radiography could be a helpful modality for diagnosing CAC in patients with incident dialysis.

Key words: Cardiovascular disease, coronary artery calcification, end-stage renal disease, L-spine radiography

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INTRODUCTION

End-stage renal disease (ESRD) is one of the most important risk factors for the development of cardiovascular disease (CVD).[1] Vascular calcification has been identified as a critical surrogate marker to predict cardiovascular complications.[2] In particular, it has been shown that coronary artery calcification (CAC) is associated with mortality from CVD in patients with ESRD.[3,4] A previous study that was conducted to determine the extent of CAC using electron beam computed tomography (EBCT) showed that CAC in patients with ESRD was more common and progressive than in control subjects with normal renal function.[5] Another study showed that CAC was found in approximately 80% to 90% of adult patients with hemodialysis.[6] Patients with evidence of at least mild CAC had significant progression, whereas new patients with hemodialysis and no evidence of CAC showed little evidence of disease development.[6] In addition, the clinical management of chronic kidney disease (CKD)-mineral and bone disorder (MBD) is typically based on repeated measurement of laboratory markers, specifically the parathyroid hormone (PTH), calcium, and phosphorus levels, and maintaining these MBD markers within specific target ranges.[7–9] However, there are few studies have assessed the correlation between CAC measured by simple imaging tests and EBCT in patients with hemodialysis.[10]

Thus, in this study, we aimed to determine the risk factors for CAC and the use of calcium-based phosphate binders in patients with incident dialysis. Additionally, we examined the relationship between CAC and abdominal aortic calcification identified by using L-spine radiography.

MATERIALS AND METHODS

Study population and data collection

The present cross-sectional, multicenter, observational study enrolled 446 patients from 10 hospitals between December 2012 and March 2014 in Korea. All patients who participated in the study provided written informed consent and agreed with the study protocol. Inclusion criteria were as follows: patients aged ≥ 20 years, and those who started maintenance dialysis within 3 months before study enrollment. Exclusion criteria were as follows: patients with a history of coronary artery stenting or artery bypass grafting; those with anticipated low-quality cardiac imaging due to tachycardia (>90 beats/min) including atrial fibrillation or flutter; patients with an artificial valve or pacemaker; those undergoing stent implantation in the esophagus, trachea, or main bronchus; patients who were pregnant or had childbearing potential; and those who participated in another clinical drug trial.

Clinical assessment

Demographic and clinical data, including age, sex, history of smoking, history of alcohol consumption, etiology of ESRD, and comorbidities were collected at baseline. The use of medications, including an antihypertensive agent, lipid-lowering agent, and calcium-based phosphate binders, was assessed. In addition, we reviewed the patients' previous drug history within 1 year from the time of enrollment, and we calculated the total dose of elemental calcium provided by the calcium-based phosphate binders.

At the time of enrollment, we assessed the patients' systolic and diastolic blood pressures. At each participating hospital, non-contrast cardiac multi-detector computed tomography (MDCT) and lateral L-spine radiography were performed within 30 days from the time of enrollment.

The primary objective was to evaluate CAC. Secondary objectives included the risk factors for CAC, sensitivity and specificity of lateral L-spine radiography based on cardiac MDCT, and the correlation between the two test methods. Additionally, the association between calcium-based phosphate binders and CAC was investigated. To analyze the primary objective, the CAC score was calculated according to the Agatston score, after CAC was identified by using noncontrast-enhanced cardiac MDCT.[11] CAC-positive subjects were defined by an Agatston score > 0. To analyze the secondary objectives, abdominal aortic calcification was identified by using L-spine radiography, and it evaluated according to Kauppila score.[12,13]

Statistical analysis

Descriptive statistics were used to analyze all the recorded data. Continuous variables were analyzed by using following statistical parameters: N, mean, and standard deviation. Categorical variables are presented as a frequency distribution and percentage. Differences in the CAC-positive rate among the baseline characteristics were tested using the χ^2 test for categorical variables. For the results, 95% confidence intervals were calculated and tested with a two-sided 5% level of significance. The distribution of the Agatston scores were not normally distributed, so these data are presented as a median with

Interquartile ranges. The CAC scores were categorized into four groups according to the CAC score[14,15]: no calcification (CAC score ≤ 0 AU), mild to moderate ($0 <$ CAC score ≤ 400 AU), severe ($400 <$ CAC score ≤ 1000 AU), and very severe (CAC score > 1000 AU). The distribution of CAC severity is presented as a frequency and percentage. To assess associations between the CAC scores and demographic data, univariate and multiple linear regression analyses were performed. Variables that had a significant association (P value ≤ 0.2) in the univariate analysis were included in the multiple linear regression models. The accuracy of noncontrast-enhanced cardiac MDCT and L-spine radiography was evaluated according to the area under the receiver operating characteristic (ROC) curve. All statistical analyses were performed using SAS, version 9.1 (SAS Institute, Inc., Cary, NC, USA).

Ethics statement

The study protocol complies with the Declaration of Helsinki and it was approved by the Institutional Review Board of Seoul National University Hospital (approval no.: No. H-1209-009-424).

RESULTS

Baseline characteristics

Among 446 patients screened from 10 hospitals, 423 were eligible for analysis. Demographic data, medication use, and laboratory values of these patients are shown in Table 1. Among 423 patients, 64.1% were men, and the mean age was 55.6 ± 14.6 years. Two hundred fifty-one participants (59.3%) were diagnosed diabetes mellitus (DM), while 393 (92.9%) with hypertension (HTN), and 56 (13.2%) with CVD. Two hundred ninety-three patients (69.3%) have received calcium-based phosphate binder, with an average cumulative total dose of calcium of 1,057 ± 731 mg/day.

Association between the clinical parameters and CAC

The distribution of Agatston scores and severity of CAC in the 423 patients are shown in Figure 1. Among a total of 423 dialysis patients, 270 (63.83%) were CAC positive.

Significant differences according to the CAC score were observed for age, sex, etiology of ESRD, and other comorbid diseases (Table 2). However, multiple regression

Table 1 Demographic data characteristics

Variables	Total (N = 423)
Age (years)[a]	55.6 ± 14.6
Sex, male (N, %)	271 (64.1)
SBP (mmHg)[a]	138.2 ± 20.3
DBP (mmHg)[a]	77.8 ± 12.4
Smoking	421 (99.5)
Current smoker	57 (13.5)
Ex-smoker	118 (28.0)
Non-smoker	246 (58.4)
Daily cigarette consumption (stick/day)[a]	16.3 ± 10.6
Smoking period (year)[a]	23.7 ± 12.9
Alcohol, yes (N, %)	85 (20.1)
Etiology of ESRD	423 (100)
Diabetes mellitus	222 (52.5)
Hypertension	70 (16.5)
Glomerular nephritis	59 (14.0)
Polycystic kidney disease	7 (1.7)
Others	65 (15.3)
Comorbid conditions	423 (100)
Diabetes mellitus (N, %)	251 (59.34)
Hypertension (N, %)	393 (92.91)
Cardiovascular disease (N, %)	56 (13.24)
Peripheral vascular disease	13 (3.07)
Hyperlipidemia	186 (43.97)
Others	99 (23.41)

[a]Data are expressed as mean ± standard deviation.
DBP = diastolic blood pressure; ESRD = end stage renal disease; SBP = systolic blood pressure.

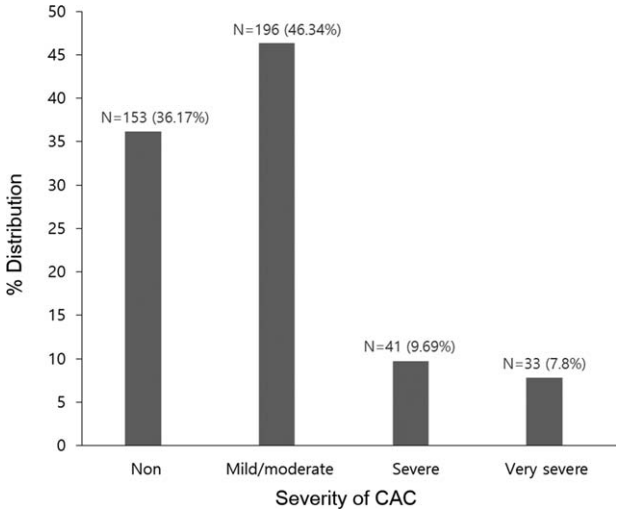

Figure 1 The distribution of Agatston scores and severity of coronary artery calcification.

Table 2 Univariate analysis on the difference of CAC-positive rate

			CAC-positive (N, %)	P value
Age	<30 years		0 (0.00)	<0.001
	30-40 years		15 (31.91)	
	40-50 years		27 (39.71)	
	50-60 years		92 (67.65)	
	>60 years		136 (87.18)	
Gender	Male		188 (69.37)	0.001
	Female		82 (53.95)	
Smoking	Current smoker		41 (71.93)	0.275
	Ex-smoker		77 (65.25)	
	Non-smoker		150 (60.98)	
Alcohol	Yes		50 (58.82)	0.293
	No		217 (64.97)	
Cause of ESRD	Diabetes mellitus		177 (79.73)	<0.001
	Hypertension		37 (52.86)	
	Glomerulonephritis		25 (42.37)	
	Polycystic kidney disease		3 (42.86)	
	Others		28 (43.07)	
Comorbid disease	Diabetes	Yes	200 (79.68)	<0.001
		No	70 (40.70)	
	Hypertension	Yes	258 (65.65)	0.005
		No	12 (40.00)	
	Cardiovascular disease	Yes	46 (82.14)	0.002
		No	222 (60.82)	
	Peripheral vascular disease	Yes	12 (92.31)	0.029
		No	256 (62.75)	
	Hyperlipidemia	Yes	125 (67.20)	0.209
		No	144 (61.28)	
Use of antihypertensive agent	Yes		255 (64.72)	0.159
	No		15 (51.72)	
Use of lipid-lowering agent	Yes		127 (68.28)	0.091
	No		143 (60.34)	
Use of calcium based phosphate binders	Yes		187 (63.82)	0.996
	No		83 (63.85)	

ESRD = end stage renal disease.

analysis produced no results due to an inadequate model and unavailable maximum likeliness estimation.

To evaluate the effect of potential factors on the CAC score, univariate analyses were performed. The median CAC score was significantly higher in elderly male patients and in those with comorbid diseases, such as DM, HTN, or CVD. However, the use of calcium-based phosphate binders was not associated with the increase in the CAC score (Table 3). In addition, the cumulative dose of calcium was not significantly correlated with the CAC score (regression coefficient [*B*] = −0.04, P = 0.381).

Multiple regression analysis was based on univariate analyses, and the results showed that only age was significantly associated with the CAC score. Additionally, the CAC score increased by up to 10.32 as age increased by 1 year ($P < 0.001$) (Table 4).

Comparison between MDCT and L-spine radiography

The imaging accuracy (sensitivity and specificity) of L-spine radiography was determined based on noncontrast-enhanced cardiac MDCT. The sensitivity and specificity of L-spine radiography were 56% and 91%, respectively, with an area under the ROC curve of 0.7348 (Figure 2). The linear relationship between noncontrast-enhanced

Table 3 Univariate analysis on the difference of CAC score

			N	Median with Interquartile ranges	P value
Age[b]	<30 years		16	0.00 (0.00–0.00)	<0.001
	30-40 years		47	0.00 (0.00–8.90)	
	40-50 years		68	0.00 (0.00–22.40)	
	50-60 years		136	28.80 (0.00–174.25)	
	>60 years		156	157.20 (33.45–567.00)	
Gender[a]	Male		271	44.10 (0.00–258.70)	0.0041
	Female		152	5.15 (0.00–154.05)	
Smoking[b]	Current smoker		57	46.50 (0.00–186.30)	0.2310
	Ex-smoker		118	49.35 (0.00–321.70)	
	Non-smoker		246	10.65 (0.00–168.60)	
Alcohol[b]	Yes		85	15.40 (0.00–286.30)	0.541
	No		334	31.35 (0.00–186.30)	
Cause of ESRD[b]	Diabetes		222	83.60 (4.20–312.80)	<0.001
	Hypertension		70	1.80 (0.00–169.10)	
	Glomerulonephritis		59	0.00 (0.00–49.20)	
	Polycystic kidney disease		7	0.00 (0.00–27.50)	
	Others		65	0.00 (0.00–143.10)	
Comorbid disease	Diabetes mellitus[a]	Yes	251	84.20 (4.50–312.80)	<0.001
		No	172	0.00 (0.00–60.00)	
	Hypertension[a]	Yes	393	39.20 (0.00–209.70)	0.001
		No	30	0.00 (0.00–22.50)	
	Cardiovascular disease[a]	Yes	56	137.25 (9.90–640.00)	<0001
		No	365	15.70 (0.00–169.40)	
	Peripheral vascular disease[b]	Yes	13	110.60 (26.00–588.60)	0.061
		No	408	22.30 (0.00–189.45)	
	Hyperlipidemia[b]	Yes	186	45.60 (0.00–259.4)	0.199
		No	235	15.30 (0.00–169.1)	
Use ofantihypertensive agent[a]	Yes		394	36.20 (0.00–202.20)	0.026
	No		29	1.20 (0.00–46.50)	
Use of lipid-lowering agent[a]	Yes		186	45.60 (0.00–254.30)	0.091
	No		237	20.50 (0.00–169.40)	
Use of calcium based phosphate binders[a]	Yes		293	31.60 (0.00–187.40)	0.982
	No		130	21.00 (0.00–237.90)	

[a]Wilcoxon rank sum test.
[b]Kruskal-Wallis test were applied.

Table 4 Multiple regression analysis on factors that may associated with CAC score

	Parameter estimation	Standard error	P value
Age	10.32	1.94	<0.001
Male	98.45	56.31	0.081
Diabetes mellitus	95.84	56.99	0.093
Hypertension	45.07	137.54	0.743
Cardiovascular disease	72.02	81.03	0.375
Peripheral vascular disease	110.13	157.65	0.485
Hyperlipidemia	47.58	65.41	0.467
Use of antihypertensive agent	82.36	137.02	0.548
Use of lipid-lowering agent	−8.54	65.44	0.896

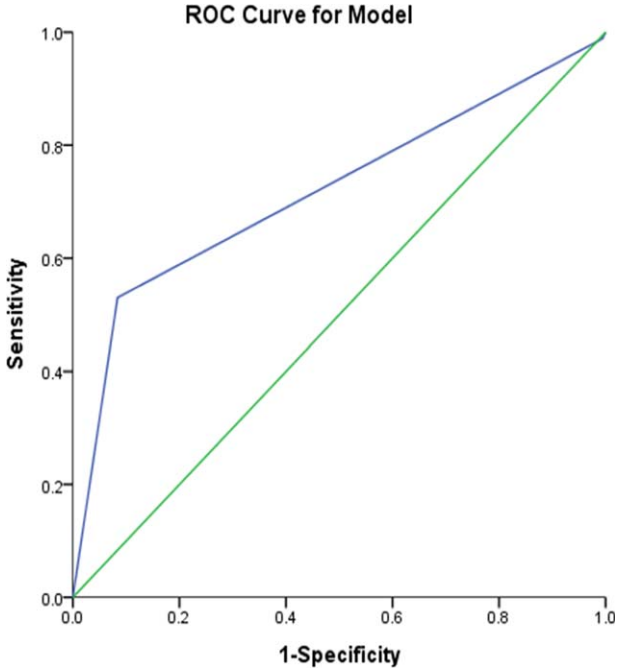

Figure 2 Receiver operating characteristic curve for detecting coronary artery calcification by L-spine radiography. [Color figure can be viewed at wileyonlinelibrary.com.]

cardiac MDCT and L-spine radiography was statistically significant ($P < 0.0001$), with a correlation coefficient of 0.52 (Table 5).

DISCUSSION

Age was found to be strongly and independently associated with CAC. We also found that L-spine radiography correlated with non-contrast-enhanced cardiac MDCT.

Vascular calcification is a common complication in CKD, and it is a predictor of subsequent vascular mortality.[16] There are two main types of vascular calcification, which have different clinical consequences.[17,18] Intimal calcification is seen with advancing age, HTN, dyslipidemia, and smoking, and it develops into atherosclerotic vascular disease.[19] This patchy, discontinuous process involves inflammatory macrophages and vascular smooth muscle cells in lipid-rich regions of the atherosclerotic plaque. Medial calcification is associated with aging, DM, and ESRD, not atherosclerotic plaque.[20] It involves sheet-like calcification in the tunica media with concentric thickening of the intima, and it was originally assumed to be a degenerative age-related problem of the vessel wall[21] without involvement of the intima. However, in adult patients with CKD, varying combinations of intimal and medial calcification may coexist because a number of traditional Framingham risk factors for atherosclerosis are also present.[22] The Agatston score is the most widely used and best established measure of CAC[23] in the general population and in patients with CKD.[24,25] Therefore, in this study, we used the Agatston score to calculate the CAC score, which is closely associated with CVD. In univariate analyses, the CAC-positive rate and score were significantly increased in elderly patients and in those with comorbid conditions, such as DM, HTN, and CVD. However, results of adjusted multiple regression analysis showed that only age was significantly associated with the CAC score. This result may be due to the small number of patients and possible residual confounding factors.

Although the associations between aortic calcification and CAC have been described previously,[10,26,27] there is a paucity of data on the imaging accuracy of L-spine radiography for identifying CAC-positive subjects.[10] CAC generally occurs in the intimal layer. However, calcification in noncoronary arteries, such as the aorta, can occur in both the intimal and medial tunica layers of the artery.[20] Aortic calcification is also independently associated with the risk of coronary heart disease.[28] In our study, L-spine radiography, which is used to assess aortic calcification, demonstrated a good ability to identify CAC-positive subjects, and it was correlated with noncontrast-enhanced cardiac MDCT. L-spine radiography can be a helpful tool for identifying CAC and predicting CVD in patients with ESRD because of these aforementioned reasons, and it is inexpensive, non-invasive, and simple to interpret.

Disturbed mineral metabolism and resulting hyperphosphatemia has been suggested to contribute to increased vascular calcification in CKD[21] and to predict cardiovascular mortality in patients with dialysis.[29] Calcium-based phosphate binders have been used for

Table 5 Correlation analysis between non-contrast cardiac MDCT and L-spine X-ray

	N	Median with Interquartile ranges	Correlation coefficient	P value
CAC score by cardiac MDCT	423	27.50 (0.00–196.70)	0.52	<0.001
AAC score by L-spine x-ray	419	0.00 (0.00–3.00)		

AAC = abdominal aortic calcification; CAC = coronary artery calcification; MDCT = multi-detector computed tomography.

decades in patients undergoing dialysis[7,30] and they are the most commonly used phosphate binders in contemporary practice worldwide.[31] However, the use of calcium-based phosphate binders has been questioned because the calcium intake is higher in patients on dialysis with CAC than in those without CAC,[5] and the dose of calcium-based phosphate binders correlates with the severity of CAC.[16,32] Yet, there is no definite guideline for the optimal use of oral phosphate binders in patients with ESRD. We evaluated the association between CAC and calcium-based phosphate binders, and we found that the cumulative dose of calcium provided by calcium-based phosphate binders was not correlated with the CAC score. However, this result should be interpreted with caution. We did not analyze other laboratory findings, such as the phosphorous or parathyroid hormone level, and we only reviewed the patients' previous calcium-based phosphate binder history within 1 year from the baseline, not total period.

There are a number of limitations to this study, including the cross-sectional design, relatively small number of patients, and deficiency of laboratory information. Nevertheless, the strengths of our study include its multicenter design and broad, detailed characteristics of the participants.

In conclusion, CAC is more frequent in older patients irrespective of sex, comorbidities, and calcium-based phosphate binders. In addition, L-spine radiography can be a helpful modality for diagnosing CAC in patients with incident dialysis.

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