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Predictors of abdominal aortic calcification progression in patients with chronic kidney disease without hemodialysis

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ABSTRACT

Background and aims: Abdominal aortic calcification (AAC) is an important predictor of cardiovascular mortality in patients with chronic kidney disease (CKD). However, little is known regarding AAC progression in these patients. This study aimed to identify risk factors associated with AAC progression in patients with CKD without hemodialysis.

Methods: We recruited 141 asymptomatic patients with CKD without hemodialysis [median estimated glomerular filtration rate (eGFR), 40.3 mL/min/1.73 m^2] and evaluated the progression of the abdominal aortic calcification index (ACI) over 3 years. To identify risk factors contributing to the rate of ACI progression, the associations between baseline clinical characteristics and annual change in ACI for each CKD category were analyzed. The annual change of ACI (ΔACI/year) was calculated as follows: (second ACI − first ACI)/duration between the two evaluations.

Results: Median ΔACI/year values significantly increased in advanced CKD stages (0.73%, 0.87%, and 2.24%/year for CKD stages G1-2, G3, and G4-5, respectively; p for trend = 0.041). The only independent risk factor for AAC progression in mild to moderate CKD (G1-3, eGFR ≥ 30 mL/min/1.73 m^2) was pulse pressure level (β = 0.258, p = 0.012). In contrast, parathyroid hormone (PTH) level was significantly correlated with ΔACI/year (β = 0.426, p = 0.007) among patients with advanced CKD (G4-5, eGFR < 30 mL/min/1.73 m^2).

Conclusions: This study suggests that the AAC progression rate was significantly accelerated in patients with advanced CKD. In addition, measuring PTH is useful to evaluate both bone turnover and AAC progression in patients with advanced CKD.

1. Introduction

Chronic kidney disease (CKD) is widely accepted as an independent risk factor for unfavorable health outcomes that include cardiovascular disease [1–3]. Moreover, patients with CKD frequently experience cardiovascular events associated with accelerated athero- and arteriosclerosis prior to the development of end-stage kidney disease [4,5]. Thus, risk stratification for preventing cardiovascular events is clinically important to improve CKD prognosis.

The mechanisms underlying the high risk for cardiovascular mortality in populations with CKD remain to be elucidated. However, vascular calcification, a major component of CKD–mineral and bone disorder (CKD–MBD), is known as an important risk factor that influences cardiovascular outcomes in these patients [6,7]. Thus, recent guidelines recommend the evaluation of vascular calcification, including abdominal aortic calcification (AAC), along with mineral/bone abnormalities in patients with early stage CKD [8].

However, little is known regarding the progression of vascular calcification in patients with CKD without hemodialysis. Therefore,

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this study aimed to identify risk factors associated with AAC progression in each CKD category.

2. Materials and methods

2.1. Subjects

Between 2008 and 2010, a total of 141 asymptomatic patients with CKD without hemodialysis were recruited from the outpatient clinic of the Department of Nephrology, Nagoya University Hospital. CKD was defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2, the presence of proteinuria, or renal disease as a complication at study entry [9]. Patients with active autoimmune disease, active malignancy, or a history of abdominal aortic artery repair and stenting were excluded. The study protocol was approved by the ethics committee of the Nagoya University Hospital and conducted according to the ethical principles described in the Declaration of Helsinki. Written informed consent was obtained from all patients.

2.2. Measurement of abdominal aortic calcification index (ACI) and ΔACI/year

Each patient underwent non-contrast computed tomography (CT) at the first examination to investigate renal morphology and the degree of subclinical vascular calcification. After 3 yrs of standard medical treatment, we conducted a second examination to evaluate the progression of vascular calcification. All patients were scanned in the supine position at a 5 mm slice thickness using a 64-slice non-contrast CT scan (Siemens Medical Solutions, Forchheim, Germany). Calcification was considered to be present if an area of ≥1 mm^2 displayed a density of ≥130 Hounsfield units. The AAC score was calculated from the site where the renal artery arises to the bifurcation of the aorta into common iliac arteries. The cross-section of the abdominal aorta on each slice was radially divided into 12 sectors. ACI was calculated as follows: ACI = (total score of calcification on all slices)/12 × 1/(number of slices) × 100% [10,11]. The ΔACI/year was calculated to assess annual changes in ACI, as follows: ΔACI/year = (second ACI − first ACI)/duration between the two evaluations (years). Semi-quantitative measurement of AAC was independently conducted by two physicians who were blinded to the patient's clinical characteristics. The cutoff point for rapid ACI progression was defined as ΔACI/year 3.0%, which was the 75th percentile for the ΔACI/year in this study population.

2.3. Baseline laboratory data

After an overnight fast of 12 h, blood samples were collected from all patients. eGFR was calculated using the equation for Japanese subjects recommended by the Japanese Society of Nephrology, as follows: eGFR (mL/min/1.73 m^2) = 194 × SCr − 1.094 × age − 0.287 (×0.739, if female) [12]. eGFRs were classified according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guidelines (eGFR ≥ 90, 60–89, 45–59, 30–44, 15–29, and <15 mL/min/1.73 m^2 for stages G1, G2, G3a, G3b, G4, and G5, respectively) [13]. Urinary protein excretion was determined as the urinary protein (mg) to creatinine (g) ratio in the morning spot urine. The protein-to-creatinine ratio was classified into three categories (<0.15, 0.15–0.5, and >0.5 g/gCr: A1, A2, and A3, respectively). Serum calcium levels were corrected for albumin using the following formula: corrected calcium = total calcium + (4.0 − albumin) × 0.8, if albumin was <4.0 g/dL. Hypertension was defined as systolic blood pressure (BP) of ≥140 mmHg, diastolic BP of ≥90 mmHg, and/or receiving treatment for hypertension. According to the 2009 guidelines of the Japan Society of Hypertension, BP was measured using a mercury sphygmomanometer. At each visit, two consecutive measurements were performed with a 1 min interval after 5 min of rest in the sitting position, and the average of the two values was adopted as the final BP [14]. Diabetes mellitus (DM) was defined as the use of any anti-hyperglycemic medication, a current diagnosis of diabetes, a fasting plasma glucose concentration of >126 mg/dL, and/or a glycosylated hemoglobin concentration of ≥6.5%, according to the guidelines of the National Glycohemoglobin Standardization Program. Current smokers were defined as those who declared themselves to be active smokers during the examinations.

2.4. Statistical analyses

Continuous variables are expressed as the mean ± standard deviation or median (interquartile range) if non-normally distributed, while categorical variables are expressed as percentages. One-way ANOVA was used to statistically analyze normally distributed data (continuous variables), while the Kruskal–Wallis test was used for data with non-normal distribution. The Chi-square or Fisher's exact test was used to statistically analyze categorical data. The association between ΔACI/year and each clinical parameter was determined using the Spearman's correlation coefficient. To obtain an independent predictor for AAC progression, multivariate stepwise regression analysis was performed for each parameter as a dependent variable. A two-sided p value of <0.05 was considered statistically significant. All statistical analyses were performed using the SPSS software, version 18.0 for Windows (IBM-SPSS, Inc., Chicago, IL, USA).

3. Results

A total of 141 patients with a mean age of 69.5 ± 10.0 years, median eGFR of 40.3 mL/min/1.73 m^2 were recruited for this study. Among the subjects, 38.3% had DM and 86.5% had hypertension. Baseline clinical characteristics of study subjects with rapid and non-rapid ACI progression are shown in Table 1. There were significant differences in age, blood pressure, hemoglobin, serum albumin, serum creatinine, intact parathyroid hormone (PTH), C-reactive protein (CRP) levels, and in the prevalence of hypertension between the 2 groups. However, other variables, such as lipid profiles, and prevalence of habitual smoking were comparable among the 2 groups. Moreover, Supplementary Table 1 shows the clinical characteristics among the eGFR grades.

Representative CTs of cases with or without rapid ACI progression between the first and second examinations are shown in Fig. 1. The inter- and intra-observer variabilities of ACI were well correlated ($r = 0.97$, $p < 0.001$ and $r = 0.96$, $p < 0.001$, respectively). Overall, the median first ACI value was 16.7%. With respect to eGFRs, baseline ACI values tended to increase with CKD progression (13.5%, 13.2%, and 25.4% for stages G1-2, G3, and G4-5, respectively; p for trend = 0.27).

The mean interval period between the first and second examinations was 3.7 years, and the median ΔACI/year value was 1.08%. As shown in Fig. 2, the median ΔACI/year values significantly increased with the CKD stage (0.73%, 0.87%, and 2.24% per year for CKD stages G1-2, G3, and G4-5, respectively; $p = 0.041$). The results of univariate linear regression analyses for ΔACI/year for each CKD category are shown in Table 2. Overall, pulse BP levels, eGFR levels, intact PTH levels (log-transformed), and CRP levels (log-transformed) were positively correlated with ΔACI/year ($r = 0.213$, $p = 0.011$; $r = -0.171$, $p = 0.043$; $r = 0.194$, $p = 0.021$; and $r = 0.188$, $p = 0.025$, respectively).

The results of multivariate stepwise analysis after adjusting for

Table 1
Baseline patient characteristics stratified by ACI progression levels.

	Rapid progression		*p*
	Yes (n = 36)	No (n = 105)	
Age (years)	73.1 ± 9.2	68.3 ± 10.1	0.014
Male, n (%)	25(69)	78(74)	0.66
Body mass index (kg/m^2)	23.1 ± 3.1	23.6 ± 3.5	0.54
Hypertension, n (%)	36(100)	86(82)	0.008
Diabetes, n (%)	17(47)	37(35)	0.24
Dyslipidemia, n (%)	28(78)	77(73)	0.66
Current smoking, n (%)	5(14)	9(9)	0.52
Systolic BP, mmHg	138.6 ± 20.1	129.1 ± 16.8	0.006
Diastolic BP, mmHg	75.3 ± 12.9	75.9 ± 11.6	0.79
Pulse pressure, mmHg	63.3 ± 18.1	53.2 ± 14.2	0.001
Serum creatinine, mg/dL	1.9 ± 1.2	1.5 ± 0.8	0.043
eGFR(mL/min/1.73m^2)	37.5 ± 22.7	41.2 ± 17.0	0.29
eGFR decline/year	2.4(0.6, 4.5)	1.3(0.3, 2.6)	0.034
Urinary protein-creatinine ratio, n (%)			0.99
A1 (<0.15 g/gCr)	17(47)	48(46)	
A2 (0.15–0.49 g/gCr)	10(28)	30(29)	
A3 (≧0.50 g/gCr)	9(25)	27(25)	
Hemoglobin (g/dL)	11.7 ± 1.7	12.5 ± 2.0	0.031
Serum albumin (g/dL)	3.6 ± 0.4	3.8 ± 0.4	0.015
LDL-C (mg/dL)	105.9 ± 28.7	108.9 ± 33.6	0.64
HDL-C (mg/dL)	49.1 ± 16.8	49.3 ± 17.0	0.95
Triglycerides (mg/dL)	124(89, 193)	130(96, 182)	0.77
HbA1c (%)	6.1 ± 0.8	6.0 ± 0.9	0.70
Corrected calcium (mg/dL)	9.4 ± 0.4	9.5 ± 0.4	0.40
Phosphorus (mg/dL)	3.5 ± 0.6	3.3 ± 0.7	0.13
Intact-PTH (pg/mL)	73.3(43.5, 97.7)	47.3(35.2, 60.5)	0.002
CRP (mg/L)	1.1(0.4, 2.2)	0.7(0.3, 1.3)	0.029
Medications			
ACE-I or ARB, n (%)	29(81)	60(57)	0.016
Ca^{2+} channel blocker, n (%)	26(72)	48(46)	0.007
Beta-blocker, n (%)	10(28)	12(11)	0.031
Statin, n (%)	16(44)	36(37)	0.32
Active vitamin D, n (%)	3(17)	4(4)	0.37
Phosphate binders, n (%)	2(6)	1(1)	0.16

eGFR, estimated glomerular filtration rate; BMI, body mass index; BP, blood pressure.
LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.
PTH, parathyroid hormon CRP, C-reactive protein; ACE-I, angiotensin-converting enzyme inhibitors.
ARB, angiotensin receptor blocker.
Data are presented as means ± SD, or as numbers (percentages).

conventional risk factors for arteriosclerosis are shown in Table 3. Overall, the independent risk factors for AAC progression were intact PTH and CRP levels ($\beta = 0.206$, $p = 0.016$ and $\beta = 0.185$, $p = 0.030$). Subgroup analyses stratified by eGFR grades in patients with mild to moderate CKD (stage G1–3, eGFR $\geq$ 30 mL/min/1.73 m^2) revealed that the only independent risk factor for AAC progression was pulse pressure level ($\beta = 0.258$, $p = 0.012$). In contrast, the intact PTH level was significantly correlated with ΔACI/year ($\beta = 0.426$, $p = 0.007$) among patients with advanced CKD (stage G4-5, eGFR < 30 mL/min/1.73 m^2).

4. Discussion

The study results revealed a clear relationship between kidney function and AAC progression in patients with CKD. Furthermore, we demonstrated that risk factors for AAC progression differed in each CKD category. Specifically, the only significant risk factor for mild to moderate CKD was pulse pressure level, while risk factor for advanced CKD were PTH levels. These findings suggest that it is important to manage these risk factors to stall progression to severe vascular calcification and reduce the risk for adverse cardiovascular outcomes.

Vascular calcification, one of the major components of CKD–MBD, is an important risk factor that influences morbidity and mortality in patients with CKD [6,7,15,16]. Recent studies reported a close relationship between AAC and other vascular beds. One study demonstrated that the presence of AAC was closely associated with the prevalence and severity of coronary artery disease [17,18] and was positively correlated with arterial stiffening and the prevalence of peripheral artery disease [19,20]. Moreover, other recent studies demonstrated that the optimal cut-off value of ACI for predicting adverse cardiovascular outcomes was 16%–20% in patients with CKD without hemodialysis [11,21]. However, little is known regarding the AAC progression rates among patients with CKD with respect to the kidney function. In this study, the AAC progression rate was significantly accelerated in patients with advanced CKD. These results emphasize the importance of considering a treatment strategy to suppress vascular calcification before CKD progression to advanced stages. In addition, measuring PTH is useful to evaluate both bone turnover and AAC progression in patients with advanced CKD.

BP levels are well-established risk factors for medial calcification and long-term renal and cardiovascular mortality in patients with CKD [22,23]. Therefore, the development of a strategy for treating hypertension is essential to attenuate the progression of vascular calcification in these patients. According to the results of previous studies [24,25], the findings of our study revealed that increased pulse BP levels significantly promoted the AAC progression rate in patients with mild to moderate CKD. However, little is known regarding the molecular mechanisms underlying the progression of vascular calcification, and there is currently no effective treatment to attenuate calcification. The renin–angiotensin system (RAS)

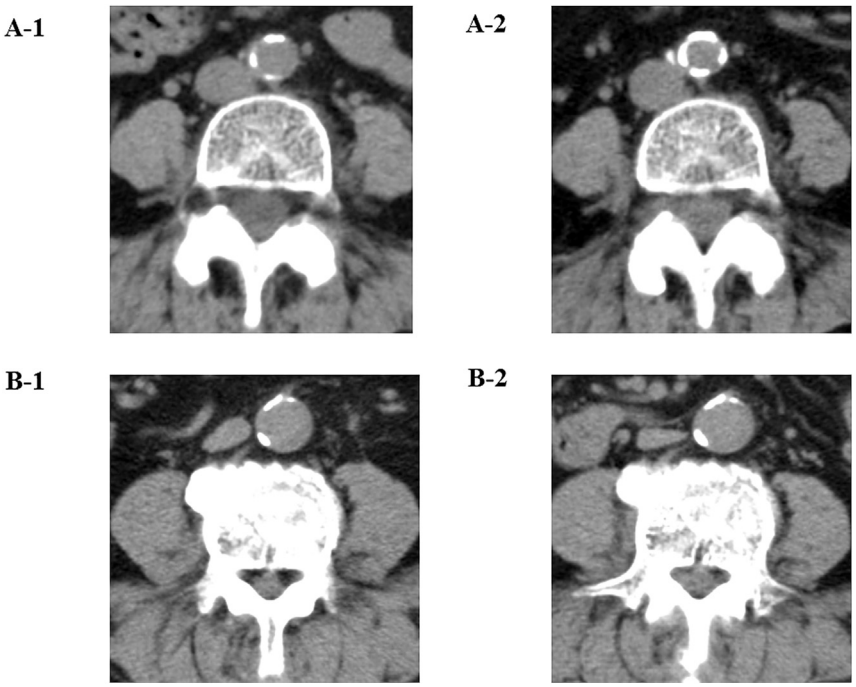

Fig. 1. Representative cross-sectional images of the abdominal aorta in patients with rapid calcification or slow calcification progressions. (A) Patient with rapid ACI progression: A-1, study entry; A-2, follow-up. (B) Patient with slow ACI progression: B-1, study entry; B-2, follow-up.

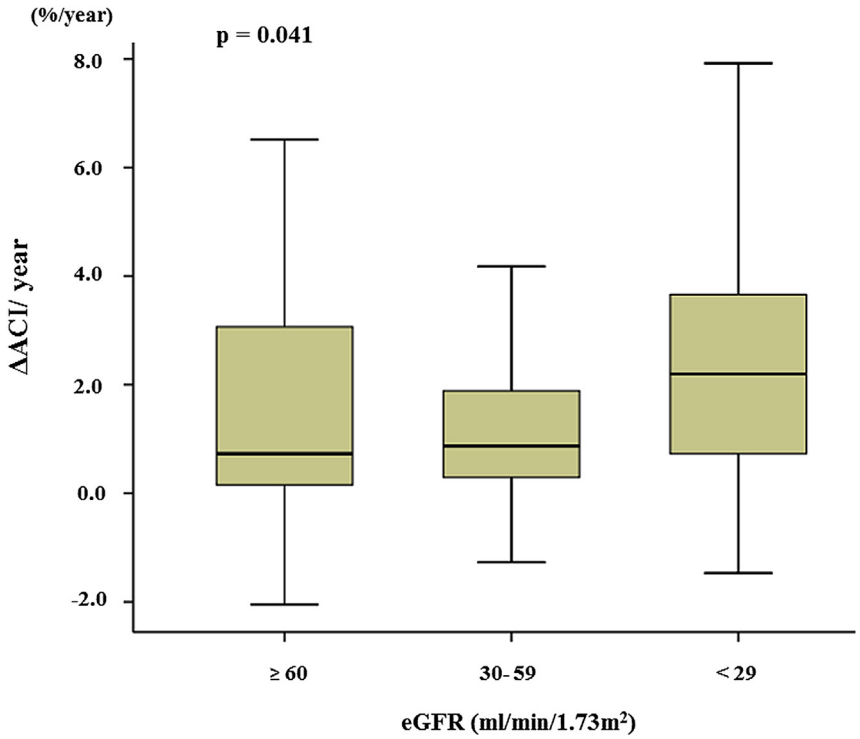

Fig. 2. Association of renal function with abdominal aortic calcification progression. Median ΔACI/year values significantly increased in advanced CKD stages (0.73%, 0.87%, and 2.24% per year for CKD stages G1-2, G3, and G4-5, respectively; p for trend = 0.041).

significantly induces vascular calcification *in vitro* and *in vivo* via the activation of the receptor activator of nuclear factor β ligand (RANKL) [26]. However, further investigations are required to ascertain whether an intervention to inhibit RAS and RANKL is sufficient to attenuate and reverse vascular calcification in clinical practice.

In patients with CKD, the severity of vascular calcification is considered to be associated with the imbalance of calcium, phosphorus, PTH, and abnormalities of various calcium regulatory factors, such as fibroblast growth factor 23 (FGF-23) and Klotho

Table 2
Univariate linear regression analysis for progressive rate of ACI.

	Total		G1-3(≥30 mL/min/1.73 m^2)		(<30 mL/min/1.73 m^2)	
	β	p	β	p	β	p
Male	−0.042	0.618	−0.176	0.081	0.320	0.039
Age (years)	0.151	0.073	0.182	0.072	−0.044	0.780
Body mass index, kg/m^2	0.043	0.609	−0.004	0.968	0.150	0.343
Current smoking	0.113	0.182	0.063	0.533	0.248	0.114
Systolic BP (mmHg)	0.113	0.180	0.152	0.134	0.063	0.691
Diastolic BP (mmHg)	−0.044	0.608	−0.057	0.577	0.093	0.558
Pulse pressure (mmHg)	0.213	0.011	0.234	0.020	0.128	0.419
Diabetes	0.042	0.621	0.074	0.468	−0.063	0.692
HDL-C, mg/dL	−0.091	0.298	−0.104	0.318	−0.009	0.955
LDL-C, mg/dL	−0.024	0.781	−0.011	0.914	0.087	0.596
eGFR (mL/min/1.73 m^2)	−0.171	0.043	−0.004	0.968	−0.057	0.719
eGFR decline/year	−0.107	0.210	−0.147	0.146	−0.113	0.480
Hemoglobin (g/dL)	−0.116	0.170	−0.044	0.666	0.062	0.694
Serum albumin (g/dL)	−0.116	0.172	−0.135	0.182	0.062	0.696
Corrected calcium (mg/dL)	−0.077	0.374	−0.040	0.704	−0.114	0.470
Phosphorus (mg/dL)	0.113	0.182	0.067	0.513	0.028	0.858
Intact-PTH (log transformed)	0.194	0.021	0.028	0.786	0.397	0.009
CRP (log transformed)	0.188	0.025	0.152	0.132	0.192	0.224

ACI, aortic calcification index; other abbreviations as in Table 1.

Table 3
Multivariate stepwise analysis for progressive rate of ACI/year as the dependent variables.

Variable	β	t-test	p
Total population			
Intact-PTH (log transformed)	0.206	2.442	0.016
CRP (log transformed)	0.185	2.191	0.030
Other independent variables included in the model were sex, age, BMI, smoking, diabetes, systolic BP, diastolic BP, pulse pressure, HDL-C, LDL-C, eGFR, eGFR decline/year, Hb, serum albumin, and phosphorus.			
G1-3 (≥30 mL/min/1.73 m^2)			
Pulse pressure (mmHg)	0.258	2.556	0.012
Other independent variables included in the model were sex, age, BMI, smoking, diabetes, systolic BP, diastolic BP, HDL-C, LDL-C, eGFR, eGFR decline/year, Hb, serum albumin, phosphorus, intact-PTH, and CRP.			
G4-5 (<30 mL/min/1.73 m^2)			
Intact-PTH (log transformed)	0.426	2.865	0.007
Other independent variables included in the model were age, BMI, smoking, diabetes, systolic BP, diastolic BP, pulse pressure, HDL-C, LDL-C, eGFR, eGFR decline/year, Hb, serum albumin, serum phosphorus, and CRP.			

Abbsreviations as in Table 1.

[27,28]. Moreover, numerous studies have reported that these pathophysiological abnormalities may already be present in patients with early stage CKD [29]. Thus, there is a growing interest in early interventions to control phosphorus levels to improve both vascular calcification and prognosis of patients with CKD without hemodialysis.

As with previous studies [30,31], our study results revealed a significant association between baseline PTH level and AAC progression, particularly in patients with advanced CKD. Several recent studies reported that lowering phosphate retention using non-calcium-based phosphate binders and moderate doses of active vitamin D may attenuate the progression of vascular calcification in CKD patients [32,33]. Furthermore, studies demonstrated that the use of calcimimetics, which are positive allosteric modulators of active parathyroid calcium receptors, convey direct effects on vascular tissues and improve vascular calcification [34]. However, established medical therapies to attenuate vascular calcification are limited, and there is currently no specific therapy to reverse vascular calcification in humans. Therefore, further investigations are required to establish a treatment strategy for CKD–MBD and improve prognosis in patients with CKD without hemodialysis.

A recent autopsy study reported that renal dysfunction is closely associated with the severity of coronary atherosclerosis [35]. In this study, the incidence of advanced atherosclerotic coronary lesions (AHA types IV–VI) [36] gradually increased with decreased renal function. In particular, the prevalence of severe calcified coronary lesions (type V and VI) was significantly higher in subjects with eGFR < 30 mL/min/1.73 m^2 than in those with eGFR > 60 mL/min/1.73 m^2. Similar findings have also been demonstrated in the progression of carotid atheroma [37]. However, there are limited data regarding the vascular calcification progression with various degrees of renal function. In this study, we demonstrated a clear relationship between eGFR grades and AAC progression in patient with CKD without hemodialysis. Moreover, we demonstrated that the AAC progression rate was significantly accelerated in advanced CKD stages (eGFR < 30 mL/min/1.73 m^2). These findings suggest the importance of considering a treatment strategy to suppress vascular calcification before the stage of CKD advances.

There are some limitations to this study. First, this study was conducted in a single center and included a relatively small sample size. Second, we performed CT twice to detect vascular calcification in the early phase of CKD; however, the radiation dose should also be considered. Third, because data was only collected from medical records, it was not possible to obtain complete information regarding the duration of hypertension and DM. Finally, other CKD–MBD factors that may be associated with vascular

calcification in patients with CKD, e.g., serum FGF-23 and Klotho levels, were not measured in this study. These limitations should be considered when applying these results to other populations.

In conclusion, the results of the present study demonstrated that the AAC progression rate was significantly accelerated in patients with advanced CKD and that risk factors for AAC progression differed among each eGFR grades. Evaluating mineral and bone disorders was useful to identify patients with advanced CKD at a high risk for the rapid progression of vascular calcification.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2016.08.004.

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