Original Article

Vascular Calcification in Patients with Early-Stage Chronic Kidney Disease: The Pivotal Role of Estimated Glomerular Filtration Rate

Suwasin Udomkarnjananun MD, MSc[1], Aksika Saling MD[1], Kullaya Takkavatakarn MD[1], Pairoj Chattranukulchai MD[2], Monravee Tumkosit MD[3], Kearkiat Praditpornsilpa MD[1], Somchai Eiam-Ong MD[1], Paweena Susantitaphong MD, PhD[1,4]

[1] Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand

[2] Division of Cardiology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand

[3] Department of Radiology, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand

[4] Research Unit for Metabolic Bone Disease in CKD Patients, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Background: Vascular calcification in advanced chronic kidney disease (CKD) is correlated with uremic toxins and severely impaired calcium-phosphate-parathyroid metabolism. The association factors of vascular calcification in early-stage CKD are still unestablished.

Objective: To identify the risk factors for vascular calcification in the early-stage CKD, which was the non-target population, different from other previous studies that explored this association in advanced stage CKD.

Materials and Methods: The present study was a longitudinal study conducted to examine the risk factors of vascular calcification in CKD stage G2 and G3 patients who had no previous cardiovascular diseases. All parameters including coronary artery calcification (CAC) and abdominal aortic calcification (AAC) at baseline and after twelve months were evaluated.

Results: Twenty-two patients without established cardiovascular diseases were included and completed the follow-up period. Mean baseline LDL was 99 mg/dL and no patient received statin. At 12-month, the median CAC score was significantly increased to 266 (126 to 956) versus 282 (198 to 846), (p=0.024]. By multivariable analysis in generalized estimating equations, only estimated glomerular filtration rate (eGFR) was associated with CAC score greater than 400 (aOR 0.92, p=0.041), and AAC score greater than 5 (aOR 0.90, p=0.023).

Conclusion: In early-stage CKD, eGFR was associated with vascular calcification. Further studies should explore the potential benefits of delaying CKD progression on vascular calcification in the early-stage CKD patients.

Keywords: Chronic kidney disease; Vascular calcification; Coronary artery calcification; Abdominal aortic calcification; Glomerular filtration rate; Renal function

Received 22 February 2021 | Revised 27 April 2021 | Accepted 28 April 2021

J Med Assoc Thai 2021;104(6):989-97

Website: http://www.jmatonline.com

Vascular calcification, including coronary artery calcification (CAC) and abdominal aortic calcification (AAC), has been demonstrated to be an independent factor for coronary artery disease (CAD) and major adverse cardiac events[1-3] in general population and patients with chronic kidney disease (CKD), including end stage renal disease (ESRD)[4-6]. CAC is more frequently detected and more severe in CKD patients than in general non-CKD subjects[7,8]. In CKD patients, CAC results from both traditional risk factors, including diabetes mellitus and smoking, and non-traditional risk factors, such as uremia and abnormal calcium-phosphate-parathyroid metabolism or CKD mineral and bone disorders (CKD-MBD)[9,10]. Several studies revealed that CAC in advanced stage CKD and ESRD patients was more frequent and severe than CKD patients with earlier stages[6,11,12].

Previous studies showed that the risk factors for developing CAC in advanced stage CKD patients comprise age, serum calcium level, serum phosphate level, body mass index, diabetes mellitus, cholesterol level, and osteocalcin level[1,13-16]. However, the risk factors in early-stage CKD are still unestablished. The role of estimated glomerular filtration rate (eGFR) as a risk factor for CAC in CKD patients is still inconclusive, reporting little role in most studies

Correspondence to:

Susantitaphong P.

Division of Nephrology, Department of Medicine, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

Phone: +66-2-2564251, **Fax**: +66-2-2564560

Email: pesancerinus@hotmail.com

How to cite this article:

Udomkarnjananun S, Saling A, Takkavatakarn K, Chattranukulchai P, Tumkosit M, Praditpornsilpa K, et al. Vascular Calcification in Patients with Early-Stage Chronic Kidney Disease: The Pivotal Role of Estimated Glomerular Filtration Rate. J Med Assoc Thai 2021;104:989-97.

doi.org/10.35755/jmedassocthai.2021.06.12611

with early and advanced stage CKD[1,8,13-18], but certain role in some studies of early-stage CKD[17,19]. Indeed, multiple confounders in more advanced CKD patients, including severe hyperphosphatemia and heightened uremic toxins might overcome the stimulating effect of various factors including eGFR on vascular calcification. Furthermore, earlier studies included CKD patients with history of cardiovascular diseases[20], which could aggravate CAC and might confound the effect of eGFR.

Regarding AAC, this condition exhibits quite similar aspects as CAC stated above[21,22]. Therefore, it is crucial to identify the risk factors for vascular calcification in CKD patients starting from the early CKD stage. This would provide more insights regarding the risk factors that might have important roles during early CKD stage but might be attenuated by other risk factors during advanced stage CKD. Indeed, most previous studies did not specifically focus on early stage of CKD and were cross-sectional basis, included certain patients with previous cardiovascular diseases, utilized categorical outcome measurement. Therefore, the present longitudinal 1-year study was conducted to examine the risk factors for CAC score of more than 400 and AAC score greater than 5 in patients with early-stage CKD, defined as having eGFR between 30 to 90 mL/minute/1.73 m². The included participants were free of preexisting cardiovascular diseases. For perspective risk factor identification, generalized estimating equation (GEE) was used to analyze all variables from the baseline and at 1-year. Closely monitoring and proper management of the risk factors for vascular calcification during the early-stage CKD would yield subsequently better renal and patient outcomes.

Materials and Methods

Study population

The present prospective study was conducted at the out-patient clinic, King Chulalongkorn Memorial Hospital, Chulalongkorn University, Bangkok, Thailand, between January 2017 and June 2018. The present study included Thai CKD patients older than 18 years old with eGFR between 30 to 90 mL/minute/1.73 m² (CKD G2, G3a, and G3b according to the KDIGO guideline[23]). The values of eGFR were calculated from enzymatic method creatinine-based CKD-EPI equation[24], collected three months apart, before entering the present study. Only patients who had stable eGFR within 10% of the initial value were included. The authors excluded patients who had been diagnosed with preexisting cardiovascular diseases, comprising CAD, heart failure, ischemic cardiomyopathy, ischemic or hemorrhagic stroke, and peripheral arterial diseases. Patients with history of cigarette smoking or substance abuse were not included. To eliminate the potential confounding factors from medications, patients who required modification in drug prescriptions during the study period were excluded. Pregnant or patients who were not suitable for X-ray were also excluded.

Variables and outcomes measurement

The patients in the present study were followed up for 12 months. Blood samples for serum creatinine, serum calcium, serum phosphate, parathyroid hormone (PTH) level, hemoglobin, serum albumin, fasting plasma glucose, glycated hemoglobin (HbA1c), and low-density lipoprotein (LDL) were collected at month 0 (before entering the study) and at month 12. CAC was evaluated by non-contrast multi-slice computed tomography coronary angiography at month 0 and month 12. Quantification of CAC severity was measured based on the Agatston method[25], by which CAC score greater than 400 is defined as a high risk for cardiovascular events[26]. Patients with progression of CAC over the 12-month follow-up period were defined by a difference of at least 2.5 units between month 0 and month 12 square root CAC scores[13]. AAC was also evaluated at month 0 and 12 by plain lateral lumbar X-ray. The scoring method described by Kauppila et al[27] was used to classify the severity of AAC. AAC score greater than 5 is considered as a high risk for cardiovascular events[21,28]. CAC and AAC score were measured by two experienced radiologists.

Statistical analysis

Data from the previous meta-analysis showed the prevalence of CAC in predialysis CKD patients of 49% to 69%(4). The authors calculated the sample size based on this data with an alpha-error of 0.05 and precision level at one-fourth of the prevalence, the minimum study population would be 21 patients as shown:

$$n = \frac{Z^2_{1-\alpha/2}\, P(1-P)}{d^2}; \text{ when } P=0.7, d=0.2, \text{ and } \alpha=0.05$$

$$n = 21$$

Continuous data were shown as mean ± standard deviation (SD) or median and interquartile range (IQR), according to data distribution. Categorical data were described as number with percentage. Unpaired t-test, Wilcoxon rank-sum test, and chi-square test were used to compare values between

high and low cardiovascular risk patients according to the CAC and AAC scores, both at baseline and at 1-year. Univariate and multivariate analyses for predicting the high cardiovascular risk groups were analyzed by GEE, which included all variables from baseline and 1-year, and the odd ratios (ORs) were reported. Binary logistic regression was utilized to assess the predicting factors for CAC progressor. Only variables with p-value less than 0.15 from univariate analysis were included into multivariable model. All statistical analyses were performed using Stata Statistical Software Release 15.1 (StataCorp LLC, College Station, TX, USA).

Ethical consideration

All patients were informed about the study protocol and consents were given to the investigators. The patients in the present study were a subpopulation of the study approved by The Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, in compliance with the International Guidelines for Human Research Protection as Declaration of Helsinki, the Belmont Report, CIOMS Guideline, and International Conference on Harmonization in Good Clinical Practice (ICH-GCP) (IRB No. 625/59, COA No. 044/2017).

Results

Patient's characteristics

From the 88 screened patients at the out-patient clinic, 22 patients who had completed the 12-month follow-up without any changes in medicine prescription during the entire study were analyzed. These patients had no established cardiovascular comorbidities. At baseline, the average age was 69.5±14.3 years and there were 14 males (64%). Six patients (27%) had diabetes mellitus. The mean HbA1c was 6.4±1.3%. The mean eGFR was 58.2±12.4 mL/minute/1.73 m². The mean serum calcium, serum phosphate, and serum PTH were 9.1±0.5 mg/dL, 3.6±0.6 mg/dL, and 64.9±28.8 ng/dL, respectively. Hemoglobin was 12.0±2.4 g/dL, while serum albumin was 3.8±0.4 g/dL. Baseline LDL was 99.0±27.1 mg/dL. The value of most of the parameters at 12-month were comparable with baseline (data not shown) except serum phosphate and LDL levels, which were slightly reduced from 3.6±0.6 to 3.4±0.7 mg/dL (p=0.047), and 101.1±28.8 to 92.8±22.6 mg/dL (p=0.037), respectively). The values of median CAC score significantly progressed from 266 (126 to 956) to 282 (198 to 864), p=0.024, while AAC scores were not significantly changed from 1 (0 to 9) to 1 (0 to 9), p=0.317. During the 12 months period, no participating patients encountered cardiovascular disorders. Since the beginning of the present study, six patients (27%) were taking angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB), 14 patients (64%) were on calcium channel blocker (CCB), and no patient was prescribed with statin. No patients received medication changes or adjustments during the 12-month study period.

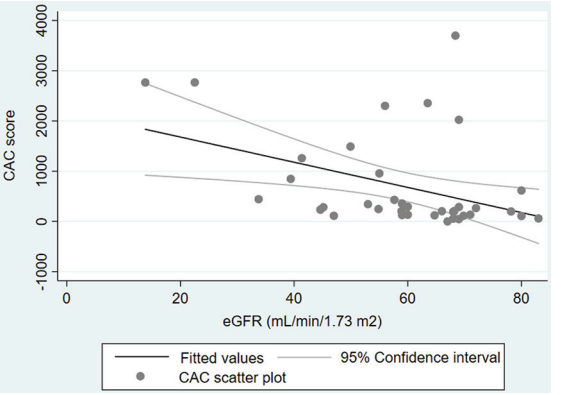

Figure 1. Scatter plot of coronary artery calcification score and eGFR by creatinine-based CKD-EPI (mL/minute/1.73 m^2).

Predicting factors for CAC score >400 and AAC score >5

As detailed in Table 1, there were comparable values of baseline and 12-month parameters between patients with CAC score greater than 400 and of less than 400. Six patients had CAC score greater than 400 at baseline and the number was increased to nine at the 12-month follow-up. Thus, the percentage of patients with CAC score greater than 400 at 12-month were greater than baseline although the statistical significance was not attained with 40.9% versus 27.3% (p=0.108). There was no difference regarding the medications used between patients with CAC score of more than 400 and 400 or less, both at baseline and at 12-month.

Univariate analysis by GEE showed that eGFR was inversely associated with CAC score greater than 400 (OR 0.93, 95% CI 0.88 to 0.99, p=0.020), while higher serum phosphate was positively associated with CAC score greater than 400 (OR 4.90, 95% CI 1.13 to 21.15, p=0.033). After adjustment in multivariable model, only eGFR was still significantly associated with CAC score greater than 400 (adjusted OR 0.92, 95% CI 0.85 to 0.99, p=0.041). Scatter plot of CAC score and eGFR is depicted in Figure 1.

Table 1. Comparison of patient characteristics between patients with CAC score ≤400 and >400 at baseline and 12th month

Variables	At baseline; mean±SD			At 12th month; mean±SD		
	CAC score ≤400 (n=16)	CAC score >400 (n=6)	p-value	CAC score ≤400 (n=13)	CAC score >400 (n=9)	p-value
Age (years)	67.5±14.3	74.8±13.8	0.294	69.0±13.6	72.6±9.4	0.522
Male; n (%)	11 (69)	3 (50)	0.416	7 (54)	7 (78)	0.251
Diabetes mellitus; n (%)	4 (25)	2 (33)	0.696	3 (23)	3 (33)	0.595
eGFR (mL/minute/1.73 m^2)	61.0±8.0	52.0±17.7	0.114	68.8±11.8	48.3±21.6	0.029
Serum calcium (mg/dL)	8.9±0.5	9.3±0.5	0.101	8.3±2.9	9.1±0.4	0.419
Serum phosphate (mg/dL)	3.5±0.6	4.0±0.6	0.145	3.2±0.5	3.8±0.6	0.051
Parathyroid hormone level (ng/mL)	63.4±29.5	68.9±28.9	0.697	55.2±20.7	74.3±32.1	0.138
Vitamin D 25-OH level (ng/mL)	21.5±4.3	22.7±6.5	0.610	23.6±9.1	23.8±6.3	0.962
Hemoglobin (g/dL)	12.1±2.7	12.0±1.6	0.928	12.9±1.6	11.6±2.6	0.247
Serum albumin (g/dL)	3.9±0.4	3.7±0.5	0.254	3.9±0.4	3.9±0.4	0.909
HbA1c (%)	6.3±1.0	6.8±1.9	0.366	6.4±1.4	6.5±0.8	0.536
LDL (mg/dL)	102.1±26.2	86.6±20.6	0.067	102.8±23.7	82.9±17.5	0.077
Coronary artery calcification score; median (IQR)	199 (112 to 289)	2,162 (1,259 to 2,768)	<0.001	200 (121 to 263)	846 (443 to 2,223)	<0.001
Abdominal aortic calcification score; median (IQR)	1 (0 to 4)	6.5 (4 to 9)	0.139	1 (0 to 5)	6 (1 to 9)	0.453

CAC=coronary artery calcification; eGFR=estimated glomerular filtration rate calculated from creatinine-based CKD-EPI equation; HbA1c=glycated hemoglobin; LDL=low-density lipoprotein; SD=standard deviation; IQR=interquartile range

Table 2. Comparison of patient's characteristics between patients with AAC score ≤5 and >5 at baseline and 12th month

Variables	At baseline; mean±SD			At 12th month; mean±SD		
	AAC score ≤5 (n=15)	AAC score >5 (n=7)	p-value	AAC score ≤5 (n=14)	AAC score >5 (n=8)	p-value
Age (years)	67.4±14.8	74.0±13.0	0.324	66.2±14.1	74.9±12.1	0.164
Male; n (%)	11 (73)	3 (43)	0.166	10 (71)	4 (50)	0.204
Diabetes mellitus; n (%)	4 (27)	2 (29)	0.926	3 (21)	3 (38)	0.477
eGFR (mL/minute/1.73 m^2); mean±SD	61.4±8.0	52.3±16.2	0.089	70.0±9.9	45.7±19.7	0.004
Serum calcium (mg/dL); mean±SD	9.0±0.4	9.2±0.6	0.296	8.4±2.7	9.2±0.5	0.419
Serum phosphate (mg/dL); mean±SD	3.6±0.6	3.8±0.6	0.550	3.3±0.7	3.6±0.6	0.344
Parathyroid hormone level (ng/mL); mean±SD	66.3±32.7	61.8±19.6	0.741	64.8±32.5	63.3±21.7	0.911
Vitamin D 25-OH level (ng/mL); mean±SD	22.6±5.3	20.3±3.6	0.320	22.2±12.9	20.1±2.9	0.657
Hemoglobin (g/dL); mean±SD	11.9±2.7	12.3±1.7	0.708	11.7±2.7	12.8±1.3	0.328
Serum albumin (g/dL); mean±SD	3.9±0.3	3.5±0.5	0.030	4.1±0.3	3.7±0.4	0.050
HbA1c (%); mean±SD	6.1±1.4	7.0±1.0	0.163	6.1±0.8	6.9±1.4	0.100
LDL (mg/dL); mean±SD	95.5±25.9	106.4±30.1	0.393	92.5±20.5	93.3±27.8	0.946
Coronary artery calcification score; median (IQR)	246 (112 to 354)	286 (126 to 2,023)	0.549	204 (121 to 430)	645 (273 to 1,857)	0.039
Abdominal aortic calcification score; median (IQR)	0 (0 to 1)	12 (9 to 17)	<0.001	0 (0 to 1)	10.5 (7.5 to 15)	<0.001

AAC=abdominal aortic calcification; eGFR=estimated glomerular filtration rate calculated from creatinine-based CKD-EPI equation; HbA1c=glycated hemoglobin; LDL=low-density lipoprotein; SD=standard deviation; IQR=interquartile range

With respect to AAC, the values of baseline characteristics of patients with AAC score greater than 5 and of 5 or less were comparable (Table 2) except for serum albumin in the higher AAC group, which was significantly greater than the lower AAC patients (p=0.030). There were seven and eight patients having AAC score greater than 5 at baseline and at 12-month, respectively. The percentage of patients with AAC score greater than 5 at 12-month was slightly higher than baseline with 36.4% versus 31.8%, (p=0.127). The medications were not different between patients who had AAC score greater than 5 or of 5 or less, both at baseline and at 12-month.

Only eGFR was the significant variable that

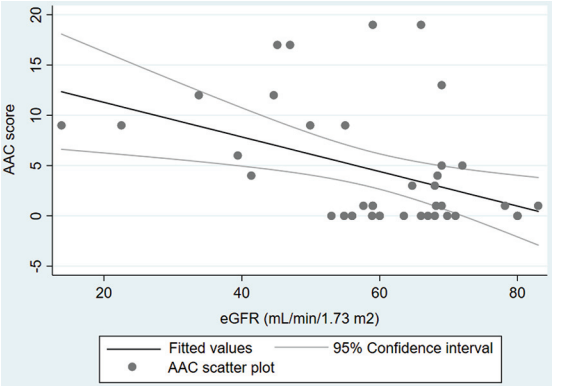

Figure 2. Scatter plot of abdominal aortic calcification score and eGFR by creatinine-based CKD-EPI (mL/minute/1.73 m^2).

was related to AAC score greater than 5 both from univariate analysis (OR 0.93, 95% CI 0.87 to 0.99, p=0.044) and multivariate analysis (OR 0.90, 95% CI 0.82 to 0.99, p=0.023). The correlation between AAC score and eGFR is plotted in Figure 2.

Regarding progression of vascular calcification, the authors applied binary logistic regression to the baseline values for predicting CAC and AAC progressor. However, univariate analysis failed to reveal any significant risk factors for CAC and AAC progressor (data not shown). Consequently, no variable was selected to the multivariable model.

Discussion

In CKD stage G2 and G3 patients with eGFR approximately 60 mL/minute/1.73 m² and without previous cardiovascular diseases, the results in the present study demonstrated that, after 12-month follow-up period, CAC scores were significantly elevated from baseline. At baseline, 27.3% of the patients had CAC score greater than 400 while 31.8% had AAC score greater than 5. As such, approximately 30% of early-stage CKD had severe vascular calcification. Following 12-month follow-up period, the percentage of patients with CAC score greater than 400 was elevated to 40.9% and those with AAC score greater than 5 was increased to 36.4%. This progression of vascular calcification within 1 year follow-up occurred despite having well-controlled conditions of both traditional risk factors, including diabetes as well as dyslipidemia, and non-traditional factors such as uremia and CKD-MBD parameters such as serum calcium, phosphate, and PTH (Table 1, 2). By using multivariate analysis in GEE, only eGFR was associated with CAC score greater than 400 and AAC score greater than 5.

CKD is an important risk factor for cardiovascular diseases[2,3]. Patients with eGFR lower than 60 mL/minute/1.73 m² are at 1.6 to 2.2 times higher risk for mortality, compared with patients who have higher eGFR[29]. Vascular calcification, including CAC and AAC, contributes to death and coronary events in CKD patients[3,30,31]. Vascular calcification in CKD patients not only results from CKD-MBD[32] but is also mediated by several factors, including uremic toxin, chronic inflammation, increased of vascular smooth muscle cells' mineralization, and imbalance between the calcification inducer and inhibitor molecules[33-35]. The more impairment of the above factors in advanced stage CKD could obviously explain the more frequently and severely detected vascular calcification in advanced stage CKD and ESRD when compared with early-stage CKD, in approximately 70% versus 40%[6,12]. Nonetheless, the incidence of vascular calcification in early-stage CKD is apparently higher than non-CKD general population[11]. Due to the less severity of the risk factors in early-stage CKD, the association factors of vascular calcification in early-stage CKD are still inconclusive and this crucially needs urgent investigations.

Impaired renal function as a risk factor of vascular calcification is recently one of the most interesting issues. Indeed, Tuttle et al examined an association between eGFR and incidence of vascular calcification by using CAC score in non-CKD patients with the mean eGFR of 104±32 mL/minute/1.73 m² and reported that eGFR can predict incident CAC score greater than 0 from multivariate analysis[7]. However, the role of eGFR as the risk factor of vascular calcification in CKD is still unestablished. Table 3 details the comparison of the previous and the present studies, which examined the association between eGFR and CAC score in CKD patients[8,16-18]. As seen in Table 3, all previous works were cross-sectional design while the current study was longitudinal basis. Earlier reports included CKD patients from stage 1 to stage 5 or mainly in advanced stage CKD, whereas the present work intentionally focused on early stage, G2 and G3 CKD patients. Most of the preceding studies did not exclude preexisting cardiovascular diseases while the CKD patients in the present study were free of underlying cardiovascular disorders. Almost all the previous studies utilized categorical outcome measurements while the present work used continuous values that would yield more precise and perspective results. Furthermore, only severe vascular calcification, represented by CAC

Table 3. Summary of studies that demonstrated the association between eGFR and CAC score

Study	Study design	Study population	Previous CVD	Race	Mean age	Mean eGFR	eGFR analysis	Outcome measurement	Results
Kramer 2005[16]	Cross-sectional	CKD stage 1 to 5 patients, excluding ESRD (n=211) Non-CKD patients (n=2,449)	Not excluded	White 68%, Black 20%, others 12%	44 years	Not stated (mean serum creatinine 0.9 m/dL)	Categorical (no CKD vs. CKD stage 1-2 vs. CKD stage 3-5)	Categorical (CAC score >10 and >400)	Only CKD stage 3 to 5, but not stage 1 to 2, was associated with CAC score >400 by multivariate analysis.
Budoff 2011[18]	Cross-sectional (substudy of CRIC study)	CKD stage 2 to 4 patients (n=1,906)	Not excluded	White 43%, Black 34%, others 23%	59 years	Not stated (the original CRIC study was 44±14 mL/minute/1.73 m^2 by MDRD)	Categorical (every 10 mL/minute/1.73 m^2 of eGFR from 30 to 60)	Categorical (CAC score 0 vs. 1 to 100 vs. 101 to 400 vs. >400)	Compared with eGFR >60 mL/minute/1.73 m^2, only eGFR <30 mL/minute/1.73 m^2 was associated with higher CAC scores
Takayama 2016[16]	Cross-sectional	CKD stage 3 to 5 patients (n=126)	Partially excluded	Asian 100%	70 years	36±14 mL/minute/1.73 m^2 (Japanese eGFR)	Continuous (true value)	Categorical (CAC score >400)	eGFR failed to predict severe CAC
Hyun 2019[17]	Cross-sectional	CKD stage 1 to 5 (n=1,533)	Not excluded	Asian 100%	53 years	54±33 mL/minute/1.73 m^2 (CKD-EPI Cr-CysC)	Categorical (CKD stage 1 vs. CKD stage 2 vs. CKD stage 3 vs. CKD stage 4 to 5)	Categorical (CAC score >100)	Compared with CKD stage 1, higher stages of CKD were associated with CAC score >100
The present study	Longitudinal	CKD stage 2 to 3 (n=22)	Excluded	Asian 100%	70 years	58.2±12.4 mL/minute/1.73 m^2	Continuous (true value)	Categorical (CAC score >400)	eGFR can predict CAC score >400

CVD=cardiovascular disease; eGFR=estimated glomerular filtration rate; CRIC=Chronic Renal Insufficiency Cohort; CKD=chronic kidney disease; ESRD=end stage renal disease; CAC=coronary artery calcification

score greater than 400 and AAC score greater than five were used in the current work[36,37]. Therefore, the results in the present study would underscore the importance of the association between the declining of eGFR and the higher risk for vascular calcification in CKD patients, particularly in the early-stage CKD. Of interest, despite the present study population were Chinese-Asian, which tend to have a lower prevalence of CAC than the Caucasian[38], the association between eGFR and CAC score was still firmly valid.

A previous study had illustrated the capability of age, diabetes, and serum phosphate to predict CAC progression[13]. However, the present study did not observe such association. Indeed, the previous study included patients with more advanced stage of CKD with the mean eGFR of 30 mL/minute/1.73 m², compared with the mean eGFR of 60 mL/minute/1.73 m² in the present study. The lower prevalence and less severity of CAC in early-stage CKD than advanced stage CKD might attenuate the precision in assessment of CAC progression[11]. Further studies with more participants would provide more accurate information regarding this issue.

In congruence with CAC, AAC is more common in advanced stage CKD compared with earlier stage with 50% in predialysis versus 30% in stage G1 to G2 CKD[39]. Previous studies in stage G3 to G5 CKD demonstrated that age, prior cardiovascular diseases, eGFR, male gender, serum phosphate, hypertension, and dyslipidemia were the risk factors for AAC[22,28]. However, another earlier study that included all stages of CKD did not find the significant association between eGFR and the presence of AAC from multivariate analysis[39]. The history of prior cardiovascular diseases in approximately 30% of included patients might be one of the various factors that attenuated the effect of eGFR, as the history of cardiovascular diseases itself was significantly related with AAC in such study[39]. In the present study, although patients with history of cardiovascular diseases were excluded, a significant relation between eGFR and AAC in the early stage of CKD could still be detected.

There were several strengths in the present study. CAC and AAC scores were determined in every patient at baseline and month 12, along with other laboratory investigations without patient dropout. The authors have shown the significant association between eGFR and both CAC and AAC in early-stage CKD patients, which was not the primary target population in previous studies. Moreover, by excluding patients with prior history of cardiovascular

diseases, the authors emphasized this association even in relatively healthier patients than in earlier reports. Despite being the pioneer in this finding, certain limitations in the present work should be considered. Admittedly, the study population is quite small and might not be able to demonstrate all other factors that might be significant risks. Statin was not used in the present study population, which negated the confounder effect from the medication. However, the authors have no information whether patients who received statin would have slower rate of vascular calcification progression.

The results from the present study could be applied in CKD patients for early screening for vascular calcification by a non-invasive test. The effectiveness and clinical benefit of early intervention in patients undergoing such screening test should be thoroughly evaluated in future studies.

Conclusion

In conclusion, eGFR is the risk factor strongly associated with vascular calcification in early-stage CKD. Further studies should explore the potential benefit of preserving eGFR on progression of vascular calcification in the early-stage CKD patients.

What is already known on this topic?

Vascular calcification is an important complication in advanced stage CKD patients and leads to cardiovascular morbidities. The correlation between predialysis eGFR and incidence of vascular calcification has been established. However, the relationship of vascular calcification and eGFR in the patients with early-stage CKD is still poorly identified.

What this study adds?

This study demonstrated the inverse correlation between eGFR in the early-stage CKD patients and vascular calcification during the complete 12-month follow-up, both for the CAC and AAC. The patients included in this study are different from the previous studies, which focused only advanced stage CKD. Moreover, the included population in this study had no previous cardiovascular diseases, indicating the pure effect of lower eGFR to vascular calcification even in the early-stage CKD.

Acknowledgement

This work was supported by the Ratchadaphiseksomphot Endowment Fund, Faculty of Medicine, Chulalongkorn University (grant number RA60/075). Research Career Development Fund from Thailand Research Fund (TRF) supported this study in protocol #RSA5880067. This study was conducted under the supervision of Research Unit for the Metabolic Bone Disease in CKD Patients, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

Conflicts of interest

The authors declare no conflict of interest related to this article. The results presented in this paper have not been published previously in whole or part.

References

1. Bhatti NK, Karimi Galougahi K, Paz Y, Nazif T, Moses JW, Leon MB, et al. Diagnosis and management of cardiovascular disease in advanced and end-stage renal disease. J Am Heart Assoc 2016;5:e003648.
2. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet 2013;382:339-52.
3. Sarnak MJ, Amann K, Bangalore S, Cavalcante JL, Charytan DM, Craig JC, et al. Chronic kidney disease and coronary artery disease: JACC State-of-the-Art review. J Am Coll Cardiol 2019;74:1823-38.
4. Wang XR, Zhang JJ, Xu XX, Wu YG. Prevalence of coronary artery calcification and its association with mortality, cardiovascular events in patients with chronic kidney disease: a systematic review and meta-analysis. Ren Fail 2019;41:244-56.
5. Ferencik M, Pencina KM, Liu T, Ghemigian K, Baltrusaitis K, Massaro JM, et al. Coronary artery calcium distribution is an independent predictor of incident major coronary heart disease events: Results from the Framingham Heart Study. Circ Cardiovasc Imaging 2017;10.
6. Chen J, Budoff MJ, Reilly MP, Yang W, Rosas SE, Rahman M, et al. Coronary artery calcification and risk of cardiovascular disease and death among patients with chronic kidney disease. JAMA Cardiol 2017;2:635-43.
7. Tuttle KR, Short RA. Longitudinal relationships among coronary artery calcification, serum phosphorus, and kidney function. Clin J Am Soc Nephrol 2009;4:1968-73.
8. Kramer H, Toto R, Peshock R, Cooper R, Victor R. Association between chronic kidney disease and coronary artery calcification: the Dallas Heart Study. J Am Soc Nephrol 2005;16:507-13.
9. Muntner P, He J, Astor BC, Folsom AR, Coresh J. Traditional and nontraditional risk factors predict coronary heart disease in chronic kidney disease: results from the atherosclerosis risk in communities study. J Am Soc Nephrol 2005;16:529-38.
10. Tonelli M, Karumanchi SA, Thadhani R. Epidemiology

and mechanisms of uremia-related cardiovascular disease. Circulation 2016;133:518-36.
11. Choi IJ, Lim S, Choo EH, Kim JJ, Hwang BH, Kim TH, et al. Differential impact of chronic kidney disease on coronary calcification and atherosclerosis in asymptomatic individuals with or without diabetes: Analysis from a Coronary Computed Tomographic Angiography Registry. Cardiorenal Med 2018;8:228-36.
12. Qunibi WY. Cardiovascular calcification in nondialyzed patients with chronic kidney disease. Semin Dial 2007;20:134-8.
13. Stavroulopoulos A, Porter CJ, Pointon K, Monaghan JM, Roe SD, Cassidy MJ. Evolution of coronary artery calcification in patients with chronic kidney disease stages 3 and 4, with and without diabetes. Nephrol Dial Transplant 2011;26:2582-9.
14. Garland JS, Holden RM, Groome PA, Lam M, Nolan RL, Morton AR, et al. Prevalence and associations of coronary artery calcification in patients with stages 3 to 5 CKD without cardiovascular disease. Am J Kidney Dis 2008;52:849-58.
15. Lamarche MC, Hopman WM, Garland JS, White CA, Holden RM. Relationship of coronary artery calcification with renal function decline and mortality in predialysis chronic kidney disease patients. Nephrol Dial Transplant 2019;34:1715-22.
16. Takayama Y, Yasuda Y, Suzuki S, Shibata Y, Tatami Y, Shibata K, et al. Relationship between abdominal aortic and coronary artery calcification as detected by computed tomography in chronic kidney disease patients. Heart Vessels 2016;31:1030-7.
17. Hyun YY, Kim H, Oh KH, Ahn C, Park SK, Chae DW, et al. eGFR and coronary artery calcification in chronic kidney disease. Eur J Clin Invest 2019:e13101.
18. Budoff MJ, Rader DJ, Reilly MP, Mohler ER 3rd, Lash J, Yang W, et al. Relationship of estimated GFR and coronary artery calcification in the CRIC (Chronic Renal Insufficiency Cohort) Study. Am J Kidney Dis 2011;58:519-26.
19. Sedaghat S, Hoorn EJ, Ikram MA, Koop-Nieuwelink C, Kavousi M, Franco OH, et al. Kidney function and arterial calcification in major vascular beds. J Am Heart Assoc 2019;8:e010930.
20. Liu W, Zhang Y, Yu CM, Ji QW, Cai M, Zhao YX, et al. Current understanding of coronary artery calcification. J Geriatr Cardiol 2015;12:668-75.
21. Chen HC, Wang WT, Hsi CN, Chou CY, Lin HJ, Huang CC, et al. Abdominal aortic calcification score can predict future coronary artery disease in hemodialysis patients: a 5-year prospective cohort study. BMC Nephrol 2018;19:313.
22. Peeters MJ, van den Brand JA, van Zuilen AD, Koster Y, Bots ML, Vervloet MG, et al. Abdominal aortic calcification in patients with CKD. J Nephrol 2017;30:109-18.
23. Group KDIGOKCW. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013;3:1-150.
24. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-12.
25. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827-32.
26. Greenland P, Bonow RO, Brundage BH, Budoff MJ, Eisenberg MJ, Grundy SM, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol 2007;49:378-402.
27. Kauppila LI, Polak JF, Cupples LA, Hannan MT, Kiel DP, Wilson PW. New indices to classify location, severity and progression of calcific lesions in the abdominal aorta: a 25-year follow-up study. Atherosclerosis 1997;132:245-50.
28. Lumlertgul D, Kantachuvesiri S, Apichaiyingyurd S, Treamtrakanpon W, Rattanasompattikul M, Gojaseni P, et al. Prevalence of and predictive factor for abdominal aortic calcification in Thai chronic kidney disease patients. Ther Apher Dial 2017;21:611-9.
29. Wang J, Wang F, Saran R, He Z, Zhao MH, Li Y, et al. Mortality risk of chronic kidney disease: A comparison between the adult populations in urban China and the United States. PLoS One 2018;13:e0193734.
30. Mizobuchi M, Towler D, Slatopolsky E. Vascular calcification: the killer of patients with chronic kidney disease. J Am Soc Nephrol 2009;20:1453-64.
31. Lingel JM, Srivastava MC, Gupta A. Management of coronary artery disease and acute coronary syndrome in the chronic kidney disease population-A review of the current literature. Hemodial Int 2017;21:472-82.
32. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl (2011) 2017;7:1-59.
33. Benz K, Hilgers KF, Daniel C, Amann K. Vascular calcification in chronic kidney disease: The role of inflammation. Int J Nephrol 2018;2018:4310379.
34. Stompór T. Coronary artery calcification in chronic kidney disease: An update. World J Cardiol 2014;6:115-29.
35. Shanahan CM, Crouthamel MH, Kapustin A, Giachelli

CM. Arterial calcification in chronic kidney disease: key roles for calcium and phosphate. Circ Res 2011;109:697-711.
36. Shantouf RS, Budoff MJ, Ahmadi N, Ghaffari A, Flores F, Gopal A, et al. Total and individual coronary artery calcium scores as independent predictors of mortality in hemodialysis patients. Am J Nephrol 2010;31:419-25.
37. Chiu YW, Adler SG, Budoff MJ, Takasu J, Ashai J, Mehrotra R. Coronary artery calcification and mortality in diabetic patients with proteinuria. Kidney Int 2010;77:1107-14.
38. Kanaya AM, Vittinghoff E, Lin F, Kandula NR, Herrington D, Liu K, et al. Incidence and progression of coronary artery calcium in South Asians compared with 4 race/ethnic groups. J Am Heart Assoc 2019;8:e011053.
39. Biyik Z, Selcuk NY, Tonbul HZ, Anil M, Uyar M. Assessment of abdominal aortic calcification at different stages of chronic kidney disease. Int Urol Nephrol 2016;48:2061-8.