J Atheroscler Thromb, 2017; 24: 1092-1104.
http://doi.org/10.5551/jat.39271

Original Article

Impact of Renal Functional/Morphological Dynamics on the Calcification of Coronary and Abdominal Arteries in Patients with Chronic Kidney Disease

Takeo Ichii[1], Ryota Morimoto[1, 2], Takahiro Okumura[1], Hideki Ishii[1], Yosuke Tatami[1], Dai Yamamoto[1], Soichiro Aoki[1], Hiroaki Hiraiwa[1], Kenji Furusawa[1], Toru Kondo[1], Naoki Watanabe[1], Naoaki Kano[1], Kenji Fukaya[1], Akinori Sawamura[1], Susumu Suzuki[1], Yoshinari Yasuda[2] and Toyoaki Murohara[1]

[1]Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan
[2]Department of CKD Initiatives Internal Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan

***Aim*: Fast-progressing vascular calcification (VC) is accompanied by renal atrophy and functional deterioration along with atherosclerosis in patients with chronic kidney disease (CKD). However, the relationship between VC progression and renal functional and/or morphological changes remains unclear.**

***Methods*: We included 70 asymptomatic patients with CKD without hemodialysis in our study. To identify temporal variations, the coronary artery calcification score (CACS), abdominal aortic calcification index (ACI), and renal parenchymal volume index (RPVI) were determined via spiral computed tomography scans taken during the study. We investigated significant factors related to annualized variations of CACS (ΔCACS/y) and ACI (ΔACI/y).**

***Results*: During the follow-up period (4.6 years), median values of CACS [in Agatston units (AU)] and ACI increased from 40.2 to 113.3 AU ($p=0.053$) and from 13.2 to 21.7% ($p=0.036$), respectively. Multivariate analysis revealed that CACS at baseline ($p<0.001$) and diabetes mellitus (DM) status ($p=0.037$) for ΔCACS/y and ACI at baseline ($p=0.017$) and hypertension (HT) status ($p=0.046$) for ΔACI/y were significant independent predictors. Furthermore, annualized RPVI variation was significantly related to both ΔCACS/y and ΔACI/y ($R=-0.565$, $p<0.001$, and $R=-0.289$, $p=0.015$, respectively). On the other hand, independent contributions of the estimated glomerular filtration rate (eGFR) and annualized eGFR variation to VC progression were not confirmed.**

***Conclusion*: The degree of VC at baseline, DM, HT, and changes in renal volume, but not eGFR, had a strong impact on VC progression in patients with CKD.**

See editorial vol. 24: 1085-1087

Key words: Coronary artery calcification, Abdominal aortic calcification index, Renal parenchymal volume, Chronic kidney disease

Introduction

In patients with chronic kidney disease (CKD), cardiovascular disease (CVD) is a major cause of morbidity and mortality[1-3]. Vascular calcification (VC) is highly prevalent in patients with CKD undergoing dialysis[4-6]. Even in pre-dialysis patients with CKD, the high prevalence and rapid progression of VC is well recognized[7-10]. In addition, the presence and progression of VC is closely related to the increased morbidity and mortality of CVD[11-15].

The progression of atherosclerosis, which results in CKD and CVD, is closely associated with lipid

Address for correspondence: Ryota Morimoto, Department of Cardiology, Nagoya University Graduate School of Medicine, Postal address: 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan
E-mail: ryota.m0726@med.nagoya-u.ac.jp
Received: December 5, 2016
Accepted for publication: February 15, 2017

abnormalities, nutrition status, and micro inflammation[16, 17]. VC is a key feature of advanced atherosclerosis and the extent of calcification is strongly correlated with the extent and severity of atherosclerotic lesions[18]. Previous studies have shown that atherosclerotic risk factors, such as hypertension (HT), dyslipidemia (DL), and diabetes mellitus (DM), affect the prevalence and progression of VC[5, 8, 9, 19-21]. These factors affect renal functional deterioration and atrophy as well[22-24]. Although both VC progression and renal functional/morphological changes are influenced by atherosclerosis, the relationship between VC and renal dynamics in patients with CKD remains unknown.

Aim

VC can be evaluated semi-quantitatively in coronary and abdominal arteries as the coronary artery calcification (CAC) score (CACS) and abdominal aortic calcification index (ACI), respectively. Therefore, this study aims to investigate the relationship between renal functional/morphological parameters and progression of CACS or ACI in patients with CKD without hemodialysis.

Methods

Patients

From September 2009 to January 2013, 261 asymptomatic, pre-dialysis patients with CKD were recruited to undergo non-contrast coronary and abdominal computed tomography (CT) scans simultaneously in the outpatient clinic at the Department of Nephrology in the Nagoya University Hospital. CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 or the presence of proteinuria and/or renal disease at study entry[25]. Among these patients, 79 underwent follow-up non-contrast coronary and abdominal CT scans by August 2016 over a 1-year interval. Among the 79 patients, no patient had a history of coronary artery disease, abdominal aortic artery repair and stenting, active malignancy, and/or active autoimmune disease. After excluding patients with polycystic kidney disease ($n=2$), hemodialysis maintenance between follow-up periods ($n=1$), unclear CT images ($n=1$), and coronary intervention during the follow-up periods ($n=5$), we evaluated 70 patients in this study. Coronary CT scans were used to determine CACS in Agatston units (AU), and abdominal CT scans were used to determine ACI as the abdominal artery calcification (AAC) score and renal parenchymal volume (RPV). In addition, all patients underwent renal functional tests and comprehensive atherosclerotic screening. When we evaluated the progression of VC, we calculated the annualized variation (calculated as [second value – first value/days of follow-up] × 365) to determine the relationship between the annualized CACS variation (ΔCACS/y) or annualized ACI variation (ΔACI/y) and baseline variables or annualized variations with regard to renal function and morphology. The study protocol was approved by the Ethics Review Board of Nagoya University School of Medicine, and written informed consent was obtained from all patients prior to performing the first CT scan.

HT was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, and/or the present use of anti-hypertensive medications. DL was defined as low-density lipoprotein (LDL) cholesterol ≥ 140 mg/dL, high-density lipoprotein (HDL) cholesterol <40 mg/dl, triglycerides ≥ 150 mg/dL, and/or the present use of anti-hyperlipidemic medications. DM was defined as fasting plasma glucose concentration >126 mg/dL, glycosylated hemoglobin concentration ≥ 6.5% (National Glycohemoglobin Standardization Program), and/or the present use of anti-hyperglycemic medications. Those who reported as presently smoking or previously smoked at least one cigarette per day for more than 1 year were defined as patients with a history of smoking.

CKD stages were classified using eGFR and urinary protein excretion data. To estimate GFR, we used a modified equation for Japanese: eGFR (mL/min/1.73 m^2) = 194 × serum creatinine $^{-1.094}$ × age $^{-0.287}$ × 0.739 (in females)[26]. Urinary protein excretion was determined via the urinary protein to creatinine ratio (PCR) in spot morning urine samples. We categorized eGFR levels into the following six groups according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative Guidelines[25]: ≥ 90, 60–89, 45–59, 30–44, 15–29, and <15 mL/min/1.73 m^2, which were G1, G2, G3a, G3b, G4, and G5, respectively. We divided patients into the following three groups with regard to the urinary PCR: <0.15, 0.15–0.49, and ≥ 0.5 g/gCr, which were A1, A2, and A3, respectively.

CACS Measurements

All patients underwent CACS measurements using a multi-slice non-contrast CT scan (Siemens Medical Solutions, Forchheim, Germany) with a gantry rotation of 0.4 s, collimation of 2.5 mm (slice thickness), and reconstruction time of 6 frames/s. The images were scored by a single physician blinded to the clinical and biochemical aspects of the study patients. CACS was determined by multiplying the area of each calcified lesion by a weighting factor corresponding to the peak pixel intensity for each lesion

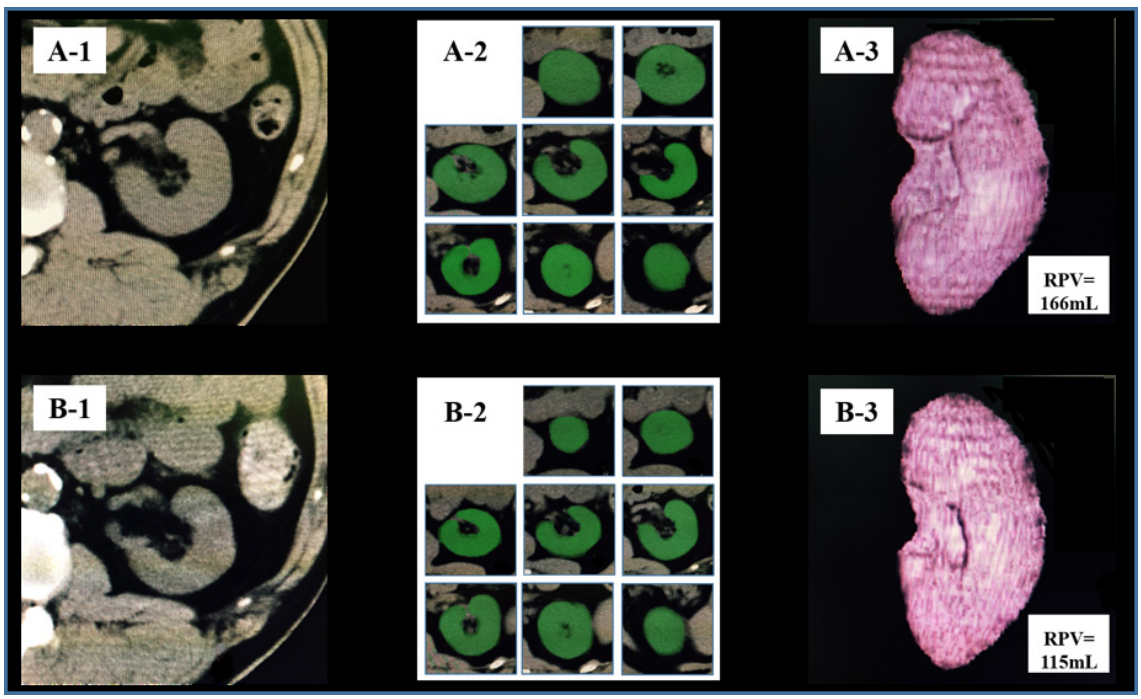


Fig. 1. Non-contrast computed tomography (CT) images on the workstation showing the measurement of the left renal parenchymal volume (RPV)

A-1 and B-1 are original non-contrast CT images, and the renal cortex that is displayed in the green area is traced manually with the exclusion of sinus fat, vessels, and cysts (A-2, B-2). After complete tracing, CT volumetric image is automatically drawn and the volume is calculated (A-3, B-3). Upper (A) and lower (B) is the same patient (68-year-old male at baseline). Upper panel (A) performed on January 2011 and lower panel (B) performed on February 2016. Left RPV volume decreases from 166 to 115 mL.

and then summing the calcification scores of all coronary arteries[27, 28]. Lesions above a threshold of 130 Hounsfield units (HU) were defined as calcified.

ACI Measurements

ACI and RPV measurements for each patient were obtained in a manner similar to that for CACS measurements; that is, using multi-slice non-contrast CT scans. It is noteworthy that images were obtained with a 5-mm slice thickness. Calcification was considered to be present if an area of ≥ 1 mm^2 displayed a density of 130 HU. The AAC score was calculated from the site where the renal artery arises to the bifurcation into the common iliac arteries of the aorta. The cross-section of the abdominal aorta on each slice was radially divided into 12 segments. ACI was calculated as follows: ACI = (total calcification score on all slices)/12 × 1/(number of slices) × 100%[6, 10, 15]. ACI was independently calculated by two physicians who were blinded to the clinical and biochemical aspects of each study patient.

RPV Measurements

RPV was calculated based on a software that measures volume, which is available on Ziostation2 (Zio Software Inc., Tokyo, Japan). This is a three-dimensional (3D) volumetric method that is widely used to measure renal volume[29, 30]. The renal cortex was traced on each image showing the renal parenchyma, with the exclusion of sinus fat, vessels, and cysts. After complete tracing of each kidney, CT volume was automatically calculated and RPV was defined as the sum of renal volume on the left and right sides (**Fig. 1**). RPV measurement was conducted independently by two physicians who were blinded to the clinical and biochemical aspects of each study patient. Previous study showed that RPV can be corrected via the body surface area (BSA) (correction value = 0.68)[30]; we applied this correction by dividing RPV with BSA and defined it as the RPV index (RPVI), which was used in downstream analyses.

Statistical Analysis

All variables were expressed as means ± standard deviations or as medians and interquartile ranges for non-parametric variables. Categorical data were expressed as a number (percentage). Between-group differences were tested using the Student's *t*-test for

parametric variables and the Mann–Whitney *U*-test for non-parametric variables. Categorical variables were examined using the Pearson chi-squared test or Fisher's exact test as appropriate. When the associations between ΔCACS/y or ΔACI/y and various parameters were evaluated, baseline variables and annualized variations were independently calculated using correlation coefficients and a linear regression analysis. To reveal the independent factors associated with the progression of VC, significant variables identified by univariate analysis were entered in multivariable linear regression models. A significant difference is assumed with $p<0.05$ for all analyses. All statistical analyses were performed using JMP statistical software version 11.0.0 (SAS Institute Inc., Cary, NC, USA).

Results

Patient Characteristics and Variable Parameter Changes

A total of 70 patients were evaluated in this study. The median duration between the first and repeated CT scans was 4.6 (3.2–5.4) years. The baseline clinical characteristics and changes of CACS, RPVI, and laboratory data are summarized in **Table 1**. The etiology of kidney disease was as follows: Nephrosclerosis in 32 patients (45.7%), glomerulonephritis in 20 patients (28.6%), diabetic nephropathy in 7 patients (10.0%), interstitial nephritis in 1 patient (1.4%), and other diseases and unknown in 10 patients (14.3%). The percentage of medication usage did not statistically increase during the study, with the exception of phosphate binders (from 5.7% at baseline to 17.1% at follow-up, $p=0.034$).

CACS (in AU) and ACI significantly increased from 40.2 (2.2–222.4) to 113.3 (11.0–576.0) AU ($p=0.053$) and from 13.2 (3.4–31.9) to 21.7 (8.3–47.1)% ($p=0.036$), respectively. The number of patients with CACS ≥ 100 or ≥ 400 increased from 26 patients (37.1%) to 35 patients (50.0%) and from 10 patients (14.3%) to 24 patients (34.3%), respectively, during the follow-up period. Although most patients had increased CAC and ACI progression, 14 patients (87.5%) out of 16 with no apparent CAC and 4 patients (66.7%) out of 6 with no apparent ACI at baseline remained during the follow-up period. RPVI and eGFR significantly decreased from 131.8 ± 43.2 to 115.5 ± 39.3 mL/m^2 ($p=0.021$) and from 40.3 ± 19.2 to 32.9 ± 19.0 mL/min/1.73 m^2 ($p=0.022$), respectively. There was a positive correlation between RPVI and eGFR ($R=0.634$, $p<0.001$) (**Supplemental Fig. 1**). The baseline values of CACS, ACI, and RPVI in each CKD stages are summarized in **Table 2**. Although patients with CKD A3 exhibited a trend of higher CACS, there were no statistical differences between both CKD G and A stages at the baseline CACS or ACI. On the other hand, as the CKD G stage worsened, RPVI significantly decreased ($p<0.001$).

ΔCACS/y or ΔACI/y profiles in patients with CKD

The comparisons of ΔCACS/y and ΔACI/y with clinical characteristics are presented in **Fig. 2**. Progressive CAC was significantly associated with risk factors, such as HT, DL, DM, and CKD stage A3 (**Fig. 2-A**), and progressive ACI was associated with HT (**Fig. 2-B**). At baseline, CACS, RPVI, serum albumin, alkaline phosphatase, glycated hemoglobin (HbA1c), and urinary PCR for ΔCACS/y and ACI, serum albumin, calcium, brain natriuretic peptide (BNP), and hemoglobin for ΔACI/y were significantly related variables (**Supplemental Table 1**). Multivariable linear regression analysis revealed that DM status ($\beta=0.161$, $p=0.037$) and CACS at baseline ($\beta=0.735$, $p<0.001$) for ΔCACS/y and HT status ($\beta=0.238$, $p=0.046$) and ACI at baseline ($\beta=0.285$, $p=0.017$) for ΔACI/y were significantly independent predictors (**Table 3-A**). In the annualized variation, there was a positive correlation between ΔCACS/y and ΔACI/y ($R=0.351$, $p=0.003$) (**Fig. 3-A**). ΔCACS/y significantly correlated with the annualized variations of BSA (ΔBSA/y) ($R=-0.249$, $p=0.038$) and RPVI (ΔRPVI/y) ($R=-0.565$, $p<0.001$) (**Supplemental Table 2**, **Fig. 3-B**). Moreover, multiple linear regression analysis revealed that ΔRPVI/y ($\beta=-0.537$, $p<0.001$) was an independent factor for ΔCACS/y (**Table 3-B**). A similar trend was observed in the analysis for ΔACI/y. Although many annualized variations, such as body weight (BW), RPVI, eGFR, calcium, intact parathyroid hormone, BNP, and HbA1c were corrected with ΔACI/y (**Supplemental Table 2**, **Fig. 3-C**), multiple linear regression analysis revealed that ΔBW/y ($\beta=-0.446$, $p=0.001$), ΔRPVI/y ($\beta=-0.371$, $p=0.015$), and ΔHbA1c/y ($\beta=-0.264$, $p=0.041$) were independent factors for ΔACI/y (**Table 3-B**). On the other hand, eGFR at baseline and annualized eGFR variation (ΔeGFR/y) did not significantly correlate with ΔCACS/y and ΔACI/y in the multivariable analysis.

Discussion

There is a high prevalence of rapid VC progression in patients with CKD[7-10], which is prognostically related to the increased morbidity and mortality of CVD[11-15]. In this study, we discerned the relationship between CAC or AAC progression and renal functional/morphological changes and revealed the following results:

Table 1. Clinical characteristics at baseline and follow-up period ($n=70$)

	Baseline	Follow-up	*p*
Age, years	68.9 ± 9.9	73.2 ± 9.9	-
Female, *n* (%)	24 (34.3)		
BW, kg	62.2 ± 12.0	61.0 ± 12.7	0.57
BMI, kg/m^2	24.0 ± 3.5	23.7 ± 3.5	0.61
BSA, m^2	1.65 ± 0.18	1.63 ± 0.20	0.56
Hypertension, *n* (%)	56 (80.0)	59 (84.3)	0.51
SBP, mmHg	135.1 ± 18.4	130.0 ± 14.5	0.072
DBP, mmHg	77.7 ± 12.1	73.0 ± 11.4	0.02
Dyslipidemia, *n* (%)	48 (68.6)	50 (71.4)	0.71
Diabetes mellitus, *n* (%)	27 (38.6)	26 (37.1)	0.86
Smoking history, *n* (%)	31 (44.3)	31 (44.3)	1.00
CKD G stage			0.091
G1, *n* (%)	1 (1.4)	1 (1.4)	
G2, *n* (%)	7 (10.0)	5 (7.1)	
G3a, *n* (%)	20 (28.6)	10 (14.3)	
G3b, *n* (%)	17 (24.3)	20 (28.6)	
G4, *n* (%)	21 (30.0)	20 (28.6)	
G5, *n* (%)	4 (5.7)	14 (20.0)	
CKD A stage			0.1
A1, *n* (%)	21 (30.0)	20 (28.6)	
A2, *n* (%)	26 (37.1)	16 (22.9)	
A3, *n* (%)	23 (32.9)	34 (48.6)	
Medications, *n* (%)			
Anti-hypertension drugs, *n* (%)	55 (78.6)	58 (82.9)	0.52
ACE-I/ARBs, *n* (%)	49 (70.0)	51 (72.3)	0.71
Warfarin, *n* (%)	2 (2.9)	4 (5.7)	0.4
Statins, *n* (%)	36 (51.4)	39 (55.7)	0.72
Anti-diabetes drugs, *n* (%)	18 (25.7)	18 (25.7)	1.00
Vitamin-D, *n* (%)	5 (7.1)	8 (11.4)	0.38
Phosphate binders, *n* (%)	4 (5.7)	12 (17.1)	0.034
CACS, AU	40.2 (2.2-222.4)	113.3 (11.0-576.0)	0.053
ACI, %	13.2 (3.4-31.9)	21.7 (8.3-47.1)	0.036
RPVI, mL/m^2	131.8 ± 43.2	115.5 ± 39.3	0.021
Laboratory data			
Serum albumin, g/dL	3.79 ± 0.45	3.91 ± 0.35	0.099
Creatinine, mg/dL	1.38 (1.06-1.90)	1.60 (1.11-2.74)	0.036
eGFR, mL/min/1.73m^2	40.3 ± 19.2	32.9 ± 19.0	0.022
Calcium, mg/dL	4.74 ± 0.18	4.68 ± 0.20	0.061
Phosphorus, mg/dL	3.37 ± 0.51	3.56 ± 0.71	0.078
Alkaline phosphatase, IU/L	237.6 ± 81.1	244.3 ± 92.6	0.65
Intact-PTH, pg/mL	62.1 (38.1-102.8)	76.8 (52.6-127.0)	0.006
BNP, pg/mL	24.1 (10.4-61.1)	25.4 (12.4-75.6)	0.42
Hemoglobin, g/dL	12.3 ± 1.7	12.4 ± 1.8	0.79
HbA1c, %	6.0 ± 0.5	6.2 ± 0.7	0.22
LDL-cholesterol, mg/dL	97.9 ± 25.6	96.9 ± 29.6	0.82
Urinary PCR, g/gCr	0.35 (0.12-0.74)	0.51 (0.11-1.37)	0.14

CT follow-up period : 4.6 (3.2-5.4) years

Data are expressed as means ± SD, or numbers (percentages), or median (interquartile range).

BW, Body weight; BMI, body mass index; BSA, body surface area; SBP, systolic blood pressure; DBP, diastolic blood pressure; CKD, chronic kidney disease; ACE-I, angiotensin converting enzyme inhibitor; ARBs, angiotensin receptor blockers; CACS, coronary artery calcification score; AU, Agatston unit; ACI, abdominal aortic calcification index; RPVI, renal parenchymal volume index; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone; BNP, brain natriuretic peptide; HbA1c, glycated hemoglobin; LDL, low-density lipoprotein; PCR, protein to creatinine ratio.

Table 2. The baseline values of CACS, ACI, and RPVI in each CKD stages

	G1-2	G3	G4-5	*p*
CACS	133.1 (38.3-582.1)	27.2 (0.6-146.6)	30.3 (1.7-350.0)	0.21
ACI	20.6 (4.6-41.2)	11.9 (3.2-30.3)	17.2 (3.3-32.0)	0.71
RPVI	172.6 ± 32.4	144.2 ± 38.2	100.5 ± 32.4	< 0.001
	A1	A2	A3	
CACS	20.0 (0-209.5)	27.3 (2.4-91.8)	153.8 (9.6-338.2)	0.11
ACI	12.1 (3.0-26.8)	9.3 (2.7-31.1)	22.7 (7.0-37.0)	0.31
RPVI	137.7 ± 39.0	118.7 ± 33.2	141.3 ± 53.8	0.14

Data are expressed as means ± SD, or median (interquartile range).
Abbreviations as in Table 1.

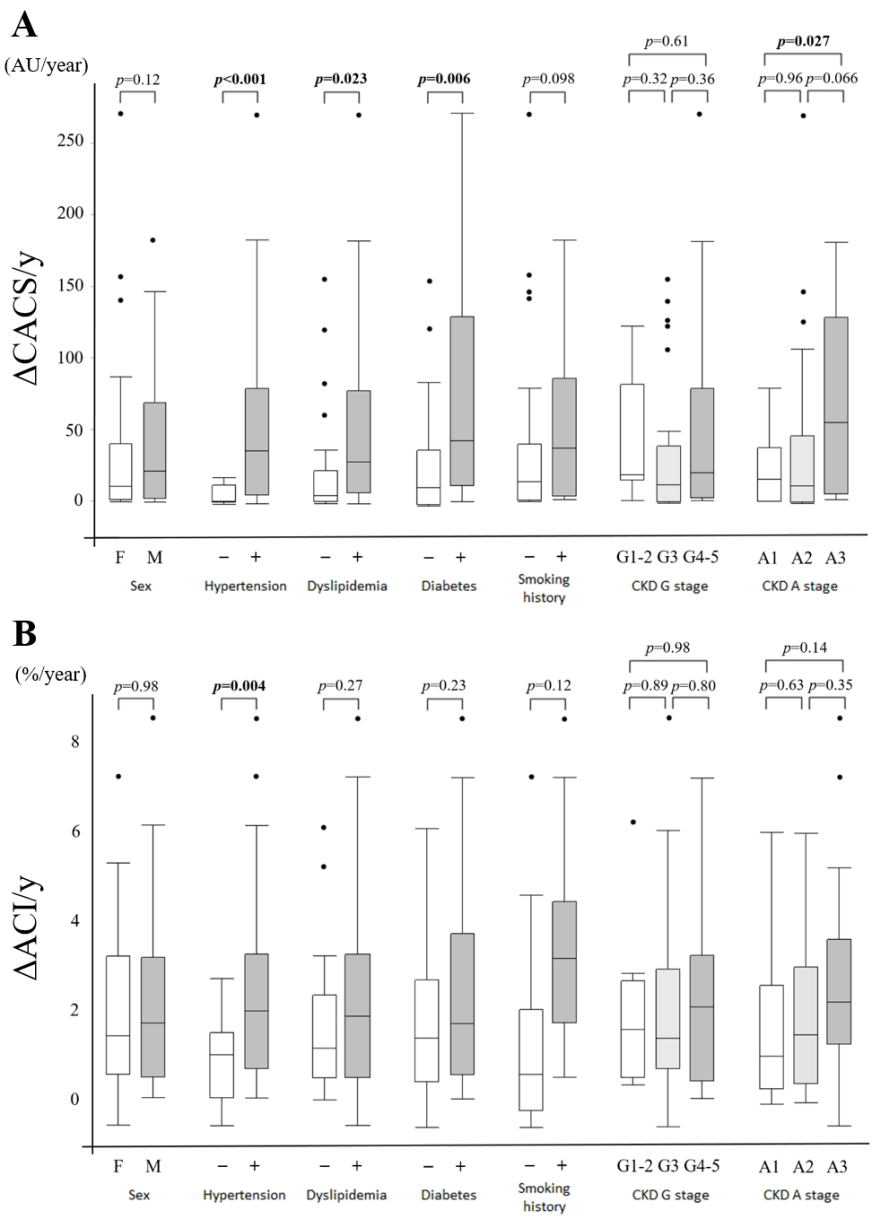


Fig. 2.

(A) Comparison of annualized coronary artery calcification score variation (ΔCACS/y) values with clinical characteristics. (B) Comparison of annualized abdominal aortic calcification index variation (ΔACI/y) values with clinical characteristics. ΔCACS/y was higher in patients with hypertension (35.7 vs. 0.6; $p < 0.001$), dyslipidemia (28.9 vs. 4.2; $p = 0.023$), diabetes mellitus (42.0 vs. 11.9; $p = 0.006$), and chronic kidney disease (CKD) stage A3 (A1: A2: A3 = 15.8: 11.6: 54.5; vs. A1, $p = 0.027$; vs. A2, $p = 0.066$). ΔACI/y was higher in patients with hypertension (1.8 vs. 0.9; $p = 0.004$). All values represented are median.

Table 3-A. Linear regression analysis in baseline variable

For ΔCACS/y	Univariate analysis		Multivariate analysis	
	R	*p*	*β*	*p*
Hypertension	0.281	<0.001	0.032	0.68
Dyslipidemia	0.203	0.023	−0.026	0.74
Diabetes mellitus	0.38	0.006	0.161	0.037
CACS	0.825	<0.001	0.735	<0.001
RPVI	0.257	0.032	0.066	0.37
Serum albumin	−0.273	0.022	−0.077	0.35
Alkaline phosphatase	0.274	0.022	0.128	0.079
Urinary PCR	0.305	0.01	−0.026	0.77
For ΔACI/y	Univariate analysis		Multivariate analysis	
	R	p	*β*	p
Hypertension	0.305	0.004	0.238	0.046
ACI	0.44	<0.001	0.285	0.017
Serum albumin	−0.3	0.012	−0.115	0.37
Calcium	0.278	0.02	0.195	0.11
BNP	0.253	0.049	0.097	0.41
Hemoglobin	−0.291	0.015	−0.188	0.13

Δ(variable)/y means annualized variation of the variable. Abbreviations as in Table 1.

Table 3-B. Linear regression analysis in annualized variation

For ΔCACS/y	Univariate analysis		Multivariate analysis	
	R	*p*	*β*	*p*
ΔBSA/y	−0.249	0.038	−0.156	0.12
ΔRPVI/y	−0.565	<0.001	−0.537	<0.001
For ΔACI/y	Univariate analysis		Multivariate analysis	
	R	*p*	*β*	*p*
ΔBW/y	−0.378	0.001	−0.446	0.001
ΔRPVI/y	−0.289	0.015	−0.371	0.015
ΔeGFR/y	−0.323	0.006	0.191	0.27
ΔCalcium/y	−0.27	0.006	−0.019	0.91
ΔIntact-PTH/y	0.321	0.012	0.227	0.22
ΔBNP/y	0.369	0.005	0.116	0.49
ΔHbA1c/y	−0.341	0.012	−0.264	0.041

Δ(variable)/y means annualized variation of the variable. Abbreviations as in Table 1.

1) CACS at baseline and DM were independent predictors for CAC progression.

2) ACI at baseline and HT were independent predictors for AAC progression.

3) In annualized variations, a decrease in RPV, but not in eGFR, were significantly related to both CAC and AAC progression.

To our knowledge, this is the first study dissecting and clarifying the intimate relationships between RPV and VC progression.

Several studies have reported that the presence of calcification, DM, and HT are strong indicators for progressive calcification, while VC absence in patients with CKD strongly implies a lack of calcification during disease progression[8, 9, 13]. Stavroulopoulos *et al.*[9] have reported that patients with CKD with DM have a higher prevalence and greater increase in CACS than patients with CKD with non-DM. Hyperglycemia

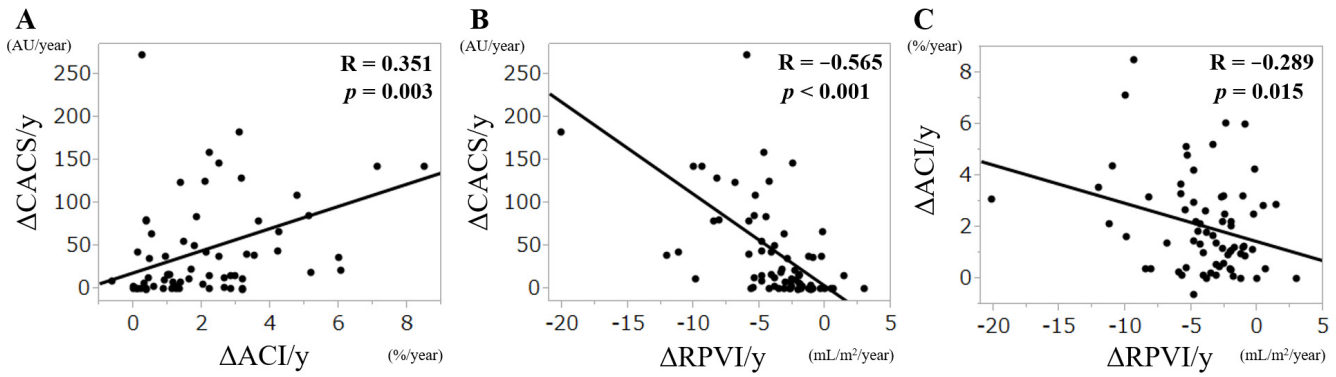


Fig. 3.

(A) Correlation between annualized coronary artery calcification score variation (ΔCACS/y) and annualized abdominal aortic calcification index variation (ΔACI/y). (B) Correlation between ΔCACS/y and annualized renal parenchymal volume index variation (ΔRPVI/y). (C) Correlation between ΔACI/y and ΔRPVI/y. ΔCACS/y revealed a positive correlation to ΔACI/y ($R=0.351$, $p=0.003$). Furthermore, ΔCACS/y revealed a negative correlation to ΔRPVI/y ($R=-0.565$, $p<0.001$). In a similar manner, ΔACI/y revealed a weak negative correlation to ΔRPVI/y ($R=-0.289$, $p=0.015$).

and insulin resistance lead to osteogenic differentiation of vascular smooth muscle cells[31], and an accumulation of advanced glycation end products resulting from long-term hyperglycemia have been reported to be associated with CAC[32]. HT is a well-established risk factor for arterial stiffness and medial calcification[33], and some previous studies have revealed that pulse blood pressure levels promote AAC progression[10, 34]. VC occurs in the intima in association with atherosclerosis, which is characterized by an increase in the deposition of plaques, and in the media in association with arteriosclerosis, which is characterized by vascular stiffening due to loss of elasticity of the arterial musculature[33, 35]. A previous study has revealed that there is a significant relationship between CAC and AAC[36], and our study revealed that both the annualized variations had a significant correlation in the same manner (**Fig. 3-A**). Although a combination of intimal and medial calcification may occur in patients with CKD, CAC is considered to be mainly due to intimal calcification and AAC to be due to medial calcification. This is why there is a difference in the predict factors between CAC and AAC progression.

Interestingly, we found that renal morphological change was associated more strongly with VC variability over time than eGFR in our patient cohort despite there being a correlation between RPVI and eGFR. This means that the more advanced renal atrophy becomes, the more severe VC is formed. Although GFR is an indicator of the filtration ability of kidneys and eGFR is an excellent marker that can be estimated based on serum creatinine levels, serum creatinine is affected by muscle mass and nutritional status. In addition, serum creatinine levels may be underestimated in the elderly[37]. On the other hand, RPV, excluding tissues that do not contribute to renal function, can be quantitatively and accurately measured based on CT images and more reflective of renal function, including renal endocrine and tubular function in addition to filtration ability. Renal atrophy results from global glomerulosclerosis, tubular atrophy, and interstitial fibrosis due to macro- and microvascular damage[22]. α-Klotho is one of the most important regulating factors influenced by vascular calcification and facilitates normal phosphaturic function of FGF23 in the kidneys[38, 39]. α-Klotho is expressed mostly in renal tubular cells and parathyroid glands, and production and serum levels decline upon decreased renal function[40, 41]. In addition, the serum level of 1,25-dihydroxyvitamin D3, which is involved in calcium regulation, decreases as renal function declines[40]. Moreover, tubular atrophy downregulates the expression of various proteins associated with vascular calcification. Thus, changes in RPV, but renal function estimated by eGFR, may strongly synchronize with VC progression.

The decrease of BW was another independent associated factor for ΔACI/y in our study. This is considered to occur because of malnutrition in patients with CKD. Recent data have suggested that malnutrition can trigger CKD–mineral bone disorder and accelerate VC progression[42]. Previous studies have revealed that phosphate overload leads to mineral bone abnormalities and directly promotes systemic malnutrition and VC in CKD[43, 44], and this is one of the reasons why lowering the phosphate level is effective in reducing calcification. In our study, HbA1c

changes are also negatively associated with ΔACI/y. This mechanism is not clear; however, because HbA1c improves according to the deterioration of renal function and malnutrition, these changes are considered to have secondarily affected ΔACI/y.

There are several limitations to our study. First, this study was conducted in a single center and included few patients. Second, 7 patients with diabetic nephropathy were enrolled in our study. Although, in some cases, renal volume is expanded in the early phase of diabetic nephropathy, there was no impact on the relationship between ΔCACS/y or ΔACI/y and Δ RPVI/y when we eliminated these patients from our study. Furthermore, the prevalence of diabetic nephropathy in this study was much less than that in the general patient population. There are two possible reasons for this. The first reason is that this study was conducted at a single university hospital and had an etiologic bias. The second reason is that some patients with diabetic nephropathy were excluded because they had undergone coronary intervention in the past. At last, when we performed the measurement of renal volume by CT scan, radiation exposure was increased in comparison with non-invasive sonography. However, we adopted this method because estimating CT-based renal parenchymal volume was more accurate than sonographic measurement.

Conclusion

VC progression was strongly associated with changes in renal volume and predicted by a high baseline VC as well as the presence of atherosclerotic diseases, such as DM and HT, in patients with CKD who were not on dialysis. With regard to VC progression, changes in renal volume provided more information than conventional indicators of kidney function, such as eGFR and urinary protein. When treating patients with CKD, clinicians should bear in mind that baseline VC presence, DM, HT, and renal volumes are crucial factors that may enhance VC progression and thus cardiovascular disease.

Acknowledgments

We express our sincere appreciation to all patients, collaborating physicians, and other medical staff for their valuable contributions to the study. This project was supported in part by the research grant from the Aichi Kidney Foundation and Grant-in-Aid for Scientific Research [No. 16K19398 (to R.M.)] from the Ministry of Education, Culture, Sports, Science, and Technology in Japan.

Disclosures

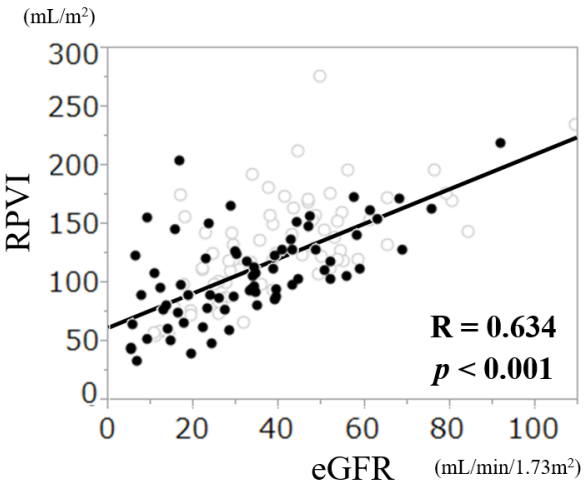
R.M. and Y.Y. belong to a development endowed by Chugai, Kowa, Kyowa Hakko Kirin, MSD, Kureha, and Nippon Boehringer Ingelheim.

References

1) Go A, Chertow G, Fan D, Mcculloch CE, Hsu C: Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization. New Eng J Med, 2004; 351: 1296-1305
2) Culleton BF, Larson MG, Wilson PWF, Evans JC, Parfrey PS, Levy D: Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. Kidney Int, 1999; 56: 2214-2219
3) Levin A: Clinical Epidemiology of Cardiovascular Disease in Chronic Kidney Disease Prior to Dialysis. Semin Dial, 2003; 16: 101-105
4) Raggi P, Boulay A, Chasan-Taber S, Amin N, Dillon M, Burke SK, Chertow GM: Cardiac calcification in adult hemodialysis patients: A link between end-stage renal disease and cardiovascular disease? J Am Coll Cardiol, 2002; 39: 695-701
5) Pencak P, Czerwieńska B, Ficek R, Wyskida K, Kujawa-Szewieczek A, Olszanecka-Glinianowicz M, Wiecek A, Chudek J: Calcification of coronary arteries and abdominal aorta in relation to traditional and novel risk factors of atherosclerosis in hemodialysis patients. BMC Nephrol, 2013; 14: 10
6) Taniwaki H, Ishimura E, Tabata T, Tsujimoto Y, Shioi A, Shoji T, Inaba M, Inoue T, NishizawaY: Aortic calcification in haemodialysis patients with diabetes mellitus. Nephrol Dial Transplant, 2005; 20: 2472-2478
7) Russo D, Corrao S, Miranda I, Ruocco C, Manzi S, Elefante R, Brancaccio D, Cozzolino M, Biondi ML, Andreucci VE: Progression of Coronary Artery Calcification in Predialysis Patients. Am J Nephrol, 2007; 27: 152-158
8) Mehrotra R, Budoff M, Hokanson JE, Ipp E, Takasu J, Adler S: Progression of coronary artery calcification in diabetics with and without chronic kidney disease. Kidney Int, 2005; 68: 1258-1266
9) Stavroulopoulos A, Porter CJ, Pointon K, Monaghan JM, Roe SD, Cassidy MJD: Evolution of coronary artery calcification in patients with chronic kidney disease Stages 3 and 4 , with and without diabetes. Nephrol Dial Transplant, 2011; 26: 2582-2589
10) Yamamoto D, Suzuki S, Ishii H, Hirayama K, Harada K, Aoki T, Shibata Y, Negishi Y, Tatami Y, Sumi T, Ichii T, Kawashima K, Kunimura A, Kawamiya T, Morimoto R, Yasuda Y, Murohara T: Predictors of abdominal aortic calcification progression in patients with chronic kidney disease without hemodialysis. Atherosclerosis, 2016; 253: 15-21
11) Hwang I-C, Park HE, Kim H-L, Kim HM, Park J-B, Yoon YE, Lee S-P, Kim H-K, Cho G-Y, Sohn D-W, Kim Y-J: Systemic Inflammation Is Associated With Coronary Artery Calcification and All-Cause Mortality in Chronic Kidney Disease. Circ J, 2016; 80: 1644-1652

12) Russo D, Corrao S, Battaglia Y, Andreucci M, Caiazza A, Carlomagno A, Lamberti M, Pezone N, Pota A, Russo L, Sacco M, Scognamiglio B: Progression of coronary artery calcification and cardiac events in patients with chronic renal disease not receiving dialysis. Kidney Int, 2011; 80: 112-118
13) Sigrist MK, Taal MW, Bungay P, McIntyre CW: Progressive vascular calcification over 2 years is associated with arterial stiffening and increased mortality in patients with stages 4 and 5 chronic kidney disease. Clin J Am Soc Nephrol, 2007; 2: 1241-1248
14) Wilson PW, Kauppila LI, O'Donnell CJ, Kiel DP, Hannan M, Polak JM, Cupples LA: Abdominal aortic calcific deposits are an important predictor of vascular morbidity and mortality. Circulation, 2001; 103: 1529-1534
15) Tatami Y, Yasuda Y, Suzuki S, Ishii H, Sawai A, Shibata Y, Ota T, Shibata K, Niwa M, Morimoto R, Hayashi M, Kato S, Maruyama S, Murohara T: Impact of Abdominal Aortic Calcification on Long-term Cardiovascular Outcomes in Patients with Chronic Kidney Disease. Atherosclerosis, 2015; 243: 349-355
16) Honda H, Hirano T, Ueda M, Kojima S, Mashiba S, Hayase Y, Michihata T, Shibata T: High-Density Lipoprotein Subfractions and Their Oxidized Subfraction Particles in Patients with Chronic Kidney Disease. J Atheroscler Thromb, 2016; 23: 81-94
17) Kubo S, Kitamura A, Imano H, Cui R, Yamagishi K, Umesawa M, Muraki I, Kiyama M, Okada T, Iso H: Serum Albumin and High-Sensitivity C-reactive Protein are Independent Risk Factors of Chronic Kidney Disease in Middle- Aged Japanese Individuals: the Circulatory Risk in Communities Study. J Atheroscler Thromb, 2016; 23: 1089-1098
18) Sangiorgi G, Rumberger JA, Severson A, Edwards WD, Gregoire J, Fitzpatrick LA, Schwartz RS: Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: A histologic study of 723 coronary artery segments using nondecalcifying methodology. J Am Coll Cardiol, 1998; 31: 126-133
19) Porter CJ, Stavroulopoulos A, Roe SD, Pointon K, Cassidy MJD: Detection of coronary and peripheral artery calcification in patients with chronic kidney disease stages 3 and 4, with and without diabetes. Nephrol Dial Transplant, 2007; 22: 3208-3213
20) Tamashiro M, Iseki K, Sunagawa O, Inoue T, Higa S, Afuso H, Fukiyama K: Significant association between the progression of coronary artery calcification and dyslipidemia in patients on chronic hemodialysis. Am J Kidney Dis, 2001; 38: 64-69
21) Tomiyama C, Higa A, Dalboni MA, Cendoroglo M, Draibe SA, Cuppari L, Carvalho AB, Neto EM, Canziani MEF: The impact of traditional and non-traditional risk factors on coronary calcification in pre-dialysis patients. Nephrol Dial Transplant, 2006; 21: 2464-2471
22) Zhou XJ, Rakheja D, Yu X, Saxena R, Vaziri ND, Silva FG: The aging kidney. Kidney Int, 2008; 74: 710-720
23) Bleyer AJ, Shemanski LR, Burke GL, Hansen KJ, Appel RG: Tobacco, hypertension, and vascular disease: risk factors for renal functional decline in an older population. Kidney Int, 2000; 57: 2072-2079
24) Bax L, Van der Graaf Y, Rabelink AJ, Algra A, Beutler JJ, Mali WPTM: Influence of atherosclerosis on age-related changes in renal size and function. Eur J Clin Invest, 2003; 33: 34-40
25) Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group: KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl, 2013; 3: 1-150
26) Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A: Revised Equations for Estimated GFR From Serum Creatinine in Japan. Am J Kidney Dis, 2009; 53: 982-992
27) Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R: Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol, 1990; 15: 827-832
28) Urabe Y, Yamamoto H, Kitagawa T, Utsunomiya H, Tsushima H, Tatsugami F, Awai K, Kihara Y: Identifying Small Coronary Calcification in Non-Contrast 0.5-mm Slice Reconstruction to Diagnose Coronary Artery Disease in Patients with a Conventional Zero Coronary Artery Calcium Score. J Atheroscler Thromb, 2016; 23: 1324-1333
29) Morrisroe SN, Su RR, Bae KT, Eisner BH, Hong C, Lahey S, Catalano OA, Sahani DV, Jackman SV: Differential renal function estimation using computerized tomography based renal parenchymal volume measurement. J Urol, 2010; 183: 2289-2293
30) Johnson S, Rishi R, Andone A, Khawandi W, Al-Said J, Gletsu-Miller N, Lin E, Baumgarten DA, O'Neill WC: Determinants and functional significance of renal parenchymal volume in adults. Clin J Am Soc Nephrol, 2011; 6: 70-76
31) Avogaro A, Fadini GP: Mechanisms of ectopic calcification: implications for diabetic vasculopathy. Cardiovasc Diagn Ther, 2015; 5: 343-352
32) Hangai M, Takebe N, Honma H, Sasaki A, Chida A, Nakano R, Togashi H, Nakagawa R, Oda T, Matsui M, Yashiro S, Nagasawa K, Kajiwara T, Takahashi K, Takahashi Y, Satoh J, Ishigaki Y: Association of Advanced Glycation End Products with coronary Artery Calcification in Japanese Subjects with Type 2 Diabetes as Assessed by Skin Autofluorescence. J Atheroscler Thromb, 2016; 23: 1178-1187
33) London GM, Marchais SJ, Guerin AP, Metivier F, Adda H: Arterial structure and function in end-stage renal disease. Nephrol Dial Transplant, 2002; 17: 1713-1724
34) Miwa Y, Tsushima M, Arima H, Kawano Y, Sasaguri T: Pulse Pressure Is an Independent Predictor for the Progression of Aortic Wall Calcification in Patients with Controlled Hyperlipidemia. Hypertension, 2004; 43: 536-540
35) Schoppet M, Shroff RC, Hofbauer LC, Shanahan CM: Exploring the biology of vascular calcification in chronic kidney disease: What's circulating? Kidney Int, 2008; 73: 384-390
36) Takayama Y, Yasuda Y, Suzuki S, Shibata Y, Tatami Y, Shibata K, Niwa M, Sawai A, Morimoto R, Kato S, Ishii H, Maruyama S, Murohara T: Relationship between abdominal aortic and coronary artery calcification as detected by computed tomography in chronic kidney disease patients. Heart Vessels, 2015; 31: 1030-1037

37) Murata K, Baumann NA, Saenger AK, Larson TS, Rule AD, Lieske JC: Relative performance of the MDRD and CKD-EPI equations for estimating glomerular filtration rate among patients with varied clinical presentations. Clin J Am Soc Nephrol, 2011; 6: 1963-1972
38) Hu MC, Shi M, Zhang J, Quinones H, Griffith C, Kuro-o M, Moe OW: Klotho Deficiency Causes Vascular Calcification in Chronic Kidney Disease. J Am Soc Nephrol, 2011; 22: 124-136
39) Kuro-O M: Phosphate and Klotho. Kidney Int Suppl, 2011; 79: S20-S23
40) Pavik I, Jaeger P, Ebner L, Wagner CA, Petzold K, Spichtig D, Poster D, Wüthrich RP, Russmann S, Serra AL: Secreted Klotho and FGF23 in chronic kidney disease Stage 1 to 5: A sequence suggested from a cross-sectional study. Nephrol Dial Transplant, 2013; 28: 352-359
41) Koh N, Fujimori T, Nishiguchi S, Tamori A, Shiomi S, Nakatani T, Sugimura K, Kishimoto T, Kinoshita S, Kuroki T, Nabeshima Y: Severely reduced production of klotho in human chronic renal failure kidney. Biochem Biophys Res Commun, 2001; 280: 1015-1020
42) Zhang K, Gao J, Chen J, Liu X, Cai Q, Liu P, Huang H: MICS, an easily ignored contributor to arterial calcification in CKD patients. Am J Physiol Renal Physiol, 2016; 311: F663-F670
43) Lau WL, Linnes M, Chu EY, Foster BL, Bartley BA, Somerman MJ, Giachelli CM: High phosphate feeding promotes mineral and bone abnormalities in mice with chronic kidney disease. Nephrol Dial Transplant, 2013; 28: 62-69
44) Yamada S, Tokumoto M, Tatsumoto N, Taniguchi M, Noguchi H, Nakano T, Masutani K, Ooboshi H, Tsuruya K, Kitazono T: Phosphate overload directly induces systemic inflammation and malnutrition as well as vascular calcification in uremia. Am J Physiol Renal Physiol, 2014; 306: F1418-F1428



Supplemental Fig. 1. Correlation between estimated glomerular filtration rate (eGFR) and renal parenchymal volume index (RPVI) (open symbols: at baseline, solid symbols: at follow-up period)

RPVI revealed a positive correlation to eGFR ($R=0.634$, $p<0.001$).

Supplemental Table 1. Correlations between baseline values and ΔCACS/y or ΔACI/y

	ΔCACS/y		ΔACI/y	
	R	p	R	p
Age	0.199	0.099	0.203	0.092
BW	−0.055	0.65	0.065	0.6
BMI	−0.044	0.72	0.124	0.31
BSA	−0.046	0.71	0.06	0.62
SBP	0.072	0.56	0.105	0.39
DBP	−0.222	0.065	−0.009	0.94
CACS	0.825	<0.001	0.255	0.033
ACI	0.452	<0.001	0.44	<0.001
RPVI	0.257	0.032	0.067	0.58
Serum albumin	−0.273	0.022	−0.300	0.012
Creatinine	−0.023	0.85	0.024	0.84
eGFR	−0.031	0.8	0.002	0.98
Calcium	0.11	0.37	0.278	0.02
Phosphorus	0.149	0.22	0.067	0.58
Alkaline phosphatase	0.274	0.022	0.179	0.14
Intact-PTH	−0.146	0.26	0.079	0.54
BNP	0.112	0.39	0.253	0.049
Hemoglobin	−0.23	0.055	−0.291	0.015
HbA1c	0.256	0.034	0.066	0.59
LDL-cholesterol	−0.025	0.84	−0.114	0.35
Urinary PCR	0.305	0.01	0.228	0.057

Δ(variable)/y means annualized variation of the variable. Abbreviations as in Table 1.

Supplemental Table 2. Correlations between annualized variations and ΔCACS/y or ΔACI/y

	ΔCACS/y		ΔACI/y	
	R	*p*	R	*p*
ΔBW/y	−0.223	0.064	−0.378	0.001
ΔBMI/y	−0.193	0.11	−0.346	0.003
ΔBSA/y	−0.249	0.038	−0.358	0.002
ΔSBP/y	−0.149	0.22	−0.156	0.2
ΔDBP/y	−0.105	0.39	−0.198	0.1
ΔCACS/y	-	-	0.351	0.003
ΔACI/y	0.351	0.003	-	-
ΔRPVI/y	−0.565	<0.001	−0.289	0.015
ΔSerum albumin/y	−0.013	0.91	0.113	0.35
ΔCreatinine/y	0.042	0.73	0.281	0.019
ΔeGFR/y	−0.184	0.13	−0.323	0.006
ΔCalcium/y	−0.088	0.47	−0.27	0.024
ΔPhosphorus/y	−0.033	0.79	0.151	0.21
ΔAlkaline phosphatase/y	−0.191	0.11	−0.134	0.27
ΔIntact-PTH/y	0.205	0.11	0.321	0.012
ΔBNP/y	0.087	0.52	0.369	0.005
ΔHemoglobin/y	−0.033	0.79	0.162	0.18
ΔHbA1c/y	−0.077	0.58	−0.341	0.012
ΔLDL-cholesterol/y	−0.162	0.18	0.13	0.29
ΔUrinary PCR/y	0.037	0.76	0.171	0.16

Δ(variable)/y means annualized variation of the variable. Abbreviations as in Table 1.