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Coronary artery calcification score and common iliac artery calcification score in non-dialysis CKD patients

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SUMMARY AT A GLANCE

Vascular calcification is a major contributor to morbidity and mortality in patients with CKD, although the optimal method and site for measurement of vascular calcification have not been determined. This study assesses and compares coronary artery calcification and common iliac artery calcification determined by CT in a cohort of non-dialysis CKD patients and reports on associated variables and outcomes.

ABSTRACT:

Aim: **Many studies have validated Agatston's coronary artery calcification score (CACS) for assessing vascular calcification (VC) in chronic kidney disease (CKD) patients. This study aimed to evaluate the CACS and common iliac artery calcification score (IACS) and to examine the variables related to each score.**

Methods: **The subjects were 145 non-dialysis CKD patients. The CACS and IACS were determined using the same thoracicoabdominal multi-detector computed tomography. Multiple regression analyses were performed to assess the factors associated with the CACS or IACS. The associations between progression to renal replacement therapy (RRT) and the CACS or IACS were studied using Cox hazards models.**

Results: **The subjects' median age, estimated glomerular filtration rate (eGFR), and follow-up period were 72 (62–78) years, 32 (18–50) mL/min/1.73m^2, and 864 (550–1425) days, respectively. Age, diabetes, the serum phosphate level, and the eGFR were found to be significant factors of the CACS [β (95% CI): 0.38 (0.02–0.04), $P < 0.0001$, 0.28 (0.19–0.50), $P < 0.0001$, 0.16 (0.03–0.45), $P < 0.05$ and −0.15 (−0.02–0.00), $P < 0.05$, respectively]. Age and diabetes were shown to be significant factors of the IACS [β (95% CI): 0.53 (0.04–0.06), $P < 0.0001$, and 0.18 (0.07–0.40), $P < 0.01$, respectively]. Progression to RRT occurred in 31 patients and was significantly associated with the CACS (hazard ratio: 1.01, $P < 0.01$), urinary protein level and eGFR, but not the IACS.**

Conclusion: **Chronic kidney disease related risk factors for VC, such as the eGFR and hyperphosphataemia, are significantly associated with a high CACS, but not a high IACS, and the CACS is a significant predictor of progression to RRT.**

Vascular calcification (VC) is associated with the risk of cardiovascular mortality and is highly prevalent in patients with chronic kidney disease (CKD).[1] Intimal calcification is an indicator of atherosclerosis, and medial calcification, as represented by Mönckeberg medial sclerosis, is an indicator of arteriosclerosis.[2–5] CKD patients exhibit both intimal and medial calcification.[2–4] Many studies have validated the use of Agatston's coronary artery calcification score (CACS) based on multi-detector computed tomography (MDCT)[6] to assess VC in CKD patients. However, the CACS is not able to distinguish between intimal (atherosclerotic) and medial (arteriosclerotic) calcification, which result in different cardiovascular insults (acute coronary syndrome and myocardial infarction vs. left ventricular hypertrophy and cardiac failure).[4] Compared with elastic arteries, such as the aorta, muscular arteries distribute blood to various organs, and are more susceptible to medial calcification.[1] It is reported that the Adragao score (AS) is useful for evaluating VC in muscular (radial and digital) or predominantly muscular (iliac and femoral) arteries, which are more susceptible to medial calcification,[7,8] and the AS has been confirmed to be an independent predictor of mortality and hospital admission in CKD patients.[8] Thus, assessing both the CACS and the common iliac artery calcification score (IACS): predominantly

muscular artery calcification score, in CKD patients using the same thoracicoabdominal MDCT images might provide further information about VC in CKD patients. An imbalance between promoters [e.g., age, inflammatory status, calcium phosphate disorders, CKD and diabetes mellitus (DM)] and inhibitors [e.g., fetuin-A, matrix Gla protein (MGP), pyrophosphate] is critical for the development of VC.[9–11] The aim of this study was to evaluate both the CACS and IACS and identify variables related to each calcification score in non-dialysis CKD patients.

METHODS

Study population

The subjects were 145 unselected, consecutive non-dialysis patients with grade 2–5 CKD. All of the patients were referred to our hospital from nearby institutions to undergo treatment for CKD between 2012 and 2015 and were followed up until April 2017 or their death. Patients aged <20 years old, with a history of neoplastic disease, with active infections, or who had undergone an organ transplant were excluded from this study. MDCT, blood and urine sampling from all CKD patients were obtained at the first visit in our hospital. The committee on human research at Ichiyokai Hospital approved this study (authorization No. 201401), and conforms to the provisions of the Declaration of Helsinki (as revised in Brazil in 2013). The patients were informed about the purpose and nature of the study, and all patients provided written informed consent.

Data collection

The patients' age, sex, blood pressure just before the MDCT, presence of DM, presence of hypertension, presence of coronary artery disease, presence of peripheral artery disease, current or former smoker and current or previous use of warfarin, statins, active vitamin D3, and/or phosphate binders were evaluated. All blood and urine samples were taken before the MDCT on the same day. The patients' (n = 145) albumin-adjusted serum calcium (Ca) levels, serum phosphate, creatinine, uric acid, alkaline phosphatase (AL-P), C-reactive protein (CRP), albumin, low-density lipoprotein cholesterol (LDL-C), triglyceride, haemoglobin (Hb), and transferrin saturation (TSAT), urinary protein, and estimated glomerular filtration rates (eGFR)[12] were examined. The CACS was assessed using the Agatston score,[6] which was obtained from thoracicoabdominal MDCT images. The MDCT was performed on an Aquilion 64 TSX-101A (Toshiba Medical Systems, Tokyo, Japan). Iliac artery visualization was achieved using the same thoracicoabdominal MDCT images as were used to calculate the CACS. The same image processing software (Aze VirtualPlace) was used to determine both scores. A scout localization image was obtained to determine the level of the bifurcation of the aorta as a guide to the location of the common iliac artery. The scanner configuration was then switched to the 5 mm, single-slice mode. Eight to 12 contiguous slices were acquired up to the upper margin of the bifurcation of the common iliac artery. Regions of interest were placed around all lesions found within the right and left common iliac arteries. The threshold for a calcific lesion was set at a computed tomographic density of 130 Hounsfield units within an area of ≥1 mm^2. The total common iliac artery calcification score was determined by adding up each of the scores for all slices (Fig. 1). Renal replacement therapy (RRT) was defined as need for chronic dialysis initiation or transplantation. Renal death was defined as the progression to RRT and all cause deaths were confirmed by documentation.

Statistical analysis

All statistical analyses were performed with JMP 10 Windows (SAS Institute Japan, Tokyo, Japan). The patients' clinical characteristics and laboratory data are shown in each CACS quartile or IACS quartile, respectively. Data for categorical variables are given as number of patients (percentage: %), data for continuous variables are given as mean ± standard deviation (SD) or median (interquartile range: IQR) values, and the significance of inter-group differences was analyzed with Fisher's exact test, Tukey's honestly significant difference test, or the Steel-Dwass test, as appropriate. CACS and IACS that exhibited non-parametric distributions were transformed to the logarithm (log) prior to the regression analyses. Regression analyses and multiple regression analyses for CACS and IACS were performed, respectively. Multiple regression analyses were respectively performed using all of the variables that were found to be significantly ($P < 0.05$) associated with the Log CACS or Log IACS by regression analyses. Kaplan–Meier cumulative survival and cumulative renal survival in each CACS quartile and in each IACS quartile were examined. Univariate and multivariate Cox proportional hazards models were used to determine the factor for progression to RRT.

RESULTS

All of the subjects (n = 145) were Japanese. The patients' underlying diseases included nephrosclerosis (58 patients, 40%), diabetic nephropathy (45 patients, 31.0%), chronic glomerulonephritis (25 patients, 17.2%), autosomal dominant polycystic kidney disease (two patients, 1.4%), other diseases (four patients, 2.8%), and unknown conditions (11 patients, 7.6%).

Calcification was observed in 118/145 (81.4%) of coronary arteries and 127/145 (87.6%) of common iliac arteries. The patients were divided into CACS quartiles: Q1 (n = 36), Q2 (n = 37), Q3 (n = 37), and Q4 (n = 35), and the clinical characteristics and laboratory data of all patients and each CACS quartile are shown in Table 1. Among all subjects

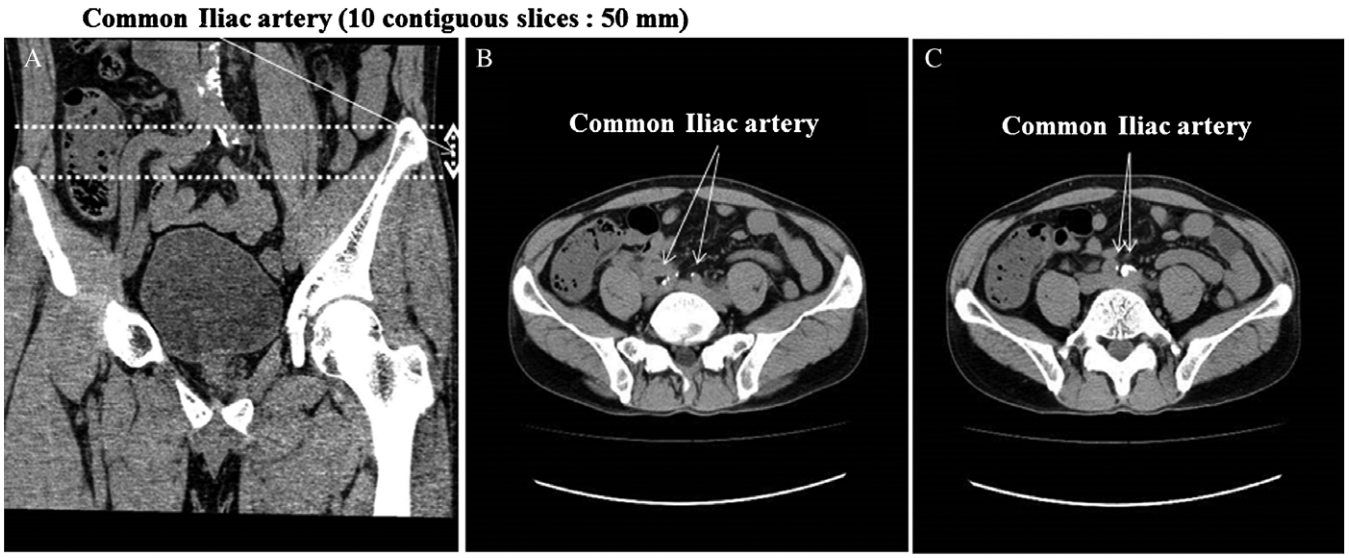


Fig. 1 (A) Longitudinal slice obtained using thoracicoabdominal multi-detector computed tomography (MDCT) at the level of the common iliac artery in a 58 year old chronic kidney disease patient due to nephrosclerosis with an eGFR of 24 mL/min/1.73m^2. Dense calcification (white specks) was seen in the right common iliac artery although the calcification in the left common iliac artery was also present. (B, C) Non-consecutive transverse 5 mm slices obtained using thoracicoabdominal MDCT in the same patient. Note the calcification in both the right common iliac artery and left common iliac artery. The total iliac calcification score was 576.6.

Table 1 Clinical characteristics and laboratory data of all patients and each CACS quartile

	All	CACS quartiles 1	CACS quartile 2	CACS quartiles 3	CACS quartile 4
CACS	84 (10–546)	0 (0–0.9)***	42 (23–71)***	267 (149–354)*	863 (372–2911)
n	145	36	37	37	35
Age (years)	72 (62–78)	62 (44–71)***	74(63–80)	72 (79–77)	77(69–81)
Sex: male (%)	89/145 (61.3)	23/36 (63.9)	30/37 (54.1)	24/37 (64.9)	22/35 (62.9)
Systolic blood pressure (mmHg)	139 ± 23	131 ± 22	141 ± 26	147 ± 24	135 ± 17
Diabetes (%)	45/145 (31.0)	5/36 (13.9)***	8/37 (21.6)**	13/37 (35.1)**	19/35 (54.3)
Hypertension (%)	123/145 (84.8)	22/36 (61.1)***	33/37 (89.2)	34/37 (91.9)	34/35 (97.1)
Coronal artery disease (%)	31/145 (21.4)	4/36 (11.1)**	7/37 (18.9)*	6/37 (16.2)*	14/35 (40.0)
Peripheral artery disease (%)	7/145 (4.8)	0/36 (0)*	0/37 (0)*	4/37 (10.8)	3/35 (8.6)
Current or former smoker (%)	43/145 (29.7)	11/36 (30.6)	10/37 (27.0)	8/37 (21.6)	14/35 (40.0)
Warfarin use (%)	5/145 (3.4)	0/36 (0)*	1/37 (2.7)	0/37 (0)*	4/35 (11.4)
Statin use (%)	52/145 (35.9)	8/36 (22.2)	13/37 (35.1)	13/37 (35.1)	18/35 (51.4)
Active vitamin D3 use (%)	11/145 (7.6)	0/36 (0)	4/37 (10.8)	2/37 (5.4)	5/35 (14.3)
Serum Ca (mmol/L)	2.33 (2.28–2.40)	2.33 (2.28–2.38)	2.33 (2.25–2.40)	2.35 (2.25–2.45)	2.35 (2.28–2.48)
Serum phosphate (mmol/L)	1.13 (1.00–1.26)	1.13 (0.94–1.16)**	1.13 (1.00–1.26)	1.10 (0.97–1.32)	1.16 (1.07–1.36)
Serum creatinine (mmol/L)	132.6 (94.6–229.8)	104.3 (79.6–143.2)***	123.8 (92.8–190.1)	168.0 (101.7–278.5)	176.8 (112.3–274.0)
Serum uric acid (mmol/L)	399 (327–452)	363 (244–458)	416 (333–440)	399 (339–470)	399 (339–482)
Serum AL-P (IU/L)	220 (175–286)	203 (163–264)	235 (183–282)	225 (176–288)	217 (182–309)
Serum C-reactive protein (mg/L)	1.0 (0–2.0)	1.0 (0–2.0)	0.8 (0–1.9)	1.0 (0.1–3.1)	1.0 (0.4–1.0)
Serum albumin (g/L)	40 (36–42)	42 (38–44)*	40 (36–42)	40 (37–42)	39 (34–42)
Serum LDL-cholesterol (mmol/L)	2.75 (2.28–3.39)	2.85 (2.33–3.57)	2.85 (2.31–3.34)	2.69 (2.38–3.13)	2.59 (2.02–3.39)
Serum triglycerides (mmol/L)	1.55 (1.12–2.19)	1.66 (1.12–2.24)	1.44 (1.15–2.23)	1.46 (1.04–2.25)	1.59 (1.34–2.15)
Haemoglobin (g/L)	123 ± 18	129 ± 16	122 ± 17	120 ± 19	119 ± 20
TSAT (%)	26 (21–33)	25 (19–34)	25 (14–31)	27 (16–31)	29 (22–35)
Urinary protein (g/gCr)	0.4 (0.1–1.7)	0.3 (0.1– 1.4)	0.1 (0.1–1.4)	0.3 (0.1–2.5)	0.6 (0.1–3.6)
eGFR (mL/min/1.73m^2)	32 (18–50)	53 (34–62)***	31 (22–44)	28 (15–44)	22 (16–46)

Data are expressed as the mean ± standard deviation, median (interquartile range), or number pf patients (%). Al-P, alkaline phosphatase; CACS: coronary artery calcification score, Diabetes, Hypertension, Coronary artery disease, Peripheral artery disease: the presence of diabetes mellitus, coronary artery disease, peripheral artery disease, respectively, eGFR: estimated glomerular filtration rates; LDL-cholesterol: low-density lipoprotein cholesterol, Systolic blood pressure: systolic blood pressure just before multi-detector computed tomography, Serum Ca: Albumin-adjusted serum calcium; TSAT: transferrin saturation *P < 0.05, **P < 0.01, ***P < 0.001 compared with CACS quartile 4.

(n = 145), the median (IQR) age was 72 (62–78) years, 89 of them were male (61.3%), and their mean (±SD) systolic blood pressure just before the MDCT was 139 ± 23 mmHg. In total, 45/145 (31.0%) subjects had DM, 123/145 (84.8%) subjects had hypertension, 31/145 (21.4%) subjects had coronary artery disease, and 7/145 (4.8%) subjects had peripheral artery disease and 43/145 (29.7%) subjects were current and former smokers, respectively. In addition, 5/145 (3.4%), 52/145 (35.9%), and 11/145 (7.6%) subjects were using warfarin, statins, and active vitamin D3, respectively, but none of the subjects were using phosphate binders. The CACS Q4 group exhibited a significantly higher age ($P < 0.001$) and a significantly higher frequency of hypertension ($P < 0.001$) compared with the CACS Q1 group, a significantly higher frequency of DM compared with the CACS Q1 ($P < 0.001$), Q2 ($P < 0.01$), and Q3 ($P < 0.01$) groups, a significantly higher frequency of coronary artery disease compared with the CACS Q1 ($P < 0.01$), Q2 ($P < 0.05$), and Q3 ($P < 0.05$) groups, a significantly higher frequency of peripheral artery disease compared with the CACS Q1 and Q2 groups ($P < 0.05$), and a significantly higher prevalence of warfarin use compared with the CACS Q1 and Q3 groups ($P < 0.05$). No other characteristics differed significantly between the CACS Q4 group and the other groups. Among all patients (n = 145), the median (IQR) urinary protein level was 0.4 (0.1–1.7) g/gCr, and the median (IQR) eGFR was 32 (18–50) mL/min per 1.73m^2. The patients in the CACS Q4 group displayed significantly higher serum phosphate ($P < 0.01$) and creatinine ($P < 0.001$) levels and significantly lower serum albumin ($P < 0.05$) levels and eGFR ($P < 0.001$) compared with the CACS Q1 group. No other laboratory data differed significantly between the CACS Q4 group and the other groups.

The patients were also divided into IACS quartiles: Q1 (n = 36), Q2 (n = 35), Q3 (n = 38), and Q4 (n = 36), and the clinical characteristics and laboratory data of the four groups are shown in Table 2. The IACS Q4 group displayed a significantly higher age compared with the IACS Q1 ($P < 0.001$), Q2 ($P < 0.001$), and Q3 ($P < 0.01$) groups, significantly higher prevalence rates of DM and hypertension compared with the IACS Q1 group ($P < 0.05$), a significantly higher prevalence of coronary artery disease compared with the IACS Q2 group ($P < 0.05$), and a significantly higher prevalence of warfarin use compared with the IACS Q1, Q2, and Q3 groups ($P < 0.05$). No other characteristics differed significantly between the IACS Q4 group and the other groups. The patients in the IACS Q4 group displayed significantly higher serum phosphate levels ($P < 0.01$) compared with the IACS Q2 and Q3 groups ($P < 0.05$), significantly higher serum AL-P ($P < 0.05$) and CRP ($P < 0.01$) levels, and significantly lower serum albumin levels ($P < 0.01$) compared with the IACS Q1 group. No other laboratory data

Table 2 Clinical characteristics and laboratory data of each iliac artery calcification score (IACS) quartile

	IACS quartiles 1	IACS quartile 2	IACS quartiles 3	IACS quartile 4
IACS	0 (0–49)***	363 (260–466)***	1237 (894–1661)***	3311 (2999–4987)
n	36	35	38	36
Age (years)	60 (44–74)***	69 (61–76)***	72 (68–78)**	79 (73–84)
Sex: male (%)	19/36 (52.8)	24/35 (68.6)	25/38 (65.8)	21/36 (58.3)
Systolic blood pressure (mmHg)	134 ± 26	140 ± 23	137 ± 22	143 ± 22
Diabetes (%)	4/36 (11.1)*	14/35 (40.0)	14/38 (36.8)	13/36 (36.1)
Hypertension (%)	7/36 (19.4)*	33/35 (94.3)	32/38 (84.2)	33/36 (91.7)
Coronal artery disease (%)	6/36 (16.7)	4/35 (11.4)*	9/38 (23.7)	12/36 (33.3)
Peripheral artery disease (%)	1/36 (2.8)	2/35 (5.7)	1/38 (2.6)	3/36 (8.3)
Current or former smoker (%)	1/36 (19.4)	12/35 (34.3)	12/38 (31.6)	12/36 (33.3)
Warfarin use (%)	0/36 (0)*	0/35 (0)*	0/38 (0)*	5/36 (13.9)
Statin use (%)	11/36 (30.6)	13/35 (37.1)	14/38 (36.8)	14/36 (38.9)
Active vitamin D3 use (%)	2/36 (5.6)	0/35 (0)	5/38 (13.2)	4/36 (11.1)
Serum Ca (mmol/L)	2.33 (2.28–2.38)	2.33 (2.25–2.40)	2.33 (2.28–2.40)	2.35 (2.28–2.50)
Serum phosphate (mmol/L)	1.13 (1.03–1.29)	1.13 (0.90–1.26)*	1.10 (0.94–1.20)*	1.20 (1.03–1.32)
Serum creatinine (mmol/L)	105.2 (85.7–166.2)	141.4 (90.2–194.5)	147.6 (106.1–265.2)	154.7 (97.2–245.8)
Serum uric acid (mmol/L)	363 (297–452)	416 (351–476)	387 (327–434)	387 (333–440)
Serum AL-P (IU/L)	197 (152–261)*	207 (178–284)	235 (200–299)	238 (183–307)
Serum C-reactive protein (mg/L)	0.1 (0–1.0)**	1.0 (0–2.3)	1.0 (0.1–2.9)	1.0 (1.0–2.0)
Serum albumin (g/L)	41 (39–45)**	40 (35–43)	39 (36–42)	39 (35–41)
Serum LDL-cholesterol (mmol/L)	3.03 (2.49–3.63)	2.64 (2.28–3.37)	2.75 (2.10–3.47)	1.36 (1.10–1.70)
Serum triglycerides (mmol/L)	1.62 (1.19–2.62)	1.64 (1.12–2.32)	1.32 (0.98–1.69)	1.55 (1.25–2.27)
Haemoglobin (g/L)	129 ± 16	122 ± 16	119 ± 19	121 ± 21
TSAT (%)	25 (21–31)	26 (22–34)	26 (21–20)	29 (20–41)
Urinary protein (g/gCr)	0.2 (0.1–2.2)	0.4 (0.1–1.5)	0.4 (0.1–3.1)	0.4 (0.1–2.4)
eGFR (mL/min/1.73m^2)	48 (21–59)	31 (22–43)	30.0 (17–47)	29 (17–42)

Data are expressed as the mean ± standard deviation, median (interquartile range), or number pf patients (%). All abbreviations are the same as in Table 1. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ compared with IACS quartile 4.

Table 3 Regression analyses and multiple regression analyses for coronary artery calcification score (CACS) or iliac artery calcification score (IACS) in patients with chronic kidney disease (CKD) (*n* = 145)

	A. Analyses for CACS									B. Analyses for IACS					
	Regression analyses			Multiple regression analyses						Regression analyses			Multiple regression analysis		
				Model 1			Model 2								
Variable	β	95% CI	*P-value*	β	95% CI	*P-value*	β	95% CI	*P-value*	β	95% CI	*P-value*	β	95% CI	*P-value*
Age (years)	0.49	0.03–0.05	*<0.0001*	0.38	0.02–0.04	*<0.0001*	0.37	0.02–0.04	*<0.0001*	0.58	0.04–0.06	*<0.0001*	0.53	0.04–0.06	*<0.0001*
Diabetes	0.36	0.25–0.62	*<0.0001*	0.28	0.19–0.50	*<0.0001*	0.27	0.17–0.49	*<0.0001*	0.25	0.11–0.52	*<0.01*	0.18	0.07–0.40	*<0.01*
Coronary artery disease	0.25	0.13–0.56	*<0.01*	0.02	−0.17 to 0.21	*0.82*	—	—	—	0.15	−0.02 to 0.44	*0.07*	—	—	—
Peripheral artery disease	0.20	0.10–0.94	*<0.05*	—	—	—	0.09	−0.11 to 0.57	*0.18*	0.09	−0.19 to 0.70	*0.26*	—	—	—
Current or former smoker	0.02	−0.18 to 0.22	*0.85*	—	—	—	—	—	—	0.10	−0.08 to 0.34	*0.21*	—	—	—
Warfarin use	0.19	0.08–1.07	*<0.05*	0.15	0.04–0.88	*<0.05*	0.16	0.09–0.88	*<0.05*	0.18	0.05–1.08	*<0.05*	0.12	−0.02 to 0.81	*0.06*
Statin use	0.19	0.03–0.41	*<0.05*	0.11	−0.02 to 0.28	*0.09*	0.12	−0.01 to 0.29	*0.07*	0.07	−0.11 to 0.29	*0.38*	—	—	—
Active vitamin D3 use	0.13	−0.07 to 0.62	*0.12*	—	—	—	—	—	—	0.09	−0.17 to 0.55	*0.31*	—	—	—
Serum phosphate (mmol/L)	0.20	0.06–0.55	*<0.05*	0.16	0.03–0.45	*<0.05*	0.15	0.01–0.43	*<0.05*	−0.01	−0.26 to 0.26	*0.98*	—	—	—
C-reactive protein (mg/L)	0.09	−0.04 to 0.13	*0.28*	—	—	—	—	—	—	0.04	−0.06 to 0.11	*0.62*	—	—	—
LDL- cholesterol (mmol/L)	0.21	−0.01 to 0.00	*0.21*	—	—	—	—	—	—	−0.11	−0.10 to 0.00	*0.18*	—	—	—
eGFR (mL/min/1.73m^2)	−0.38	−0.03 to −0.01	*<0.0001*	−0.15	−0.02 to −0.00	*<0.05*	−0.15	−0.02 to−0.00	*<0.05*	−0.26	−0.02 to −0.01	*<0.01*	−0.06	−0.01 to 0.00	*0.42*

95% CI: 95% confidence interval; β: standardized partial regression coefficient, Diabetes, Coronary artery disease, Peripheral artery disease: the presence of diabetes mellitus, coronary artery disease, peripheral artery disease, respectively, eGFR: estimated glomerular filtration rate, LDL cholesterol: Low-density lipoprotein cholesterol

Model 1: All of the significant variables in the regression analyses for Log CACS, except the presence of peripheral artery disease.

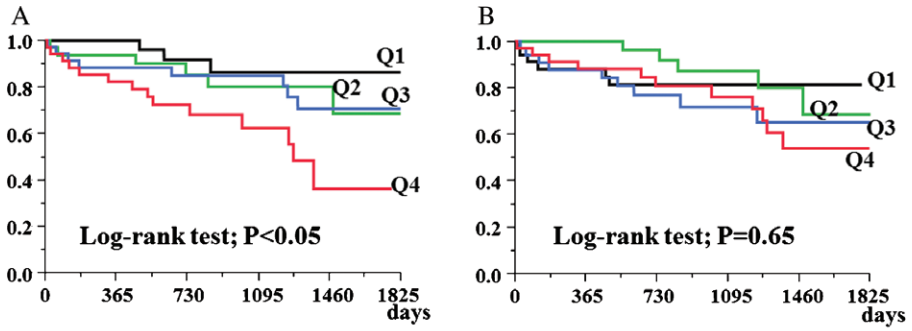
Model 2: All of the significant variables in the regression analyses for Log CACS, except the presence of coronary artery disease.

differed significantly between the IACS Q4 group and the other groups.

The results of the regression analyses and multiple regression analyses of predictors of the CACS in patients with CKD are shown in Table 3A, and the results of the analyses of predictors of the IACS are shown in Table 3B. The independent variables included in the (univariate) regression analyses for the CACS/IACS were age, the presence of DM, coronary artery disease, or peripheral artery disease, being a current or former smoker, warfarin use, statin use, active vitamin D3 use, the serum levels of phosphate, C-reactive protein, and LDL-cholesterol, and the eGFR. In the regression analyses for Log CACS, age ($P < 0.0001$), the presence of DM ($P < 0.0001$), the presence of coronary artery disease ($P < 0.01$), the presence of peripheral artery disease ($P < 0.05$), warfarin use ($P < 0.05$), statin use ($P < 0.05$), the serum phosphate level ($P < 0.05$), and the eGFR ($P < 0.0001$) were found to be significantly associated with the Log CACS. In the multiple regression analysis for Log CACS, Model 1 included all of the variables that were found to be significant in the regression analyses, except the presence of peripheral artery disease, and Model 2 included all of the variables that were found to be significant in the regression analyses, except the presence of coronary artery disease. Age, DM, warfarin use, the serum phosphate level, and the eGFR were found to be significant factors of the Log CACS [β (95% confidence interval: CI): 0.38 (0.02–0.04), $P < 0.0001$, 0.28 (0.19–0.50), $P < 0.0001$, 0.15 (0.04–0.88), $P < 0.05$, 0.16 (0.03–0.45), $P < 0.05$ and −0.15 (−0.02 to 0.00), $P < 0.05$], respectively in model 1 or [β (95% CI): 0.37 (0.02–0.04), $P < 0.0001$, 0.27 (0.17–0.49), $P < 0.0001$, 0.16 (0.09–0.88), $P < 0.05$, 0.15 (0.01–0.43), $P < 0.05$ and −0.15 (−0.02 to 0.00), $P < 0.05$], respectively in model 2. In the regression analyses for the Log IACS, age ($P < 0.0001$), the presence of DM ($P < 0.01$), warfarin use ($P < 0.05$), and the eGFR ($P < 0.01$) were found to be significantly associated with the Log IACS. In the multiple regression analysis, only age and the presence of DM were demonstrated to be significantly associated with the Log IACS [β (95% CI): 0.53 (0.04–0.06), $P < 0.0001$ and 0.18 (0.07–0.40), $P < 0.01$], respectively.

The overall median (IQR) follow-up time was 864 (550–1425) days. Twelve patients died, and 31 patients progressed to RRT during the follow-up period. No differences in Kaplan–Meier cumulative survival were detected among the CACS or IACS quartiles (data not shown). Kaplan–Meier plots showed significantly worse renal survival in the CACS Q4 group than in the CACS Q1, Q2, and Q3 groups (Log-rank test, $P < 0.05$), but no significant differences in renal survival were detected among the IACS Q1, Q2, Q3, and Q4 groups (Fig. 2).

Cox proportional hazard analyses of predictors of progression to RRT involving the vascular calcification score and other variables in patients with CKD are shown in Table 4. Independent variables for the univariate Cox models were age, sex (male), presence of DM, presence of coronary artery disease, presence of peripheral artery disease, CACS, IACS, systolic blood pressure (just before MDCT), serum phosphate, uric acid, LDL-cholesterol, urinary protein and eGFR. In the univariate analyses, the CACS, serum phosphate level, urinary protein level, and eGFR were found to be significantly associated with progression to RRT ($P < 0.0001$). In the multivariate analyses, Model 1 included all of the variables that were found to be significant in the univariate analyses, and Model 2 included IACS and all significant variables in the univariate analyses, except CACS. Multivariate analyses showed that the CACS [hazard ratio (HR) (95% CI): 1.01 (1.00–1.02), $P < 0.01$], urinary protein level [HR: 1.32 (1.17–1.48), $P < 0.0001$], and eGFR [HR: 0.91 (0.87–0.95), $P < 0.0001$] were significantly associated with progression to RRT (Model 1), but the IACS was not significantly associated with progression to RRT (Model 2).



	Progression to RRT (n)
Q1 (n=36)**	3
Q2 (n=37)*	6
Q3 (n=37)*	8
Q4 (n=35)	14

	Progression to RRT (n)
Q1 (n=36)	6
Q2 (n=35)	5
Q3 (n=38)	9
Q4 (n=36)	11

* Log rank; P<0.05 compared with CACS Q4
**Log rank; P<0.01 compared with CACS Q4

Fig. 2 Kaplan–Meier's renal survival curves in each coronary artery calcification score (CACS) quartile (A) and in each iliac artery calcification score (IACS) quartile (B) in patients with chronic kidney disease (n = 145). CACS: coronary artery calcification score, IACS: common iliac artery calcification score, Q: quartile, RRT: renal replacement therapy

Table 4 Cox proportional hazard analyses of predictors of progression to renal replacement therapy involving the vascular calcification score and other variables in patients with chronic kidney disease (CKD) (n = 145)

Independent variable	Univariate analyses			Multivariate analyses					
				Model 1			Model 2		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age (years)	1.01	0.98–1.04	*0.62*	—	—	—	—	—	—
Sex: male	1.33	0.63–3.05	*0.46*	—	—	—	—	—	—
Diabetes	1.90	0.92–3.84	*0.08*	—	—	—	—	—	—
Coronary artery disease	1.59	0.71–3.30	*0.24*	—	—	—	—	—	—
Peripheral artery disease	0.13	0.72–6.29	*0.13*	—	—	—	—	—	—
CACS	1.01	1.00–1.02	*<0.0001*	1.01	1.00–1.02	*<0.01*	—	—	—
IACS	1.00	0.99–1.00	*0.11*	—	—	—	1.00	0.99–1.00	*0.67*
Systolic blood pressure (mmHg)	1.01	0.99–1.03	*0.06*	—	—	—	—	—	—
Serum phosphate (mmol/L)	3.37	2.18–5.14	*<0.0001*	1.72	0.95–3.13	*0.07*	1.80	1.02–3.16	*<0.05*
Serum uric acid (mmol/L)	1.00	0.90–1.04	*0.95*	—	—	—	—	—	—
LDL-cholesterol (mmol/L)	1.00	0.99–1.01	*0.77*	—	—	—	—	—	—
Urinary protein (g/gCr)	1.29	1.16–1.42	*<0.0001*	1.32	1.17–1.48	*<0.0001*	1.32	1.18–1.48	*<0.0001*
eGFR (mL/min/1.73m^2)	0.90	0.86–0.93	*<0.0001*	0.91	0.87–0.95	*<0.0001*	0.91	0.86–0.95	*<0.0001*

HR: hazard ratios, 95%CI: 95% confidence interval, Systolic blood pressure: systolic blood pressure just before multi-detector computed tomography
All abbreviations are the same as in Table 3.
Model 1: All of the significant variables in the univariate analyses.
Model 2: IACS and all of the significant variables in the univariate analyses except CACS.

DISCUSSION

According to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, lateral abdominal radiographs can be used as a reasonable alternative to computed tomography to detect VC in patients with stage 3–5D CKD.[13] While, Hong *et al.* reported that calcification of the digital arteries, but not the abdominal aorta, is a good predictor of mortality in dialysis patients because of the high prevalence of aortic calcification and its association with age.[14] The same reasoning could be applied to non-dialysis CKD patients, in whom the presence of VC was found to be age-related and very prevalent.[8,15,16] Thus, we consider that calcification scores (the CACS and IACS) might be more useful than simply detecting the existence of VC in non-dialysis CKD patients.

The relative distributions of intimal versus medial calcification in an arterial segment can differ substantially in CKD patients.[3,4,17] Intimal and medial calcification might be related, however, there are some specific pathophysiological factors that are more relevant to intimal or medial calcification. Thus, medial and intimal calcification are considered to be distinct entities in CKD.[18] The risk factors for VC in CKD include traditional risk factors, such as older age, DM, dyslipidaemia, and inflammation, as well as novel risk factors that are more specific to patients with CKD, such as hyperphosphataemia, uraemic toxins, and dialysis vintage.[1,19] Medial calcification appears to be the parallel occurrence of a phenotype switch of vascular smooth muscle cell and local inflammation, in an environment with changed profiles of calcification-regulating humoral factors, which include calcium and phosphate itself.[11,20] More so than in the medial layer, intimal calcification appears to be secondary phenomenon of inflammation.[11]

According to previous reports,[7,8] we considered that the IACS reflects medial calcification to a greater extent than the CACS and the addition of the IACS to the CACS might have greater prognostic power in CKD patients. We were looking for associated variables of CACS and IACS that would suggest either a predominance of intimal or medial calcification in certain anatomical areas in CKD patients. However, this study is an observational study looking at associations, and therefore, it is not possible to determine the exact nature of the VC that arose in each patient. Actually, the prevalence of VC was extremely high in both the coronary arteries and common iliac arteries of the examined CKD patients with median (IQR) eGFR: 32 (18–50) mL/min/1.73m^2; i.e., calcification was observed in 81.4% of coronary arteries and 87.6% of common iliac arteries. Both VC scores seemed to increase with the deterioration of renal function, as shown in Tables 3 and 4. Our results support the hypothesis that the uraemic milieu promotes VC.[8,15] In this study, age and the presence of DM seemed to be common elements that were associated with both the CACS and IACS, which is consistent with previous reports.[1,10] However, some variables that were associated with one score but not the other were also found in this study. Unexpectedly, the eGFR and the serum phosphate level were found to be significantly associated with the CACS, but not the IACS in the current study. Further studies using other imaging techniques such as vascular ultrasonography[21] and optical coherence tomography[22] are necessary to confirm whether

renal function is related to intimal calcification, medial calcification, or both in CKD patients.

Vascular calcification can be caused by multiple biological processes, as well as by pharmacological interventions. Vitamin K is an essential cofactor for the activation of MGP, a calcification inhibitor found in blood vessel walls.[23] Warfarin promotes VC via vitamin K deficiency-based effects on MGP metabolism.[24,25] While, it is possible that warfarin was prescribed following a clinical event that was induced by the presence of VC, and so the possibility of reverse causality should be considered. Our study showed that warfarin use was associated with CACS by multiple regression analysis. However, only 5 of 145 patients were taking warfarin in this study, therefore, it is hard to interpret the association between warfarin and VC from our results. It was reported that vitamin D exerts a biphasic 'dose-response' curve for VC, with both excessive amounts of vitamin D and vitamin D deficiency having deleterious consequences.[26,27] According to the recent met-analysis, statins are indicated in CKD3, probably indicated in CKD4, not indicated in CKD5/5D to reduce the burden of vascular disease,[28] although it had been reported that statins lower cardiovascular events in non-dialysis CKD patients.[29] It is suggested that active vitamin D and statin should be used with caution in CKD patients. Neither of these drugs was found to be significantly related to CACS or IACS in the present multiple regression analyses, although the patients using active vitamin D3 were only 11/145 patients in this study. Further randomized controlled trial of potential treatments for VC in CKD patients is desired.

The limitations of this study include its observational nature, relatively small study population and the absence of external validation of risk factors for each type of VC. In addition, the low number of warfarin users and active vitamin D3 users limited the analyses of the CACS and IACS. Another limitation is that inhibitors of VC were not assessed in this study. Furthermore, we did not measure the subjects' levels of 25OH-D3, PTH, FGF23, or klotho, which are established or emerging risk factors for cardiovascular disease in CKD patients.

In conclusion, CKD related risk factors for VC, such as the eGFR and hyperphosphataemia, are significantly associated with a high CACS, but not a high IACS, and the CACS is a significant predictor of progression to RRT.

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DISLOSURE

The authors have no conflicts of interest to declare.

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