Calcif Tissue Int (2014) 95:267–274
DOI 10.1007/s00223-014-9891-2

ORIGINAL RESEARCH

Arterial Location-Specific Calcification at the Carotid Artery and Aortic Arch for Chronic Kidney Disease, Diabetes Mellitus, Hypertension, and Dyslipidemia

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Received: 27 March 2014 / Accepted: 26 June 2014 / Published online: 15 July 2014

Abstract Several risk factors for arterial calcification have been reported but controversial. The aim of this study was to clarify the interactions among chronic kidney disease (CKD), diabetes mellitus (DM), hypertension, and dyslipidemia in altering the risk of arterial calcification in the three different arterial locations and the intramural location at the internal carotid artery (ICA) origins. Calcified burdens at the ICA origins, the aortic arch, and its orifices were evaluated in a retrospective fashion by using computed tomography angiography in 397 patients. The multivariate analyses were adjusted for age, gender, CKD, DM, hypertension, dyslipidemia, and current smoking status. Additionally, subgroup analyses in each variable were conducted. Our multivariate logistic regression analyses revealed that CKD was significantly associated with the outside-wall calcification at the ICA origins, whereas DM was only associated with the inside-ICA-wall calcification. Additionally, we found that DM increased the association between CKD and arterial calcification at the aortic arch and its orifices, and the outside-wall at the ICA origins. Hypertension was significantly associated with the calcification at the orifices of the aortic arch branches synergistically with CKD. Dyslipidemia did not have any significant association with calcification in any of the three vascular beds. CKD had the highest prevalence risk of calcification in common with the three different vascular beds. CKD in combination with DM, as well as hypertension in combination with CKD, were key relationships affecting the risk of arterial calcification, especially at the aortic arch and its orifices.

Keywords Arterial calcification · Aortic arch · Carotid bifurcation · Chronic kidney disease · Diabetes mellitus · Hypertension · Dyslipidemia

Conflict of Interest Dr. Yamada and all coauthors declare no disclosures or conflicts of interest. This research was supported by research grants intended to promote the hospital functions of the Japan Labor Health and Welfare Organization. None of the authors received royalties or financial support for this work. All authors take responsibility for data management, accuracy of statistical analysis, conduct of the research, and drafting of the manuscript. All the authors have made substantial contributions to the intellectual content of the paper, have approved the final manuscript, and agree with submission to this journal and full contact details from the journal office.

Electronic supplementary material The online version of this article (doi:10.1007/s00223-014-9891-2) contains supplementary material, which is available to authorized users.

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Introduction

Arterial calcification has been discussed with distinction by the arterial types and the locations [1–11]. Arterial intimal calcification is defined as the presence of calcified burdens located in the intima (mainly in the plaque) and is recognized to be related to atherosclerosis; it is frequently observed in the large arteries including the internal carotid arteries (ICAs) in advanced-stage atherosclerosis [1, 2, 4–6, 9–12]. On the other hand, arterial medial calcification is defined as the presence of calcification located in the media and is recognized to be closely associated with increasing arterial stiffness and is most frequently observed among patients with diabetic nephropathy, particularly those on haemodialysis [1–3, 5, 7, 8, 11]. Arterial stiffness has been reported to be associated with age, male gender, chronic kidney disease (CKD), diabetes mellitus (DM), hypertension, dyslipidemia, metabolic syndrome, body mass index, and cigarette smoking, although some of these associations remain controversial [1, 3, 4, 7, 11, 13–22]. Among them, DM and metabolic syndrome have been reported to affect the risk of arterial stiffness in CKD patients [7, 11, 17, 20, 22]. Earlier, we showed that calcified burdens at the orifices to the three main branches from the aortic arch, not the arch itself, were significantlly associated with stenosis at the carotid bifurcation and intracranial arteries [23]. Furthermore, we found there was a significant association between the carotid bifurcation stenosis and calcification located outside the plaque, rather than with inside or intra-plaque calcification at the carotid bifurcation [24]. These location-specific differentials in the risk of arterial calcification lead us one hypothesis whether prevalence risks of arterial calcification were different by its location. Therefore, we investigated that CKD, DM, hypertension, and dyslipidemia were associated with the arterial calcification specifically to the carotid bifurcation including intramural location, such as outside- or inside-wall type, the aortic arch, and the orifices of the aortic arch branches, respectively.

Methods

The study design and protocol were approved by the Institutional Ethical Committee. From May 2009 to January 2013; 579 consecutive patients underwent multi-slice detector-row computed tomography angiography (MDCTA; Aquilion 64, Toshiba Medical, Tokyo, Japan) at the time of a stroke or during a follow-up study after neurosurgical treatment. Details of the participants, data management, reliability and validity for evaluating arterial calcification from the aortic arch to the cervical ICA on MDCTA have been described in the prior publication [23, 24]. Briefly, the arterial calcification was evaluated in the bilateral ICA

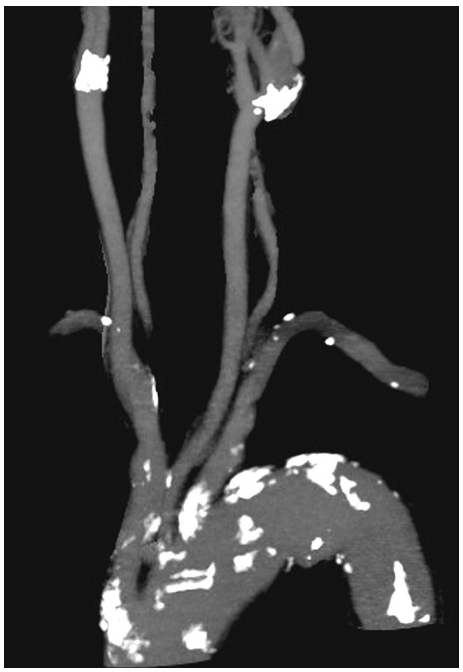

Fig. 1 Sample of the multidirectional maximum-intensity-projection reconstruction image obtained by multi-detector computed tomography angiography (MDCTA). This case had severe calcification in the aortic arch, the orifices of the aortic arch branches, and the origins of the bilateral internal carotid arteries

origins, the orifices of the aortic arch branches, and the aortic arch by maximum intensity projection reconstruction images over a 360° rotation, using a workstation (Ziostation, Ziosoft Co., Tokyo, Japan), as shown in Figure 1. The presence of calcifications in the orifices of the aortic arch branches was recorded as calcifications observed in the brachiocephalic artery origin, left common carotid artery origin, and/or left subclavian artery origin. The intramural location of calcification at the ICA origins was evaluated using cross-sectional multiplanar reformatted reconstruction sequences perpendicular and parallel to the longitudinal axis of the ICAs. Outside-wall calcification was defined as calcified burdens located away from the enhanced vascular lumen and/or outside the plaque. Inside-wall calcification was defined as calcified burdens located in contact with the vascular lumen and on the internal side of the plaque or within the plaque. Laboratory data and clinical histories including internal medicines were reviewed by retrospective examination of patient medical records. The inclusion criterion for this study was that each participant had undergone a blood examination that included determinations of the levels of blood glucose, haemoglobin A_{1C} (HbA_{1C}), serum creatinine, total cholesterol, low density lipoprotein (LDL), and high density lipoprotein (HDL) cholesterol, and triglycerides. In total, 397 patients (249 men and 148 women; mean age, 68.7 ± 11.7 years) were enrolled in the study. The estimate of glomerular filtration rate (eGFR) was

calculated by considering the patient's age, gender, and serum creatinine level, using the Modification of Diet in Renal Disease Study Group formula: eGFR (mL/min/1.73 m^2) = 186.3 × (serum creatinine [mg/dL])$^{-1.154}$ × age (years)$^{-0.203}$ × (0.742, if female) [25]. CKD staging was defined using eGFR data: Stage 1 (normal), eGFR ≥90 mL/min/1.73 m^2; Stage 2 (mild CKD), 60–89 mL/min/1.73 m^2; Stage 3 (moderate CKD), 30–59 mL/min/1.73 m^2; Stage 4 (severe CKD), 15–29 mL/min/1.73 m^2; and Stage 5 (very severe CKD), <15 mL/min/1.73 m^2; proteinuria was not considered because most of participants had not undergone a urine test. For statistical analyses, an eGFR cutoff point of 60 mL/min/1.73 m^2 was used, because the patients with CKD stage 4 or 5 comprised less than 5 % of this study population. The HbA_{1C} value was estimated from an equivalent value measured according to the methods of the National Glycohemoglobin Standardization Program (NGSP), calculated by the formula HbA_{1C} = HbA_{1C} (Japan Diabetes Society) +0.4 %. DM was defined as an HbA_{1C} (NGSP) ≥6.5 % and/or receiving insulin treatment and/or oral hypoglycemic medication. The DM patients in this study were all diagnosed with non-insulin-dependent diabetes. Hypertension was defined as a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg, and/or the use of antihypertensive medications at the time of the MDCTA examination, according to the World Health Organization blood pressure criteria. Dyslipidemia was defined as levels of LDL cholesterol ≥140 mg/dL, HDL cholesterol <40 mg/dL, or triglycerides ≥150 mg/dL, and/or taking statins or other cholesterol-lowering drugs. The patients were also classified according to their smoking habits (current smoker, ex-smoker, or non-smoker), and alcohol consumption (no alcohol consumption, occasional alcohol consumption, a mean alcohol intake of <20 g/day, or a mean alcohol intake of >20 g/day). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m2). Serum calcium level (Ca) was corrected in patients with serum albumin levels <4.0 g/dL, using the following formula: Corrected Ca (mg/dL) = measured total Ca (mg/dL) + 0.8 (4.0−serum albumin [g/dL]).

After the univariate analyses for the associations with arterial calcification in each location, multivariate logistic regression analyses were conducted after adjusting for age, gender, CKD, DM, hypertension, dyslipidemia, and current smoking status at the time of the MDCTA examination. Serum Ca and BMI were not used as multivariate variables, because these contained a large amount of missing values. Additionally, stratification analyses were conducted in each subgroup of patients with CKD, DM, hypertension, and dyslipidemia. All the missing data were treated as deficit data, and not changed the other variables. Statistical significance was assumed at a probability value (p) < 0.05. Statistical analyses were performed using R software (version 3.1.0, R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org.).

Table 1 Clinical characteristics of the study population

Stage of CKD		Normal to Mild CKD		Moderate to Severe CKD		
eGFR	All	Stage 1 ≥90	Stage 2 60–89	Stage 3 30–59	Stage 4 15–29	Stage 5 <15
Total number	397	45	213	121	11	7
Age (years), mean ± SD	68.7 ± 11.7	58.6 ± 13.0	67.1 ± 11.2	74.1 ± 8.0	79.5 ± 10.7	69.6 ± 15.8
Male gender, N (%)	249 (63 %)	24 (53 %)	132 (62 %)	83 (69 %)	5 (45 %)	5 (71 %)
Diabetes mellitus, N (%)	112 (28 %)	12 (27 %)	50 (23 %)	44 (36 %)	3 (27 %)	3 (43 %)
Diabetes mellitus without medication	26 (6.5 %)	4 (8.9 %)	11 (5.2 %)	11 (9.1 %)	0 (0 %)	0 (0 %)
HbA1c (NGSP) (%), mean ± SD	6.2 ± 1.2	6.2 ± 1.4	6.2 ± 1.1	6.4 ± 1.3	6.3 ± 1.0	6.2 ± 1.6
Hypertension, N (%)	283 (71 %)	27 (60 %)	147 (69 %)	94 (78 %)	8 (73 %)	7 (100 %)
Hypertension without medication	15 (3.8 %)	4 (8.9 %)	9 (4.2 %)	2 (2 %)	0 (0 %)	0 (0 %)
Dyslipidemia, N (%)	247 (62 %)	26 (58 %)	128 (60 %)	81 (67 %)	8 (73 %)	4 (57 %)
Dyslipidemia without medication	89 (22.4 %)	12 (27 %)	47 (22 %)	25 (21 %)	3 (27 %)	2 (29 %)
LDL cholesterol (mg/dL), mean ± SD	115 ± 34.5	115 ± 26.6	119 ± 35.5	112 ± 34.5	87.5 ± 28.4	96.6 ± 38.9
HDL cholesterol (mg/dL), mean ± SD	51.9 ± 15.3	55.0 ± 16.2	54.2 ± 15.2	47.9 ± 14.1	42.4 ± 11.7	50.7 ± 19.1
LDL/HDL ratio (%), mean ± SD	2.4 ± 1.0	2.3 ± 0.8	2.4 ± 1.0	2.6 ± 1.1	2.1 ± 1.0	2.4 ± 1.5
Triglyceride (mg/dL), mean ± SD	123 ± 77.6	118 ± 59.4	122 ± 84.8	130 ± 73.4	105 ± 52.6	73.2 ± 30.9
Current smoker, N (%)	63 (16 %)	8 (18 %)	27 (13 %)	24 (20 %)	2 (18 %)	2 (29 %)
Serum Ca (mg/dL), mean ± SD	9.0 ± 0.8	9.0 ± 0.5	9.1 ± 0.9	9.0 ± 0.4	8.8 ± 0.6	8.2 ± 1.5
BMI (kg/m^2), mean ± SD	23.0 ± 3.9	22.8 ± 3.7	23.0 ± 4.0	23.2 ± 4.0	22.9 ± 3.9	20.6 ± 2.2

eGFR estimate of glomerular filtration rate

Table 2 Multivariate odds ratio (M-OR) of the arterial location-specific calcification for moderate or severe chronic kidney disease (CKD)

	CKD	non-CKD	M-OR	95 %CIs	*p*
Total number	139	258			
ICA origins[a]	91	121	**1.69**	**(1.03–2.74)**	**0.036**
Outside-wall at the ICA origins[b]	56	53	**2.38**	**(1.46–3.90)**	**<0.001**
Inside-wall at the ICA origins[c]	79	112	1.31	(0.82–2.10)	0.259
Orifices from the aortic arch[d]	96	129	1.59	(0.99–2.58)	0.057
Aortic arch	126	182	**2.18**	**(1.10–4.35)**	**0.026**
Subgroup of Diabetes Mellitus ($n = 112$)	50	62			
ICA origins[a]	36	40	2.03	(0.80–5.16)	0.137
Outside-wall at the ICA origins[b]	23	13	**3.85**	**(1.58–9.34)**	**0.003**
Inside-wall at the ICA origins[c]	32	38	1.37	(0.58–3.22)	0.474
Orifices from the aortic arch[d]	40	35	**2.81**	**(1.14–6.93)**	**0.025**
Aortic arch	48	47	**6.44**	**(1.28–32.4)**	**0.024**
Subgroup of Hypertension ($n = 283$)	109	174			
ICA origins[a]	74	87	**1.90**	**(1.08–3.36)**	**0.026**
Outside-wall at the ICA origins[b]	44	39	**2.33**	**(1.32–4.11)**	**0.004**
Inside-wall at the ICA origins[c]	65	83	1.41	(0.82–2.44)	0.212
Orifices from the aortic arch[d]	81	92	**2.20**	**(1.24–3.90)**	**0.007**
Aortic arch	100	129	**2.27**	**(1.00–5.15)**	**0.049**
Subgroup of Dyslipidaemia ($n = 247$)	93	154			
ICA origins[a]	61	76	1.72	(0.94–3.16)	0.080
Outside-wall at the ICA origins[b]	39	34	**2.61**	**(1.42–4.79)**	**0.002**
Inside-wall at the ICA origins[c]	54	72	1.35	(0.76–2.42)	0.306
Orifices from the aortic arch[d]	65	81	**1.89**	**(1.04–3.42)**	**0.036**
Aortic arch	83	112	1.98	(0.88–4.43)	0.097

Statistically significant values are given in bold

M-OR multivariate odds ratio of moderate or severe, CKD compared with normal or mild, CKD after adjusting for age, gender, CKD, DM, hypertension, and dyslipidemia

[a] Calcification at the ICA origins was defined that calcified burdens were located at the left or right ICA origin

[b] Outside-wall calcification was defined as calcified burdens located away from the enhanced vascular lumen and/or outside the plaque

[c] Inside-wall calcification was defined as calcified burdens located in contact with the vascular lumen and on the internal side of the plaque or within the plaque

[d] Calcification at the orifices from the aortic arch branches was defined that calcified burdens were located at the origins of the brachiocephalic artery, left common carotid artery, or left subclavian artery

Results

Among the 397 patients, the mean age and eGFR among the 249 men were significantly lower than those for the 148 women (age, 68.4 vs. 70.4 years; eGFR, 64.7 vs. 69.5 mL/min/1.73 m^2). The mean HbA_{1C} (NGSP), LDL cholesterol, HDL cholesterol, and triglyceride levels were not significantly different between the men and women. The clinical characteristics and proportions of several risk factors for vascular calcification in each stage of CKD are shown in Table 1. The patients with higher CKD stage tend to higher mean age, higher proportions of male gender, DM, hypertension, and current smoker, and lower mean values of LDL cholesterol, serum Ca, and BMI. Multivariate analyses revealed that age $\geq$70 years, male gender, hypertension, and current smoking status were significantly associated with the moderate to severe CKD (data not shown). The multivariate-adjusted odds ratios (M-ORs) for the calcification in the patients with moderate to severe CKD were 1.69 at the bilateral ICA origins and 2.18 at the aortic arch, whereas it was not statistically significant at the orifices of the aortic arch branches (Table 2). According to the intramural location of calcification at the ICA origins, CKD was significantly associated with the outside-wall calcification (M-OR = 2.38), but not with inside-wall calcification. In the DM subgroup, the M-ORs for the CKD were increased to 3.85 at the outside-wall calcification of the ICA origins, 6.44 at the aortic arch and 2.81 at the orifices of the aortic arch branches. In the subgroups of hypertension or dyslipidemia, the M-OR of calcification at

Table 3 Multivariate odds ratio (M-OR) of the arterial location-specific calcification for diabetes mellitus (DM)

	DM	non-DM	M-OR	95 %CIs	*p*
Total number	112	285			
ICA origins[a]	76	136	**2.32**	**(1.39–3.86)**	**0.001**
Outside-wall at the ICA origins[b]	36	73	1.25	(0.75–2.08)	0.395
Inside-wall at the ICA origins[c]	70	121	**2.17**	**(1.33–3.52)**	**0.002**
Orifices from the aortic arch[d]	75	150	1.50	(0.92–2.45)	0.104
Aortic arch	95	213	1.45	(0.76–2.76)	0.263
Subgroup of CKD ($n = 139$)	50	89			
ICA origins[a]	36	55	2.05	(0.83–5.03)	0.118
Outside-wall at the ICA origins[b]	23	33	1.70	(0.79–3.65)	0.176
Inside-wall at the ICA origins[c]	32	47	1.72	(0.76–3.89)	0.190
Orifices from the aortic arch[d]	40	56	1.92	(0.81–4.55)	0.137
Aortic arch	48	78	4.12	(0.82–20.9)	0.087
Subgroup of Hypertension ($n = 283$)	88	195			
ICA origins[a]	61	100	**2.28**	**(1.27–4.11)**	**0.006**
Outside-wall at the ICA origins[b]	30	53	1.27	(0.71–2.27)	0.417
Inside-wall at the ICA origins[c]	56	92	**1.99**	**(1.14–3.48)**	**0.016**
Orifices from the aortic arch[d]	59	114	1.21	(0.68–2.14)	0.513
Aortic arch	76	153	1.42	(0.66–3.03)	0.372
Subgroup of Dyslipidaemia ($n = 247$)	79	168			
ICA origins[a]	56	81	**2.58**	**(1.38–4.83)**	**0.003**
Outside-wall at the ICA origins[b]	28	45	1.34	(0.72–2.47)	0.354
Inside-wall at the ICA origins[c]	51	75	**2.11**	**(1.17–3.81)**	**0.013**
Orifices from the aortic arch[d]	52	94	1.23	(0.68–2.21)	0.493
Aortic arch	67	128	1.37	(0.63–2.95)	0.428

Statistically significant values are given in bold

M-OR multivariate odds ratio of moderate or severe, CKD compared with normal or mild, CKD after adjusting for age, gender, CKD, DM, hypertension, and dyslipidemia

[a] Calcification at the ICA origins was defined that calcified burdens were located at the left or right ICA origin

[b] Outside-wall calcification was defined as calcified burdens located away from the enhanced vascular lumen and/or outside the plaque

[c] Inside-wall calcification was defined as calcified burdens located in contact with the vascular lumen and on the internal side of the plaque or within the plaque

[d] Calcification at the orifices from the aortic arch branches was defined that calcified burdens were located at the origins of the brachiocephalic artery, left common carotid artery, or left subclavian artery

the orifices of the aortic arch branches was increased to statistically significant level. DM was significantly associated with calcification at the ICA origins (M-OR = 2.32), especially inside-wall calcification (M-OR = 2.17, Table 3). This association remained significant in the subgroups of hypertension and dyslipidemia, but not in the CKD subgroup. Hypertension was significantly associated with calcification at the orifices of the aortic arch branches (M-OR = 1.69), but neither at the aortic arch itself nor bilateral ICA origins (Table 4). In the CKD subgroup, the M-OR for hypertension was increased to 2.84 at the orifices of the aortic arch branches. Dyslipidemia itself was not significantly associated with calcification in any of the threevascular beds (data not shown). In the subgroups of CKD, DM, or hypertension, there was no significant risk of dyslipidemia for arterial calcification in the three vascular beds. Additionally, we assessed the M-ORs of calcification in the three different vascular beds and intramural location at the ICA origins after stratification in the CKD stage (Supplementary Table 1). The M-ORs for the CKD stage 3 compared with CKD stage 1 (normal) remained statistically significant in the all vascular locations, but not stepwise elevation as the CKD stage increased.

Discussion

We investigated whether CKD, DM, hypertension, and dyslipidemia had potential risks of arterial calcification

Table 4 Multivariate odds ratio (M-OR) of the arterial location-specific calcification for hypertension (HT)

	HT	non-HT	M-OR	95 %CIs	*p*
Total number	283	114			
ICA origins[a]	161	51	1.44	(0.89–2.32)	0.142
Outside-wall at the ICA origins[b]	83	26	1.22	(0.72–2.08)	0.465
Inside-wall at the ICA origins[c]	148	43	**1.64**	**(1.02–2.65)**	**0.041**
Orifices from the aortic arch[d]	173	52	**1.69**	**(1.05–2.70)**	**0.029**
Aortic arch	229	79	1.66	(0.95–2.91)	0.077
Subgroup of CKD ($n = 139$)	109	30			
ICA origins[a]	74	17	1.81	(0.74–4.45)	0.194
Outside-wall at the ICA origins[b]	44	12	1.04	(0.44–2.47)	0.934
Inside-wall at the ICA origins[c]	65	14	1.86	(0.77–4.46)	0.165
Orifices from the aortic arch[d]	81	15	**2.84**	**(1.19–6.81)**	**0.019**
Aortic arch	100	26	1.34	(0.35–5.11)	0.665
Subgroup of Diabetes Mellitus ($n = 112$)	88	24			
ICA origins[a]	61	15	1.27	(0.45–3.57)	0.656
Outside-wall at the ICA origins[b]	30	6	1.37	(0.45–4.19)	0.576
Inside-wall at the ICA origins[c]	56	14	1.21	(0.45–3.26)	0.707
Orifices from the aortic arch[d]	59	16	1.05	(0.38–2.93)	0.924
Aortic arch	76	19	2.49	(0.58–10.7)	0.221
Subgroup of Dyslipidaemia ($n = 247$)	182	65			
ICA origins[a]	106	31	1.26	(0.67–2.37)	0.476
Outside-wall at the ICA origins[b]	58	15	1.44	(0.72–2.89)	0.303
Inside-wall at the ICA origins[c]	99	27	1.46	(0.79–2.70)	0.229
Orifices from the aortic arch[d]	116	30	**1.84**	**(1.00–3.37)**	**0.048**
Aortic arch	151	44	**2.09**	**(1.02–4.25)**	**0.043**

Statistically significant values are given in bold

M-OR[§]; Multivariate Odds ratio of moderate or severe CKD compared with normal or mild CKD after adjusting for age, gender, CKD, DM, hypertension, and dyslipidemia

[a] Calcification at the ICA origins was defined that calcified burdens were located at the left or right ICA origin

[b] Outside-wall calcification was defined as calcified burdens located away from the enhanced vascular lumen and/or outside the plaque

[c] Inside-wall calcification was defined as calcified burdens located in contact with the vascular lumen and on the internal side of the plaque or within the plaque

[d] Calcification at the orifices from the aortic arch branches was defined that calcified burdens were located at the origins of the brachiocephalic artery, left common carotid artery, or left subclavian artery

specifically to the ICA origins, the orifices of the aortic arch branches, and the aortic arch, respectively. Among four basal diseases, we confirmed that CKD had the most significant association with the arterial calcification in common with the three different vascular beds, and this relationship between arterial calcification and CKD became stronger in the DM subgroup. These results are in agreement with previous studies [1–5, 7, 12, 17, 22]. Diabetic nephropathy has been reported to be the most important risk factor for the development of arterial calcifications in the aorta, although the direct relationship between diabetes and arterial calcification remains controversial [7, 17, 22, 26–28]. Interestingly, CKD-related calcification at the ICA origins was specific to the outside-wall calcification, whereas DM-related calcification was to the inside-wall. In our previous study, the inside- and outside-wall calcification at the ICA origins on MDCTA were confirmed the intimal and medial calcification by histological examination [24]. Our findings and previous evidences support the view that CKD has much concern with arterial medial calcification which leads to increased vascular stiffness and reduced vascular compliance. [1–3, 5, 7, 8, 11] In contrast, DM is significantly associated with arterial intimal calcification which is known to be related with inflammation and lipid deposition in the necrosis core of advanced-stage atherosclerosis [1, 4, 6, 9, 10]. We also confirmed that hypertension and CKD had a synergistic effect in the arterial calcification at the orifices from the aortic arch branches and aortic arch itself. The uncontrolled hypertension is known to be linearly associated with the

progression of CKD [29]. In this study, >90 % of patients with hypertension have been already treated for several antihypertensive drugs. Dyslipidemia did not have any direct associations or any confounding effects in the arterial calcification. The present results will be helpful for elucidating the mechanism of calcification in the large arteries. Mineral and bone metabolisms such as high levels of the serum Ca and phosphate, and osteoporosis are reported to be the pathogenesis for arterial calcification in CKD patients [5, 11, 12, 30, 31]. The evaluation of osteoporosis, the serum phosphate, parathyroid hormone, vitamin D, alkaline phosphatases, and other inflammatory biomarkers which might modify the relationships between CKD and arterial calcification could not be assessed in this study. The other limitation of our study is its retrospective, cross-sectional design, and the consequent possibility of selection bias. The majority of the patients in this study had been diagnosed with some cerebrovascular disease, treated with hypertension and may have had a higher risk for the development of atherosclerosis than the general population. Additionally, there is too small in the CKD stage 4 + 5 subgroup for stratified analyses, because all the patients in this study underwent MDCTA examinations using iodinated contrast material. Therefore, several findings in this study should be further assessed in large-sample or severe CKD population.

In conclusion, we identified complex interactions among CKD, DM, hypertension, and dyslipidemia that influenced the risk of arterial calcification by using high-resolution MDCTA. We confirmed that CKD was the most important basal disease concerned with arterial calcification in common with the three different arterial types; the ICA origins, the orifices of the aortic arch branches, and the aortic arch. We found that CKD was specific to the medial calcification, and DM was to the intimal calcification at the carotid bifurcation. Additionally, DM modified the association between CKD and arterial calcification. Hypertension and CKD were influenced each other in the development of arterial calcification at the orifices from the aortic arch branches and aortic arch itself. There was no significant association or confounding factor in the dyslipidemia and arterial calcification. Further study is warranted to determine whether intensive control of blood pressure or blood glucose levels might prevent the progression of arterial calcification in patients with CKD and/or hypertension.

Acknowledgments We would like to thank the radiology staff of the Hamamatsu Rousai Hospital. This work was supported by the research fund intended to promote the hospital functions of the Japan Labour Health and Welfare Organization.

Human and Animal Rights and Informed Consent The study design and protocol were approved by the Institutional Ethical Committee. All patients were confirmed to have the appropriate indications for the MDCTA and signed an informed consent form before the MDCTA.

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