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The association of renal impairment with different patterns of intracranial arterial calcification: Intimal and medial calcification

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ABSTRACT

Background and aims: Increasing knowledge about calcification together with improved imaging techniques provided evidence that intracranial arterial calcification (IAC) can be divided into two distinct entities: intimal and medial calcification. The purpose of this study was to investigate the association between kidney function and the two patterns of IAC, which could clarify the underlying mechanisms of intimal or medial calcification and its clinical consequence.

Methods: A total of 516 participants were enrolled in this study. Kidney function was assessed using the estimated glomerular filtration rate (eGFR) based on modified glomerular filtration rate estimating equation. The degree of IAC measured by IAC scores was evaluated on non-contrast head computed tomography (CT) images and IAC was classified as intimal or medial calcification. Associations of kidney function with IAC scores and patterns were assessed sing multivariate logistic regression analysis.

Results: In 440 patients (85.27%) with IAC, 189 (42.95%) had predominant intimal calcifications and 251 (57.05%) had predominant medial calcifications. Multivariate analysis revealed that lower eGFR level (eGFR <60 ml/min/1.73 m^2) was associated with higher IAC scores (odds ratio [OR] 2.01; 95% confidence interval [CI], 1.50–2.71; $p < 0.001$). Medial calcification was more frequent in the lower eGFR group (eGFR <60 ml/min/1.73 m^2) compared to the other two groups with eGFR 60 to 89 and eGFR >90 ml/min/1.73 m^2 (78.72% *vs.* 53.65%, $p < 0.001$; 78.72% *vs.* 47.78%, $p < 0.001$). In multivariable analysis, impaired kidney function was associated with an increased odds of medial calcification presence in patients with eGFR <60 ml/min/1.73 m^2 (OR, 1.47; 95% CI, 1.05 to 2.06).

Conclusions: Our findings demonstrated that impaired renal function was independently associated with a higher degree of calcification in intracranial arteries, especially medial calcification, which reflects a distinction between two types of arterial calcification and raise the possibility for specific prevention of lesion formation.

1. Introduction

Intracranial arterial calcification (IAC) can be easily identified on computed tomography (CT) [1]. The highest prevalence of IAC was seen in the internal carotid artery (80.4%), followed by the vertebral artery (35.6%), basilar artery (7.3%) and middle cerebral artery (4.5%) [2]. Previously regarded as a proxy indicator of intracranial atherosclerosis (ICAS), IAC has been reported to be a risk factor of ischemic stroke, white-matter disease or microbleeds, and cognitive impairment [3,4]. Our histological study based on 32 adult autopsy cases classified IAC as intimal or medial calcification according to its specific location in the vessel wall and demonstrated that intimal calcification was more closely associated with ICAS in our subsequent multimodal imaging-based comparison study [5–7]. Moreover, differences between intimal and medial calcification in some specific diseases may reflect risk factors and mechanisms behind their development.

Kidney dysfunction affects 13% of the population worldwide and up to 35% of individuals aged 70 years or older [3,8]. Kidney dysfunction is correlated with coronary artery calcification (CAC) but the association of impaired kidney function with IAC is less studied [9]. In coronary

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artery disease studies, a different distribution of intimal calcification and medial calcification was found in case of renal impairment in both animal studies and clinical trials, suggesting the unique mechanism of renal impairment in their development [10–12]. However, to the best of our knowledge, there are no clinical studies to explore the relationship between kidney dysfunction and IAC types. More importantly, considering that calcification in different vascular layers may lead to different clinical outcomes, understanding the relationship between renal impairment and IAC patterns may help optimize cerebrovascular disease prevention and therapeutics.

In this hospital-based study, we aimed to investigate the correlation between kidney dysfunction and intimal or medial calcification, which will provide useful information to explain the underlying mechanism accounting for two different patterns of IAC.

2. Patients and methods

2.1. Study participants

This study included consecutive hospitalized patients who underwent brain CT scans and were admitted to the Department of Neurology, The Second Affiliated Hospital of Guangzhou Medical University, between January 1, 2021, and March 1, 2022. Inclusion criteria were as follow: (1) age ≥18 years; (2) having performed brain CT with 0.625-mm slice thickness as measurement of calcification; and (3) estimating estimated glomerular filtration rate (eGFR) using modified glomerular filtration rate estimating equation. The exclusion criteria were: (1) poor CT imaging quality; (2) insufficient clinical data for analysis.

This study was approved by the clinical ethics committees of the participating hospital. The following clinical information was obtained from the electronic medical records of the patients: age; sex; diagnosis; total cholesterol [TC], low-density lipoprotein-cholesterol [LDL-C], high-density lipoprotein-cholesterol [HDL-C], triglyceride [TG], hemoglobin A1c [HbA1c], homocysteine, eGFR; past medical history; medication history. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic pressure ≥90 mmHg or history of hypertension. Diabetes mellitus (DM) was determined using a 75 g oral glucose tolerance test, or as HbA1c ≥ 6.0%, or medical history of diabetes.

2.2. Image acquisition

CT imaging was performed using a 64-row multidetector scanner without contrast administration. All CT exams (120 kVp, 170 mAs, 1-sec rotation time) were acquired in axial mode with tilting along the occipito-meatal line, covering the region from skull base to vertex. For detection of subtle or thin calcifications, only CT exams with 0.625-mm slice thickness were included.

2.3. IAC assessment

Reconstructed CT images were independently evaluated by two readers (JR. C. and XL. L.) with at least two years of experience in CT image interpretation, who were blinded to clinical information of the patients. The presence of IAC was assessed using visual grading method. Seven main intracranial arteries (bilateral internal carotid artery [ICA] C2–C7 segments, bilateral middle cerebral artery [MCA], bilateral vertebral artery [VA] V4 segments, and basilar artery [BA]) were assessed. The presence of IAC was defined as the hyperdense artery sign considered with a density of more than 130 Hounsfield units. As previously described [13,14], the severity of IAC was evaluated by grading values (extent and thickness) for each cerebral artery, and a highest composite CT score of 0–2, 3–5 and 6–8 was classified as mild, moderate, and severe IAC, respectively. The vessel with the highest score was used for the final score (Fig. 1).

IAC patterns were classified according to a previous calcification scoring method [6,15]. The morphological patterns of calcifications were scored as follows (Fig. 2): calcification circularity: absent (0 point); dots (1 point); <90° (2 points); 90–270° (3 points); 270–360° (4 points). Calcification thickness: thick ≥1.5 mm (1 point); thin <1.5 mm (3 points). Calcification morphology: indistinguishable (0 point); irregular/patchy (1 point); continuous (4 points). The sum of the calcification scores was used to classify intimal (1–6 points) and medial calcifications (7–11 points). For the patients with several calcifications, we counted the number of calcifications in each patient as well as comparing which pattern of calcification had a higher proportion. Thus, all patients were divided into two groups: patients with predominant medial calcifications and patients with predominant intimal calcifications.

2.4. Kidney function

Serum levels of creatinine were measured at admission. The eGFR was assessed by calculating serum creatinine (sCr) concentrations using the modified glomerular filtration rate estimating equation for Chinese subjects: eGFR (ml/min/1.73 m^2) = 175 × (sCr)$^{-1.234}$ × (age)$^{-0.179}$ (0.79 if female). eGFR >90 ml/min/1.73 m^2 would indicate normal kidney function, eGFR 60–90 ml/min/1.73 m^2 mildly reduced kidney function and eGFR <60 ml/min/1.73 m^2 as decreased eGFR.

2.5. Statistical analysis

Baseline demographics, clinical characteristics and laboratory findings were compared between the three eGFR groups. Continuous variables were presented as mean and standard deviation (SD), and categorical variables were presented as numbers and percentages. Characteristics of participants were compared according to the severity of renal function using the chi-squared test for categorical data. Continuous variables were compared across groups using the Kruskal-Wallis test.

Logistic regression analysis was used to determine the association of eGFR with degree and patterns of IAC, adjusting for age and sex (model 1), body mass index (BMI), smoking status, alcohol use, SBP and DBP (model 2), and history of coronary artery disease (CAD), history of

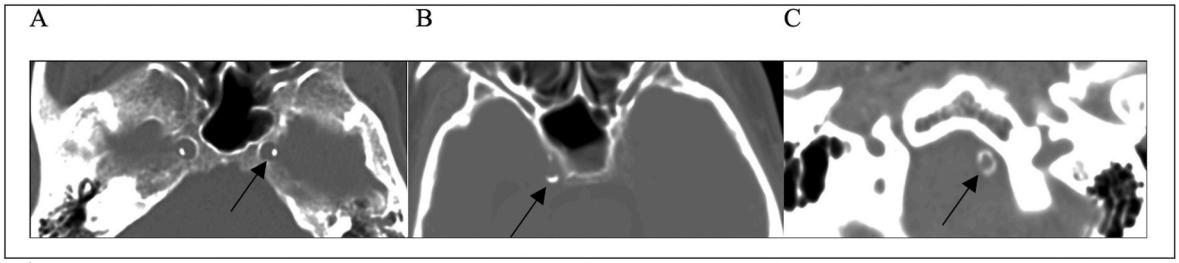


Fig. 1. Examples of IAC scores on CT image.
According to Babiarz's visual grading scales, IAC were graded as follows. (A) 1 point for extent and 1 point for thickness (mild). (B) 2 points for extent and 2 points for thickness (moderate). (C) 4 points for extent and 2 points for thickness (severe).

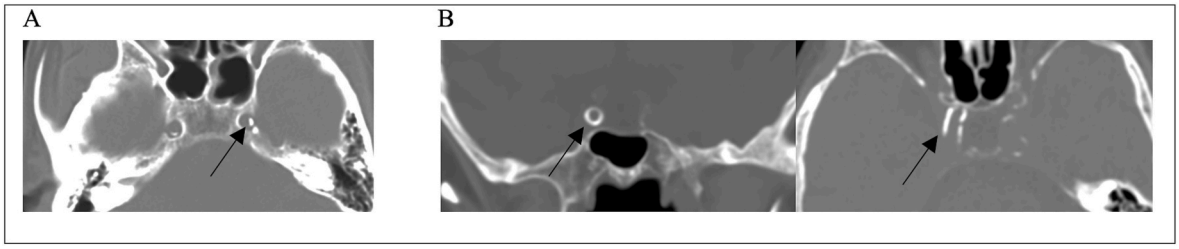


Fig. 2. Examples of calcification score for categorizing ICA calcification patterns.
(A) 1 point for circularity, 3 points for thickness and 1 point for morphology (intimal calcification). (B) 4 points for circularity, 3 points for thickness and 4 points for morphology (medial calcification).

Table 1
Baseline characteristics in participants by baseline eGFR.

Characteristics	eGFR ≥90 (n = 205)	eGFR 60 to 89 (n = 210)	eGFR <60 (n = 101)	*p* value
Age, years	64.33 ± 10.28	69.40 ± 10.72	74.73 ± 10.08	<0.001
Male, n (%)	102 (49.76)	119 (56.67)	48 (47.52)	0.118
Current smoking, n (%)	35 (17.07)	31 (14.76)	17 (16.83)	0.806
Current drinking, n (%)	12 (5.86)	13 (6.19)	9 (8.91)	0.574
SBP, mmHg	141.65 ± 21.87	143.20 ± 20.12	149.03 ± 20.14	0.012
DBP, mmHg	86.02 ± 12.64	85.10 ± 11.70	83.82 ± 10.50	0.505
BMI, kg/m^2	23.73 ± 3.47	23.49 ± 3.06	23.70 ± 3.03	0.853
Blood test, mean (SD)				
TCH, mmol/L	4.25 ± 1.01	4.40 ± 1.06	4.21 ± 1.07	0.277
HDL-C, mmol/L	1.16 ± 0.30	1.12 ± 0.28	1.05 ± 0.28	0.009
LDL-C, mmol/L	2.61 ± 0.92	2.75 ± 0.91	2.57 ± 0.93	0.167
TG, mmol/L	1.27 ± 0.78	1.40 ± 0.77	1.38 ± 0.64	0.038
HbA1c, (%)	6.14 ± 1.38	6.10 ± 1.30	6.35 ± 1.25	0.005
Hcy, umol/L	10.49 ± 2.74	11.20 ± 3.41	14.10 ± 5.25	<0.001
eGFR, ml/min/1.73 m^2	106.65 ± 15.91	77.86 ± 7.67	46.92 ± 12.29	<0.001
Medical history, n (%)				
Hypertension, n (%)	113 (55.12)	125 (59.52)	84 (83.17)	<0.001
Diabetes, n (%)	41 (20)	39 (18.57)	43 (42.57)	<0.001
Ischemic stroke, n (%)	22 (10.73)	21 (10)	16 (15.84)	0.275
Any CAD, n (%)	14 (6.83)	30 (14.29)	24 (23.76)	<0.001
Medications, n (%)				
Antihypertensives, n (%)	96 (46.83)	101 (48.10)	75 (74.26)	<0.001
Antidiabetics, n (%)	36 (17.56)	33 (15.71)	37 (36.63)	<0.001
Antiplatelets, n (%)	17 (8.29)	21 (10)	17 (16.83)	0.069
Statins, n (%)	12 (5.85)	11 (5.24)	13 (12.87)	0.034

Categorical variables are shown as number (percentage); continuous variables as mean ± standard deviation.
SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; TCH, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, glycated hemoglobin; Hcy, homocysteine; eGFR, estimated glomerular filtration rate; CAD, coronary artery disease.

stroke, history of hypertension, history of diabetes, TG, TC, LDL, HDL, HbA1c, Hcy, and the use of antihypertensives medication, hypertension medication, antiplatelets medication and statins medication (model 3). A two-sided p value < 0.05 indicated statistical significance. Statistical analyses were performed using the SPSS software version 26 (IBM, Chicago, Illinois, USA).

3. Results

3.1. Participants

A total of 541 patients with thin-slice CT scans and renal function tests were initially included in this study. After excluding 20 patients with image artifacts on CT and 5 patients with insufficient clinical data, 516 patients were included.

Baseline characteristics of the participants are shown in Table 1. The mean age was 68.4 ± 11.1 years, and 269 (52.1%) patients were male. The mean value of eGFR was 83.24 ml/min/1.73 m^2 (SD, 25.34) and 101 (19.57%) had a value < 60 ml/min/1.73 m^2. Compared with the normal kidney function group, participants with lower eGFR were older, tended to have higher SBP, TG, HbA1c, and Hcy levels, and more frequently to have hypertension, diabetes, and a history of antihypertensive and hypoglycemic medications.

Participant characteristics by IAC patterns are shown in Table 2. For the 440 participants with calcification, 189 (42.95%) showed predominantly intimal IAC patterns and 251 (57.05%) showed predominantly medial patterns of calcification. Compared to the intimal IAC group, patients with medial IAC were older, had higher SBP, HbA1c and Hcy levels, and lower level of eGFR.

3.2. Kidney function and IAC scores

Mean IAC scores were higher in the mildly reduced eGFR group and decreased eGFR group compared with the normal kidney function group (5.30 *vs.* 2.82; 3.88 *vs.* 2.82, $p < 0.001$) (Fig. 3). eGFR <60 ml/min/1.73 m^2 was associated with IAC scores in univariate logistic regression (OR 2.70, 95% CI 2.18–3.33; $p < 0.001$). In multivariate analyses (Table 3), eGFR <60 ml/min/1.73 m^2 remained independently associated with the IAC scores in all three models (OR, 2.43; 95% CI, 1.93–3.207; $p < 0.001$ in model 1; OR, 2.48; 95% CI, 1.92–3.19; $p < 0.001$ in model 2; OR, 2.01; 95% CI, 1.50–2.71; $p < 0.001$ in model 3).

3.3. Kidney function and IAC patterns

As seen in Fig. 3, medial calcification was more prevalent in the lower eGFR group (eGFR <60 ml/min/1.73 m^2) than the other two

Table 2
Baseline characteristics in participants by calcification patterns.

Characteristics	Medial (n = 251)	Intimal (n = 189)	*p* value
Age, years	73.36 ± 9.54	66.70 ± 9.87	<0.001
Male, n (%)	133 (53.2)	102 (53.97)	0.873
Current smoking, n (%)	34 (13.55)	36 (19.05	0.118
Current drinking, n (%)	13 (5.17)	15 (7.98)	0.235
SBP, mmHg	147.98 ± 21.85	141.19 ± 19.09	0.001
DBP, mmHg	85.36 ± 11.99	84.77 ± 11.35	0.705
BMI, kg/m^2	23.49 ± 3.25	23.76 ± 3.14	0.343
Blood test, mean (SD)			
TCH, mmol/L	4.24 ± 1.03	4.35 ± 1.06	0.402
HDL-C, mmol/L	1.10 ± 0.28	1.13 ± 0.27	0.282
LDL-C, mmol/L	2.62 ± 0.88	2.68 ± 0.96	0.504
TG, mmol/L	1.37 ± 0.71	1.38 ± 0.87	0.500
HbA1c, (%)	6.30 ± 1.42	6.13 ± 1.29	0.02
Hcy, umol/L	12.27 ± 4.44	10.89 ± 3.12	0.003
eGFR, ml/min/1.73 m^2	76.06 ± 25.66	88.62 ± 21.94	<0.001
Medical history, n (%)			
Hypertension, n (%)	186 (74.10)	108 (57.14)	<0.001
Diabetes, n (%)	72 (28.69)	42 (22.22)	0.126
Ischemic stroke, n (%)	32 (12.75)	19 (10.05)	0.374
Any CAD, n (%)	41 (16.33)	19 (10.05)	0.057
Medications %			
Antihypertensives, n (%)	156 (62.15)	93 (49.21)	0.007
Antidiabetics, n (%)	59 (23.51)	39 (20.63)	0.474
Antiplatelets, n (%)	31 (12.35)	15 (7.94)	0.134
Statins, n (%)	17 (6.77)	11 (5.82)	0.685

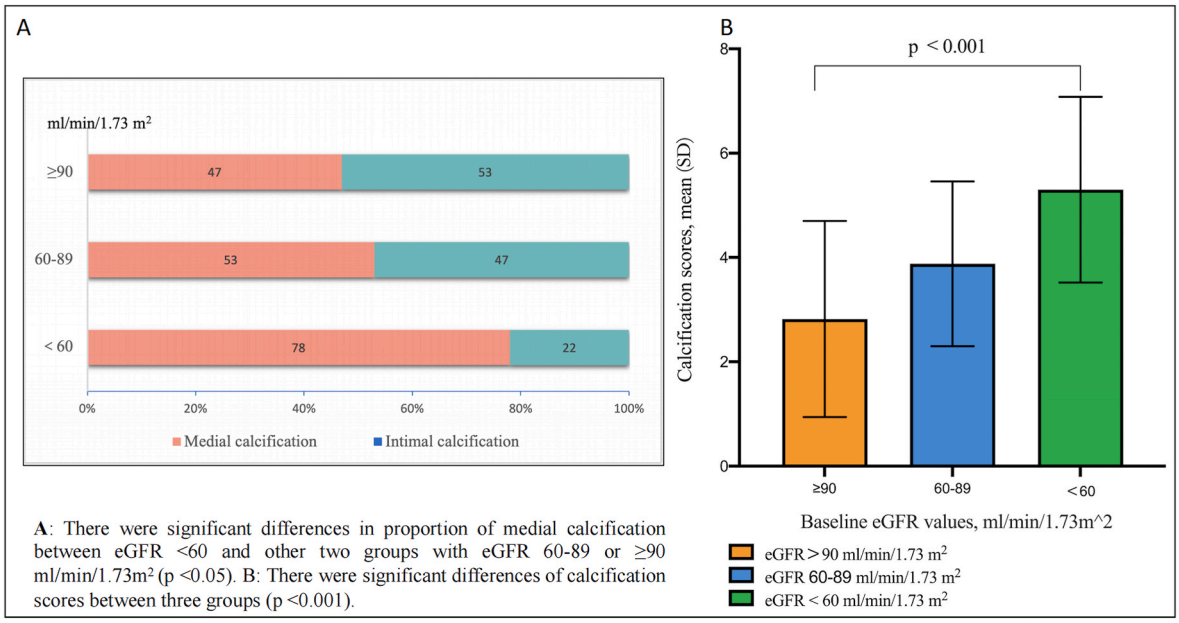
Categorical variables are shown as number (percentage); continuous variables as mean ± standard deviation.
SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; TCH, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, glycated hemoglobin; Hcy, homocysteine; eGFR, estimated glomerular filtration rate; CAD, coronary artery disease.

groups with eGFR 60 to 89 and eGFR >90 ml/min/1.73 m^2 (78.72% *vs.* 53.65%, $p < 0.001$; 78.72% *vs.* 47.78%, $p < 0.001$). No significant difference in the frequency of medial calcification was found between eGFR 60 to 89 and eGFR >90 ml/min/1.73 m^2 ($p > 0.05$). Multivariate regression analyses (Table 4) demonstrated lower eGFR level was associated with higher prevalence of medial calcification in all three models (OR, 3.47; 95% CI, 1.92–6.28; $p < 0.001$ in model 1; OR, 3.52; 95% CI, 1.85–6.71; p < 0.001 in model 2; OR, 2.75; 95% CI, 1.36–5.53; $p < 0.001$ in model 3).

4. Discussion

In this study, we examined whether kidney function evaluated by eGFR was associated with the degrees and patterns of IAC. The results obtained showed that a lower eGFR was associated with higher degrees of calcification in the intracranial arteries after adjusting for demographic and cardiovascular risk factors. Compared to participants with normal kidney function and mildly reduced eGFR, patients with lower eGFR below 60 ml/min/1.73 m^2 had greater medial calcification in intracranial larger arteries.

Renal impairment has been reported to be related to arterial calcification in different populations. In a clinical study of 38 renal dialysis



A: There were significant differences in proportion of medial calcification between eGFR <60 and other two groups with eGFR 60-89 or ≥90 ml/min/1.73m² (p <0.05). B: There were significant differences of calcification scores between three groups (p <0.001).

Fig. 3. The degree and pattern of IAC in participants by baseline eGFR.

Table 3
Multiple analysis of eGFR and IAC scores.

eGFR	Unadjusted OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
eGFR ≥90	Ref.	Ref.	Ref.	Ref.
eGFR 60 to 89	1.37 (1.22, 1.53)[a]	1.27 (1.07, 1.44)	1.32 (1.14, 1.52)[a]	1.34 (1.13, 1.59)
eGFR <60	2.70 (2.18, 3.30)[a]	2.43 (1.93, 3.07)[a]	2.48 (1.92, 3.19)[a]	2.01 (1.50, 2.71)[a]

[a] $p < 0.001$.
Model 1: adjusted for age and sex.
Model 2: further adjusted for body mass index (BMI), smoking status, alcohol use, SBP and DBP.
Model 3: further adjusted for CAD, history of stroke, history of hypertension, history of diabetes, TG, TC, LDL, HDL, HbA1c, Hcy, and the use of antihypertensives medication, hypertension medication, antiplatelets medication and statins medication.

Table 4
Multiple analysis of eGFR and medial calcification.

eGFR	Unadjusted OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
eGFR ≥90	Ref.	Ref.	Ref.	Ref.
eGFR 60 to 89	1.61 (1.09, 2.38)[a]	1.14 (0.75, 1.76)	1.27 (0.80, 2.02)	1.21 (0.74, 1.97)
eGFR <60	5.56 (3.24, 9.54)[a]	3.15 (1.76, 5.61)[a]	3.17 (1.69, 5.95)[a]	2.45 (1.23, 4.85)[a]

[a] $p < 0.05$.
Model 1: adjusted for age and sex.
Model 2: further adjusted for body mass index (BMI), smoking status, alcohol use, SBP and DBP.
Model 3: further adjusted for CAD, history of stroke, history of hypertension, history of diabetes, TG, TC, LDL, HDL, HbA1c, Hcy, and the use of antihypertensives medication, hypertension medication, antiplatelets medication and statins medication.

patients, the prevalence of vascular calcification increased from 39% at initiation to 92% during a mean follow-up of 16 years [16]. Similarly, Sedaghat et al. found that a lower eGFR was associated with higher volumes of calcification in different vascular beds among community-dwelling individuals aged 45 or above [9]. However, the effect estimates attenuated after adjusting for traditional cardiovascular risk factors. In the present study, based on hospitalized patients, lower eGFR was found to be prominently associated with the degree of IAC after adjusting for traditional risk factors, showing that arterial calcification does not only occur in specific types of blood vessels, but is a more systemic phenomenon.

Although the underlying mechanisms of decreased renal function on IAC are not fully understood, previous studies have suggested a specific contribution to the development of arterial calcification in patients with impaired renal function. Emerging evidence shows that nontraditional risk factors, including uremic toxins, CKD-mineral and bone disease (CKD-MBD), oxidative stress, and inflammation, may contribute to the development of vascular calcification and cardiovascular disease in CKD patients [17–20]. Moreover, vascular calcification is not only considered a consequence of chronic kidney disease but may be a possible mechanism in the pathogenesis of chronic kidney disease. Several recent studies reported that renal function deteriorated more rapidly in subjects with higher degrees of vascular calcification, suggesting that arterial calcification might be associated with CKD progression, which may be explained indirectly by arterial stiffness exposing the glomerular capillaries to higher pulse pressure [21,22].

IAC in large intracranial arteries is found not only in the tunica intima, but also in the tunica medial layers of arteries, which may differ with respect to clinical risk factors and outcomes. In this study, we found that IAC was dominated by medial calcification in 57% of patients. But interestingly, when we classified calcification types by renal function, medial calcification was predominantly detected (79.8%) in patients with eGFR<60 ml/min/1.73 m^2 compared with subjects with normal and mildly decreased kidney function, suggesting the deterioration of renal function may be one of the key factors causing the differentiation of calcification types. The relationship between decreased kidney function and calcification types remains controversial [23,24]. A study of patients with end-stage kidney disease found a high percentage of medial calcification in the inferior epigastric artery. Similarly, in studies of adolescents on dialysis without traditional risk factors, medial calcification was found almost exclusively. However, several previous studies reported the coexistence of intimal and medial calcification [25], which may be attributed to the fact that many traditional atherosclerotic risk factors are more likely to be present in adult CKD patients.

Decreased renal function is theoretically more likely to lead to medial calcification rather than intimal calcification, and the possible mechanisms are as follows: first, disturbances in calcium and phosphate metabolism due to decreased kidney function trigger abnormal mineral deposition on the medial layer of the arterial wall [26,27]. Second, previous studies showed medial calcification to be paralleled by significant higher *in situ* expression of proinflammatory markers, suggesting media calcification may be associated with local inflammation of the vascular wall [28,29]. Third, the kidney is one of the main sources of antioxidant enzymes, and increased oxidative stress in response to decreased renal function may further lead to medial vascular calcification [30].

In the present study, we found a high prevalence of medial calcification among asymptomatic patients with eGFR <60 ml/min/1.73 m^2, suggesting medial calcification may begin at the early stage of kidney disease. Based on pathological studies [5,6,31], intimal arterial calcification existed in advanced stage of atherosclerotic plaques and could be used as a marker of atherosclerosis. However, although medial calcification does not generally lead to atherosclerosis, given that cerebral artery stiffness caused by medial calcification was strongly associated with future cerebrovascular disease events and collateral vessel formation, a comprehensive treatment strategy for patients with early renal impairment is needed to reduce the risk of future cerebrovascular events.

Compared to those with traditional cardiovascular risk factors such as hypertension or diabetes, the prevalence of IAC among patients with early renal impairment has been less studied. Understanding the connections between renal function and IAC patterns may arouse the clinicians' and researchers' interests and attention to the occurrence of cerebral artery calcification among patients with early renal impairment. Secondly, our previous studies, together with this study, demonstrated that intimal and medial calcification are two distinct entities in the risk factors and clinical correlations with arterial stiffness or atherosclerosis. Compared to intimal calcification as an indicator of atherosclerosis, medial calcification is more associated with calcium and phosphate homeostasis and loss of inhibition and matrix vesicles [32,33]. Therefore, considering the possible etiology of medial calcification and its close relationship with renal dysfunction, timely intervention of

early renal dysfunction to adjust calcium and phosphate metabolism could be effective in preventing medial calcification. According to the updated literature, early physical exercise is helpful in moderating vessel flexibility. We plan to conduct a follow-up study to investigate the role of blood biomarkers in earlier detection and prediction of IAC in patients with early renal impairment. In the long run, we will investigate the effects of interventional rehabilitations in preventing arterial stiffness caused by medial calcification.

There are several limitations to our study. First, direct causal relationships cannot be established, further longitudinal cohort studies could help identify the potential effect of impaired kidney function on the progression of IAC. Second, given the relatively preserved kidney function of the population included in this study, it is difficult to further classify those with eGFR <60 ml/min/1.73 m^2. Third, despite adjustment for some main potential confounders in analysis, serum phosphorus and calcium levels were not considered in this analysis. Serum phosphorus and serum calcium have been found to be associated with the risk of subclinical atherosclerosis in both the general population and CKD patients. Future studies are needed to investigate the role of calcium and phosphorus levels in the development of IAC. Lastly, a body of evidence has suggested that vitamin K status is associated with arterial calcifications, particularly in patients with end-stage renal disease (ESRD) [34,35]. Considering relatively early and mild renal dysfunctions in this cohort of patients, the effects of vitamin K status were not investigated. Future studies are needed to clarify the relationship between vitamin K status and different patterns of IAC.

In conclusion, our findings demonstrated that impaired kidney function was independently associated with a higher degree of calcification in the intracranial arteries, especially medial calcification, which reflects that different underlying mechanisms account for these two types of arterial calcification commonly identified in cerebral arteries.

CRediT authorship contribution statement

Xuelong Li: carried out the implementation, analyzed the data, wrote the manuscript. **Heng Du:** analyzed the data. **Wenjie Yang:** helped shape the manuscript, All authors discussed the results and contributed to the final manuscript. **Junru Chen:** analyzed the data. **Xianliang Li:** devised the project, the main conceptual ideas and proof outline. **Xiangyan Chen:** devised the project, the main conceptual ideas and proof outline.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] J.W. Bartstra, T.C. van den Beukel, W. Van Hecke, W. Mali, W. Spiering, H.L. Koek, et al., Intracranial arterial calcification: prevalence, risk factors, and consequences: Jacc review topic of the week, J. Am. Coll. Cardiol. 76 (2020) 1595–1604.

[2] X.Y. Chen, W.W. Lam, H.K. Ng, Y.H. Fan, K.S. Wong, Intracranial artery calcification: a newly identified risk factor of ischemic stroke, J. Neuroimaging 17 (2007) 300–303.

[3] C.P. Kovesdy, Epidemiology of chronic kidney disease: an update 2022, Kidney Int. Suppl. 12 (2022) 7–11, 2011.

[4] C. Koop-Nieuwelink, S. Sedaghat, U. Mutlu, S. Licher, O.H. Franco, M.A. Ikram, et al., Kidney function and the risk of stroke and dementia: the rotterdam study, J Alzheimers Dis 67 (2019) 821–826.

[5] W.J. Yang, L. Zheng, X.H. Wu, Z.Q. Huang, C.B. Niu, H.L. Zhao, et al., Postmortem study exploring distribution and patterns of intracranial artery calcification, Stroke 49 (2018) 2767–2769.

[6] W.J. Yang, B.A. Wasserman, L. Zheng, Z.Q. Huang, J. Li, J. Abrigo, et al., Understanding the clinical implications of intracranial arterial calcification using brain ct and vessel wall imaging, Front. Neurol. 12 (2021), 619233.

[7] H. Du, J. Li, W. Yang, D. Bos, L. Zheng, L.K.S. Wong, et al., Intracranial arterial calcification and intracranial atherosclerosis: close but different, Front. Neurol. 13 (2022), 799429.

[8] D.M. Kelly, P.M. Rothwell, Prevention and treatment of stroke in patients with chronic kidney disease: an overview of evidence and current guidelines, Kidney Int. 97 (2020) 266–278.

[9] S. Sedaghat, E.J. Hoorn, M.A. Ikram, C. Koop-Nieuwelink, M. Kavousi, O.H. Franco, et al., Kidney function and arterial calcification in major vascular beds, J. Am. Heart Assoc. 8 (2019), e010930.

[10] J.S. Kim, H.S. Hwang, Vascular calcification in chronic kidney disease: distinct features of pathogenesis and clinical implication, Korean Circ. J. 51 (2021) 961–982.

[11] A.J. Nelson, P. Raggi, M. Wolf, A.M. Gold, G.M. Chertow, M.T. Roe, Targeting vascular calcification in chronic kidney disease, JACC Basic Transl. Sci. 5 (2020) 398–412.

[12] M. Rogers, C. Goettsch, E. Aikawa, Medial and intimal calcification in chronic kidney disease: stressing the contributions, J. Am. Heart Assoc. 2 (2013), e000481.

[13] L.S. Babiarz, D.M. Yousem, B.A. Wasserman, C. Wu, W. Bilker, N.J. Beauchamp Jr., Cavernous carotid artery calcification and white matter ischemia, AJNR Am. J. Neuroradiol. 24 (2003) 872–877.

[14] L.S. Babiarz, D.M. Yousem, W. Bilker, B.A. Wasserman, Middle cerebral artery infarction: relationship of cavernous carotid artery calcification, AJNR Am. J. Neuroradiol. 26 (2005) 1505–1511.

[15] R. Kockelkoren, A. Vos, W. Van Hecke, A. Vink, R.L. Bleys, D. Verdoorn, et al., Computed tomographic distinction of intimal and medial calcification in the intracranial internal carotid artery, PLoS One 12 (2017), e0168360.

[16] D.J. Goldsmith, A. Covic, P.A. Sambrook, P. Ackrill, Vascular calcification in long-term haemodialysis patients in a single unit: a retrospective analysis, Nephron 77 (1997) 37–43.

[17] W.G. Goodman, J. Goldin, B.D. Kuizon, C. Yoon, B. Gales, D. Sider, et al., Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis, N. Engl. J. Med. 342 (2000) 1478–1483.

[18] L. Hénaut, J.M. Chillon, S. Kamel, Z.A. Massy, Updates on the mechanisms and the care of cardiovascular calcification in chronic kidney disease, Semin. Nephrol. 38 (2018) 233–250.

[19] D. Kelly, P.M. Rothwell, Disentangling the multiple links between renal dysfunction and cerebrovascular disease, J. Neurol. Neurosurg. Psychiatry 91 (2020) 88–97.

[20] S. Yamada, M. Taniguchi, M. Tokumoto, J. Toyonaga, K. Fujisaki, T. Suehiro, et al., The antioxidant tempol ameliorates arterial medial calcification in uremic rats: important role of oxidative stress in the pathogenesis of vascular calcification in chronic kidney disease, J. Bone Miner. Res. 27 (2012) 474–485.

[21] S. Park, N.J. Cho, N.H. Heo, E.J. Rhee, H. Gil, E.Y. Lee, Vascular calcification as a novel risk factor for kidney function deterioration in the nonelderly, J. Am. Heart Assoc. 10 (2021), e019300.

[22] S. Sedaghat, F.U. Mattace-Raso, E.J. Hoorn, A.G. Uitterlinden, A. Hofman, M. A. Ikram, et al., Arterial stiffness and decline in kidney function, Clin. J. Am. Soc. Nephrol. 10 (2015) 2190–2197.

[23] K. Amann, Media calcification and intima calcification are distinct entities in chronic kidney disease, Clin. J. Am. Soc. Nephrol. 3 (2008) 1599–1605.

[24] R. Shroff, D.A. Long, C. Shanahan, Mechanistic insights into vascular calcification in ckd, J. Am. Soc. Nephrol. 24 (2013) 179–189.

[25] J. Voelkl, D. Cejka, I. Alesutan, An overview of the mechanisms in vascular calcification during chronic kidney disease, Curr. Opin. Nephrol. Hypertens. 28 (2019) 289–296.

[26] K.S. Park, Y. Lee, G.M. Park, J.H. Park, Y.G. Kim, D.H. Yang, et al., Association between serum phosphorus and subclinical coronary atherosclerosis in asymptomatic Korean individuals without kidney dysfunction, Am. J. Clin. Nutr. 112 (2020) 66–73.

[27] K.S. Park, J. Park, S.H. Choi, S.H. Ann, G.B. Singh, E.S. Shin, et al., Serum phosphorus concentration and coronary artery calcification in subjects without renal dysfunction, PLoS One 11 (2016), e0151007.

[28] M. Huang, L. Zheng, H. Xu, D. Tang, L. Lin, J. Zhang, et al., Oxidative stress contributes to vascular calcification in patients with chronic kidney disease, J. Mol. Cell. Cardiol. 138 (2020) 256–268.

[29] Y. Wang, L. Gao, Inflammation and cardiovascular disease associated with hemodialysis for end-stage renal disease, Front. Pharmacol. 13 (2022), 800950.

[30] G. Coppolino, G. Leonardi, M. Andreucci, D. Bolignano, Oxidative stress and kidney function: a brief update, Curr. Pharmaceut. Des. 24 (2018) 4794–4799.

[31] W.J. Yang, M. Fisher, L. Zheng, C.B. Niu, A. Paganini-Hill, H.L. Zhao, et al., Histological characteristics of intracranial atherosclerosis in a Chinese population: a postmortem study, Front. Neurol. 8 (2017) 488.

[32] M. Cozzolino, P. Ciceri, A. Galassi, M. Mangano, S. Carugo, I. Capelli, et al., The key role of phosphate on vascular calcification, Toxins (2019) 11.

[33] K. Sheridan, J.V. Logomarsino, Effects of serum phosphorus on vascular calcification in a healthy, adult population: a systematic review, J. Vasc. Nurs. 35 (2017) 157–169.

[34] N. Kaesler, L.J. Schurgers, J. Floege, Vitamin k and cardiovascular complications in chronic kidney disease patients, Kidney Int. 100 (2021) 1023–1036.

[35] L. Dai, L. Li, H. Erlandsson, A.M.G. Jaminon, A.R. Qureshi, J. Ripsweden, et al., Functional vitamin k insufficiency, vascular calcification and mortality in advanced chronic kidney disease: a cohort study, PLoS One 16 (2021), e0247623.