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Original Article

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Chronic Kidney Disease is Associated with Intracranial Artery Stenosis Distribution in the Middle-Aged and Elderly Population

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Aims: To investigate the association of chronic kidney disease (CKD) and intracranial artery stenosis (ICAS), as well as its effects on ICAS distribution in the middle-aged and elderly population.

Methods: Data from the China Hypertension Survey in Beijing was analyzed. Estimated glomerular filtration rate (eGFR) was used to evaluate CKD, and ICAS was assessed by transcranial doppler. Clinical and biochemical variables were compared between the ICAS group and the non-ICAS group, as well as in different vascular distribution groups. Univariable and multivariable logistic regression analyses were introduced to demonstrate the association between CKD and ICAS.

Results: A total of 3678 subjects were included in this study, with a mean age of 62 years old. Of which, 19.2% presented with decreased eGFR (eGFR <60 ml/min/1.73 m^2) and 17.4% for ICAS. The percentage of anterior circulation ICAS was 3.5 times than that of posterior circulation (10.9% vs. 3.1%). In multivariable regression analysis, eGFR <45 ml/min/1.73 m^2 was independently associated with ICAS after correction for covariates, odds ratio (OR) = 1.69, 95% confidence interval (CI) (1.08, 2.65); in particular, this association had a preference for posterior circulation but not anterior circulation ICAS with OR = 2.29, 95% CI (1.28, 4.07) and OR = 1.44, 95%CI (0.89, 2.33), respectively.

Conclusion: Severe eGFR decline is associated with ICAS in the middle-aged and elderly population, and this correlation is more related to posterior circulation ICAS.

Key words: Chronic kidney disease, Intracranial artery stenosis, Atherosclerosis, Ischemic stroke

Introduction

Intracranial artery stenosis (ICAS) account for nearly 30%–50% of ischemic stroke cases. Subjects with ICAS have higher stroke risk and recurrence rate[1, 2]. To identify the potential causes of ICAS is of paramount importance in stroke prevention. At the same time, to distinguish the risk factors particularly related to certain vascular distribution will provide a better understanding of relevant pathophysiological mechanisms, as well as prognosis evaluation.

Chronic kidney disease (CKD) is becoming a rapidly growing global disease with the aging of population and has been reported to be associated with increased cardiovascular risk[3, 4]. It has been known that CKD is also a nontraditional risk factor of ischemic stroke[5]. Stroke patients with CKD usually have a poor outcome and high recurrence risk[6, 7]. As for the possible causes, some studies indicated that subjects with CKD have a higher incidence of atrial fibrillation; thus, cardiac embolism could be the most important mechanism[8, 9], while others proposed that

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it is atherosclerosis that contributes to stroke in subjects with CKD. However, evidence regarding CKD and cerebral atherosclerosis is limited. Some studies established the association of CKD and carotid atherosclerosis by retrospective analysis and their results revealed that subjects with CKD usually have much more severe atherosclerosis burden, which could be seen in both the stroke and non-stroke population[10]. There was also a study indicated that subjects with CKD are more likely to suffer from asymptomatic ICAS, but this association is limited to subjects over 60 years old[11].

Despite the population-based study results, the debate of CKD and ICAS persists regarding their relationship. Some scholars believed that CKD and ICAS share some risk factors; thus, this association could be the result of common risk factors. While others against that CKD is an independent risk factor of ICAS. The purpose of this study was to investigate the association of CKD and ICAS, considering the selectivity of the risk factors on ICAS distribution[12, 13], we would focus on the association of CKD and ICAS distribution. A thorough investigation of the association between CKD and ICAS will facilitate the understanding of stroke mechanism and identification of a high-risk population, as well as help us develop a better preventive strategy.

Methods

Study Design and Subjects

Data were derived from the Beijing subgroup of the "China Hypertension Survey" (CHS), supported by the Ministry of Science and Technology of the People's Republic of China. The study design had been published elsewhere[14], and the main findings were also reported[15]. Briefly, a stratified multistage multicentered national cross-sectional survey was conducted during 2012–2015 to investigate the prevalence of hypertension in subjects over 15 years old from 31 provinces in China. Beijing, as one of the most important part, was included.

For this sub-survey, the sampling process in Beijing was briefly summarized here: First, 3 cities in the urban area (Xicheng, Fangshan, and Tongzhou) and 1 county from the rural area (Yanqing) were selected using the probability proportional to size method; Second, 2–3 districts or 2 townships were selected within each urban area or county respectively by the simple random sampling (SRS) method. Then, using the same method above, 3 communities or villages were chosen within each district(urban) or township (rural) individually. Lastly, the SRS method was used again in the final selection of participates to ensure the representativeness in demographic characteristics.

A predefined standardized questionnaire was administered by experienced researchers to obtain relevant information on demographic characteristics and cardiovascular risk factors. In addition to the standard questionnaire, subjects over 35 years old were also required to complete the blood and urine biochemical testing, as well as cerebral vascular evaluation by carotid ultrasound and transcranial doppler (TCD) as secondary analysis for atherosclerosis. To ensure the quality of the survey, all of the investigators received standard training before participation, including the TCD operators. All physical examination and the laboratory testing were conducted as the protocol required.

As a result, a total of 6906 subjects over 35 years old were recruited in the CHS in the Beijing site. Of which, 3953 subjects completed the TCD vascular evaluation. After excluding those without creatinine tests, or subjects with transient kidney dysfunction caused by dehydration or use of nephrotoxic drugs (275 subjects in total), 3678 subjects were finally included in this analysis, which includes 1583 males and 2095 females (**Fig. 1**). The baseline characteristics of the subjects included and excluded are shown in **Supplemental Table 1**.

The protocol of the study design was approved by the Ethics Committee of Xuanwu Hospital of the Capital Medical University and Fuwai Hospital (National Center for Cardiovascular Disease). Written informed consent was obtained from all participants before enrollment.

Data Collection and Risk Factor Definition

Baseline characteristics, including demographics and cardiovascular risk factors, were collected by the investigators (trained neurologists or graduates) through face-to-face interview and recorded in a predefined questionnaire. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, or have been on antihypertensive medication. Diabetes mellitus was diagnosed in those who have a previous history of diabetes or on insulin or oral hypoglycemic medication; subjects with fasting glucose levels of over 7 mmol/L were also counted. Hyperlipidemia was diagnosed according to the adult treatment panel III guidelines[16] (Total cholesterol ≥ 6.1 mmol/L or Triglyceride [TG] ≥ 2.26 mmol/L) or who have been on lipid-lowering medications. Atrial fibrillation, coronary heart disease, and previous stroke history were identified according to the self-report history, and participants were also diagnosed as atrial fibrillation if the ECG indicated positive findings in this survey. Previous stroke events were

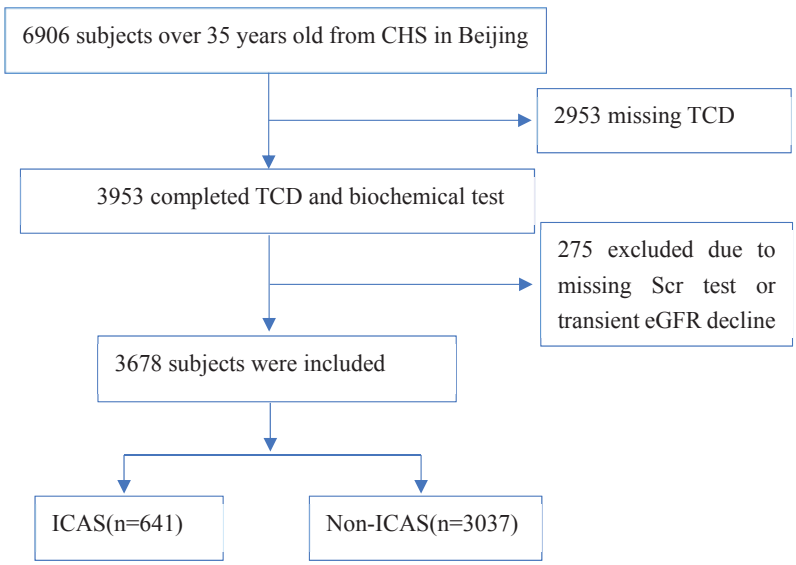

Fig. 1. Flow chart of subjects screening

judged by the neurologist or the physician from medical history and neuroimaging (CT or MRI) according to the AHA criteria. Smoking and drinking habits were recorded in self-report history. Smoking was confirmed for those who have been smoking for over 1-year period and those who are current smokers; Drinking was confirmed for those with moderate or heavy alcohol consumption (≥ 2 standardized alcohol drinks per day). All of the laboratory measurements were completed in Fuwai Hospital, National Center for Cardiovascular Disease according to predefined protocols to ensure the accuracy and controllability of the results.

CKD Assessment

Baseline serum creatinine level was tested to calculate the estimated glomerular filtration rate (eGFR) using the Jaffe method. In this study, eGFR was acquired by the CKD epidemiology collaboration creatinine equation with an adjusted coefficient of 1.1 for the Asian population[17]. Subjects were divided into four groups according to eGFR level: eGFR <45, 45–59, 60–89, and ≥ 90 ml/min/1.73 m^2 [18]. Participants with CKD were defined as those with eGFR < 60 ml/min/1.73 m^2 in this study. In order to increase the reliability of the renal function assessment, we also measured urinary microalbumin levels as reference.

Assessment of ICAS

TCD was performed by two independent vascular ultrasound practitioners with more than 5 years' experience using portable machines (TC 8080, EME, Germany). All procedures were carried out as required by the standard protocol and each vessel in the intracranial artery was detected, including bilateral anterior cerebral artery (ACA), middle cerebral artery (MCA), posterior cerebral artery (PCA), terminal of internal carotid artery (ICA), vertebral artery (VA), and basilar artery (BA). The diagnosis of ICAS is referred to Wong's criteria based on peak systolic flow velocity (Vp)[19]. The cut-off value of Vp for ICAS diagnosis was 140 cm/s in MCA, 120 cm/s in ACA and the internal carotid siphon, and 100 cm/s in PCA and the vertebral-basilar artery. Additional criteria of stenosis in MCA were: Vp ranging from 140 to 160 cm/s, together with disturbance in echo frequency and turbulence, or Vp reduction by ≥ 30% compared with the contralateral depth-corresponding homologous segment. Apart from the velocity criteria, the subjects' age was also considered. In the absence of good temporal windows, intracranial blood flow signals were detected via the orbital window. Any cerebral arteries that could not be detected via both temporal and orbital windows were considered non-stenotic. As a result, a total of 310 subjects (8.4%) were considered as non-stenotic due to the failed detection of blood flow by both temporal and orbital windows. The ICAS distribution was classified as anterior circulation and posterior circulation according to anatomy. The operators and reviewers of the TCD studies were blind to the clinical information.

Statistical Analysis

Variables distribution according to eGFR levels and between different groups were presented as numbers (percentages) for categorical variables and mean ±

Table 1. Baseline characteristics of subjects included according to eGFR category

		eGFR, ml/min/1.73 m^2				
	Total (n = 3678)	≥ 90 (n = 552)	60-89 (n = 2421)	45-59 (n = 599)	< 45 (n = 106)	p-value
eGFR (ml/min/1.73 m^2)	73.31 ± 15.27	96.50 ± 5.84	74.28 ± 8.47	54.32 + 4.08	37.71 + 7.20	< 0.001
Age (year), M ± SD	62 ± 13	52 ± 11	62 ± 12	73 ± 8	77 ± 8	< 0.001
Male, n (%)	1583 (43.0)	304 (55.1)	1037 (42.8)	205 (34.2)	37 (34.9)	< 0.001
Risk factors, n (%)						
Hypertension	2127 (58.4)	210 (38.5)	1384 (57.7)	443 (74.8)	90 (87.4)	< 0.001
Diabetes	816 (22.2)	74 (13.4)	521 (21.5)	180 (30.1)	41 (38.7)	< 0.001
Hyperlipidemia	2235 (60.8)	315 (57.1)	1478 (61.0)	374 (62.4)	68 (64.2)	0.216
Atrial fibrillation	85 (2.4)	5 (1.00)	47 (2.1)	28 (4.8)	5 (5.1)	< 0.001
CAD	333 (9.1)	28 (5.1)	190 (7.9)	90 (15.2)	25 (24.5)	< 0.001
Previous history of stroke	330 (9.0)	15 (2.7)	202 (8.3)	85 (14.2)	28 (26.4)	< 0.001
Smoking	1104 (30.0)	225 (40.8)	726 (30.0)	124 (20.7)	29 (27.4)	< 0.001
Drinking	968 (26.3)	209 (37.9)	645 (26.6)	106 (17.7)	8 (7.5)	< 0.001
BMI (kg/m^2)	25.78 ± 3.83	25.60 ± 3.86	25.81 ± 3.83	25.79 ± 3.79	26.03 ± 3.83	0.610
Glucose(mmol/L)	6.23 ± 1.77	5.93 ± 1.73	6.23 ± 1.74	6.46 ± 1.82	6.64 ± 2.21	< 0.001
TC (mmol/L)	4.92 ± 2.34	4.82 ± 0.96	4.94 ± 0.99	4.91 ± 1.04	4.82 ± 1.23	0.067
LDL-C (mmol/L)	2.88 ± 0.84	2.73 ± 0.82	2.90 ± 0.82	2.93 ± 0.88	2.86 ± 0.96	< 0.001
HDL-C (mmol/L)	1.41 ± 0.37	1.44 ± 0.34	1.43 ± 0.37	1.35 ± 0.35	1.20 ± 0.29	< 0.001
TG (mmol/L)	1.37 ± 0.83	1.40 ± 0.98	1.35 ± 0.79	1.39 ± 0.68	1.68 ± 1.54	0.001
Scr (umol/L)	85.93 ± 19.15	70.90 ± 11.42	83.71 ± 11.47	99.43 ± 13.27	138.74 ± 54.43	< 0.001
UMA (mg/L)*	12.5 (24.1)	11.4 (21.4)	11.9 (20.9)	15.7 (32.1)	36.3 (116.3)	< 0.001
Bp(mmHg)						
Sp	135 ± 18	130 ± 17	135 ± 18	138 ± 19	140 ± 19	< 0.001
Dp	76 ± 11	78 ± 10	76 ± 11	73 ± 11	70 ± 11	< 0.001
ICAS, n (%)	641 (17.4)	82 (14.9)	405 (16.7)	117 (19.5)	37 (34.9)	< 0.001

*: M (IQR)
eGFR = estimated glomerular filtration rate; CAD: coronary heart disease; BMI: body mass index; TC: total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TG: triglyceride; Scr: serum creatinine; UMA: urinary microalbumin; Bp: blood pressure; Sp: Systolic pressure; Dp: Diastolic pressure; ICAS: intracranial artery stenosis

standard deviation or median (interquartile range) for continuous variables. Chi-square test or t-test was used to compare variables between groups. Univariate and multivariate logistic regression analyses were performed to calculate the odds ratio (OR) and corresponding 95% confidence interval (95%CI). All of the statistics were two-sided and $p < 0.05$ was considered statistically significant in this analysis. All data analysis was conducted by SPSS 19.0.

Result

Basic Characteristics of Subjects Included According to eGFR Level

Of the included 3678 subjects, the mean age was 62 years old (range from 35 to 94 years old), and 57% were female. The overall prevalence of CKD (eGFR < 60 ml/min/1.73 m^2) was 19.2% (95%CI, 17.9%–20.4%). Hypertension and hyperlipidemia were the top two risk factors in this population, with a prevalence of 58.4% and 60.8% respectively.

The baseline characteristics and risk factors according to the classification of eGFR are shown in Table 1. Subjects with different eGFR levels differ in age, gender, and cardiovascular risk factors. Compared with other groups, subjects with low eGFR were much older, more likely to be female, had a higher percentage of hypertension, diabetes, atrial filtration, coronary heart disease, and had previous stroke history (all $p < 0.01$). As for biochemical results, glucose, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and TG also differ among different groups ($p < 0.01$). Correspondingly, the level of urinary microalbumin and serum creatinine were increasing along with the decline of eGFR. The mean systolic pressure was increasing and diastolic pressure decreasing with the deterioration of renal function (both $p < 0.01$). In addition, we can

Table 2. Risk factors associated with ICAS status and distribution

Variables	ICAS Status (n = 3678)			Distribution of ICAS (n = 513)		
	Present (n = 641)	Absent (3037)	p-value	Anterior (n = 400)	Posterior (n = 113)	p-value
Age (year), M ± SD	66 ± 11	62 ± 13	< 0.001	64 ± 12	69 ± 11	< 0.001
Male, n (%)	327 (51.0)	1256 (41.4)	0.004	204 (51)	59 (52.2)	0.820
Risk factors, n (%)						
Hypertension	464 (73.1)	1663 (55.3)	< 0.001	271 (68.3)	84 (75.7)	0.132
Diabetes	202 (31.5)	614 (20.2)	< 0.001	108 (27.0)	39 (34.5)	0.128
Hyperlipidemia	398 (62.1)	1837 (60.5)	0.450	233 (58.3)	71 (62.8)	0.381
Atrial fibrillation	12 (2.0)	73 (2.5)	0.393	7 (1.8)	1 (1.0)	0.531
CAD	81 (12.7)	252 (8.4)	0.001	37 (9.3)	18 (16.2)	0.038
Previous stroke	101 (15.8)	229 (7.5)	< 0.001	35 (8.8)	26 (23.0)	< 0.001
history						
Smoking	221 (34.5)	883 (29.1)	0.007	134 (33.5)	35 (31.0)	0.614
Drinking	170 (26.5)	798 (26.3)	0.898	105 (26.3)	33 (29.2)	0.532
BMI (kg/m^2)	25.55 ± 3.58	25.83 ± 3.88	0.088	25.69 ± 3.51	25.44 ± 3.47	0.574
Glucose (mmol/L)	6.64 ± 2.22	6.15 ± 1.65	< 0.001	6.52 ± 2.18	6.67 ± 2.07	0.496
TC (mmol/L)	4.94 ± 1.07	4.91 ± 0.99	0.589	4.94 ± 1.07	4.88 ± 1.06	0.985
LDL-C (mmol/L)	2.93 ± 0.88	2.87 ± 0.83	0.074	2.91 ± 0.86	2.93 ± 0.90	0.816
HDL-C (mmol/L)	1.36 ± 0.37	1.42 ± 0.37	< 0.001	1.38 ± 0.39	1.32 ± 0.31	0.137
TG (mmol/L)	1.41 ± 0.84	1.37 ± 0.83	0.249	1.39 ± 0.87	1.35 ± 0.59	0.622
Scr (ummol/L)	89.35 ± 24.01	85.21 ± 17.88	< 0.001	87.07 ± 20.81	91.22 ± 23.98	0.071
UMA (mg/L)	13.1 (30.2)	12.4 (22.7)	0.697	12.9 (24.7)	11.4 (25.9)	0.377
Bp (mmHg)						
Sp	140 ± 19	133 ± 17	< 0.001	139 ± 18	141 ± 20	0.295
Dp	75 ± 11	76 ± 11	0.008	75 ± 11	75 ± 10	0.952
eGFR (ml/min/1.73 m^2)	70.64 ± 15.94	73.87 ± 15.07	< 0.001	73.10 ± 15.30	68.09 ± 15.97	0.002
eGFR as ≥ 90	82 (12.8)	470 (15.5)	< 0.001	64 (16.0)	10 (8.8)	0.017
category 60-89	405 (63.2)	2016 (66.4)		264 (66.0)	70 (61.9)	
variable, 45-59	117 (18.3)	482 (15.9)		57 (14.3)	23 (20.4)	
n (%) < 45	37 (5.8)	69 (2.3)		15 (3.8)	10 (8.8)	

CAD: coronary heart disease; TC: total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TG: triglyceride; Scr: serum creatinine; UMA: urinary microalbumin; Bp: blood pressure; Sp: Systolic pressure; Dp: Diastolic pressure

also see the increasing prevalence of ICAS with the decrement of eGFR ($p < 0.01$).

ICAS Distribution and Associated Risk Factors

A total of 641 subjects (17.4%) suffered from ICAS in this population. Of all the intracranial vessels tested, the terminal of ICA and MCA were mostly involved, with a total prevalence of 9.5% (350 subjects), followed by ACA (9.3%, 343), VA (5.4%, 199), and PCA (1.8%, 65). BA (1.7%, 64) was the least affected. The incidence of ICAS in the anterior circulation was significantly higher than that in the posterior circulation (10.9% vs. 3.1%).

Table 2 generalizes the demographic characteristics and risk factors comparison between subjects with or without ICAS, as well as in different ICAS distribution statuses. As the results suggested, subjects with ICAS tended to be older, more likely to have hypertension, diabetes, coronary heart disease and previous stroke history, lower HDL-C, and higher LDL-C, glucose, and serum creatinine (all $p < 0.05$). Of particular, the mean eGFR in the ICAS group was significantly lower than that in the non-ICAS group (70.64 vs. 73.87 ml/min/1.73 m^2, $p < 0.05$), but urinary microalbumin had no significant difference between the two groups.

As for the risk factors affecting ICAS distribution, subjects with posterior circulation vascular stenosis were older, had higher proportion of coronary heart disease, previous stroke history, and declined eGFR ($p < 0.05$); other risk factors seemed to have no significant distinctions between different vascular stenosis

Table 3. Association of CKD and ICAS by regression analysis

eGFR (ml/min/1.73 m^2)	Model I OR (95%CI)	Model II OR (95%CI)	Model III OR (95%CI)
≥ 60	1.00 (reference)	1.00 (reference)	1.00 (reference)
45-59	1.24 (0.99, 1.55)	0.93 (0.73, 1.19)	0.88 (0.69, 1.14)
<45	2.74 (1.82, 4.13)	1.85 (1.20, 2.85)	1.69 (1.08, 2.65)

Model I: unadjusted, crude model; Model II: adjusted for age and gender; Model III: adjusted for age, gender, hypertension, diabetes, hyperlipidemia, coronary heart disease, previous stroke history, smoking, drinking, and BMI.

Table 4. Association of CKD and ICAS distribution

	Location of ICAS distribution			
	Anterior circulation		Posterior circulation	
eGFR (ml/min/1.73 m^2)	Univariate regression OR (95%CI)	Multivariate regression OR (95%CI)	Univariate regression OR (95%CI)	Multivariate regression OR (95%CI)
≥ 60	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
45-59	1.19 (0.94, 1.52)	0.91 (0.70, 1.19)	2.27 (1.66, 3.10)	1.22 (0.86, 1.73)
<45	2.16 (1.38, 3.39)	1.44 (0.89, 2.33)	5.90 (3.54, 9.85)	2.29 (1.28, 4.07)

Adjusted for age, gender, hypertension, diabetes, hyperlipidemia, coronary heart disease, previous stroke history, smoking, drinking and BMI in multi-variables regression analysis.

distribution groups.

Association of CKD and ICAS, ICAS Distribution by Logistic Regression Analysis

Table 3 shows the association of CKD and ICAS in different eGFR levels by univariate and multivariate regression analyses. When the group of eGFR ≥ 60 ml/min/1.73 m^2 was taken as a reference group, moderate eGFR decrease (45 ≤ eGFR <60)was not associated with ICAS in univariate analysis, OR=1.24, 95%CI (0.99, 1.55), nor in multivariate regression analysis, OR=0.88, 95%CI (0.69, 1.14); However, subjects with a severe decrease in eGFR (eGFR<45) were independently associated with ICAS even after correction for age, gender, and related atherosclerosis risk factors in multivariate analysis, OR=1.69, 95%CI (1.08, 2.65).

As a further analysis of CKD and ICAS distribution, we found that a severe decrease in eGFR (eGFR <45 ml/min/1.73 m^2) was associated with posterior circulation but not anterior circulation vessel stenosis. The OR was 5.90, 95%CI (3.54, 9.85) and 2.29, 95%CI (1.28, 4.07) before and after adjusted covariables, respectively (Table 4).

Discussion

This study investigated the association of CKD and ICAS as well as its distribution in the middle-aged and elderly population. The results demonstrated that: (1) Both CKD and ICAS are prevalent in the middle-aged and elderly population; (2) Subjects with severe eGFR decline (eGFR<45 ml/min/1.73 m^2) were independently associated with ICAS, even after adjusted for confounders; (3) Most importantly, we found that CKD, as a risk factor of ICAS, had a preference for posterior circulation vascular distribution; (4) Despite the higher proportion of atrial fibrillation in the elderly population with CKD, stroke mechanism should be explained with caution. These results could add some knowledge to the association of CKD and ICAS, and provide solid data about the contribution of CKD in cerebrovascular disease.

Association between CKD and Atherosclerosis

Previous epidemiological studies have already recognized CKD as a risk factor of cardiovascular disease and ischemic stroke[20-22]. CKD could significantly increase stroke risk and have an effect on stroke prognosis, especially in large artery atherosclerosis stroke[23]. As we know, the association of CKD and carotid atherosclerosis had been verified in previous studies with ischemic stroke[10, 24, 25]. Subjects with CKD usually have a much severe luminal stenosis and higher percentages of vulnerable plaques in the carotid artery. Both of these could result in ischemic stroke. As for its association with ICAS, Li Z reported the association of CKD and asymptomatic ICAS in Kailuan Study- a community-based non-stroke population in 2016, and found that declined eGFR is associated with

asymptomatic ICAS in this population[11]. This is quite consistent with our results. However, compared with their results, several innovations could be identified in our study. First, our study focused on the middle-aged and elderly populations, which were sampled by demographics. Some bias could be avoided in this process. Second, the ICAS distribution was also presented in our study, and the association of CKD and ICAS distribution was analyzed; this would definitely provide much more meaningful information to explain clinical correlation and explore the possible pathophysiological mechanism.

In fact, the association between CKD and ICAS has not been conclusive so far. Some scholars prefer to contribute this association to their common risk factors. There is no doubt that both CKD and ICAS share some traditional risk factors to some degree[26, 27], including age, hypertension, and diabetes. CKD could be a complication of these diseases; conversely, kidney dysfunction could also result in hypertension, and they are connected in some way. However, in our multivariable regression analysis, CKD was independently associated with ICAS after adjustment for these variables. Meta-analysis about CKD and cardiovascular disease also exemplified that CKD is a risk factor for CVD mortality independent of diabetes and hypertension[28, 29]. From the results above, we can conclude that despite the fact that older age, hypertension, and diabetes could be common in both the CKD and ICAS population, their contribution in the association between CKD and ICAS need to be explained with caution. A prospective cohort study about CKD and ICAS need to be conducted in the future to settle the argument.

CKD and ICAS Distribution

Of all the results presented above, what needs to be outlined is that we found CKD was more related to posterior circulation vascular stenosis in this population. To our knowledge, this is the first study about the association of CKD and ICAS distribution. For one thing, its preference for posterior circulation ICAS could possibly provide some evidence for the worse prognosis in stroke patients with CKD. For another, the selectivity of CKD on posterior circulation vessels might also suggest certain pathophysiological mechanisms different from anterior circulation.

Previous studies concerning risk factor and ICAS distribution were quite inconsistent. Some researchers proposed that the distribution of ICAS location differs among different risk factor groups by summarizing the data from the Warfarin–Aspirin Symptomatic Intracranial Disease study. They found that subjects with BA stenosis are older and much more likely to have hyperlipidemia[13]. While another study indicated that metabolic syndrome is associated with posterior circulation ICAS[30], there were also studies suggesting that hypertension and diabetes are more related to posterior circulation vessel stenosis[31]. However, the results are not conclusive due to the heterogeneous subjects and potential risk factors included. In this study, the prevalence of hypertension and diabetes had no significant difference between anterior and posterior circulation in univariate analysis, while in multivariate analysis, CKD was an independent risk factor of posterior circulation vessel stenosis after correction of all covariates. Thus, there must be some undetermined mechanism that needs to be clarified in the future to explain this association. Considering the anatomy difference, we assumed that some hemodynamic factors could possibly play a role in this pathophysiological process.

Possible Mechanisms of CKD in the Contribution of Cerebrovascular Disease

The mechanism of CKD in contributing to cardiovascular disease is seldom explored. It has been known that subjects with CKD are usually accompanied with vascular calcification, which results in decreased arterial compliance and present as widening pulse pressure[32]. This phenomenon could also be verified in our study. A similar study also demonstrated that the decreased vascular reserve capacity and cerebral autoregulation could be the interconnection between CKD and stroke[33, 34], subjects with CKD usually have increased arterial stiffness[35], and consequently decreased cerebrovascular reactivity. Integrating with the evidence at present, the contribution of CKD in ischemic stroke could be assumed that CKD could promote atherosclerosis vessel stenosis, decrease vascular reactivity, and further reduce vascular reserve in case of ischemia. All of these could contribute to the cerebrovascular events.

In addition to ICAS, subjects with CKD usually have a higher percentage of atrial fibrillation[36] and correspondingly , a higher risk of embolism. We can also see the increasing trend of atrial fibrillation with the decrease of eGFR in our study; however, we did not find any difference of atrial fibrillation in the ICAS and non-ICAS group, which also suggested that atrial fibrillation could not be a confounding factor between CKD and ICAS.

Strengths and Limitations

The strength of this study is (1) the large sample size and randomly sampled population; (2) the association of CKD and ICAS were comprehensively clarified in this study, including its association with ICAS

distribution; (3) we validated CKD as a risk factor of ICAS, which could help to understand the role of CKD plays in contributing to stroke.

There are several limitations to this study. First, the cause and consequence relationship could not be deduced from this cross-sectional design, and more prospective cohort studies need to be carried out in the future. Second, all of the ICAS assessments were based on TCD instead of more direct vessel imaging (CTA or MRA), and we defined those acoustic window failures as non-stenotic in this study, which could underestimate the detection of ICAS. Furthermore, failure to identify the causes of ICAS is another limitation of TCD. Some non-atherosclerotic intracranial artery disease could not be identified in this population. However, in view of the sensitivity and specificity of TCD in evaluating ICAS, the lower possibility of non-atherosclerotic ICAS in the elderly population, as well as the health economics considerations, TCD is undoubtedly the most convenient and appropriate method in this large population. Third, compared with anterior circulation ICAS, the relatively few subjects with posterior circulation stenosis could also have some effects on regression analysis, but the limited number of variables adjusted and narrow confidence interval validate the credibility of the results.

Conclusion

In summary, despite the limitations above, we can draw the conclusion that severe eGFR decline (eGFR <45 ml/min/1.73 m^2) is associated with ICAS in the middle-aged and elderly populations, and this correlation has a preference for posterior circulation vessels. This study could provide some evidence to explain the pathophysiological mechanism between CKD and stroke, and at the same time, bring about more questions about stroke prevention in this population.

Conflicts of Interest and Funding Declaration

The authors declared that we have no conflicts of interest. This study was supported by National Key Program in the Twelfth Five-year Plan (Grant No. 2011BAI11B01) from the Chinese Ministry of Science and Technology, Commission of Science and Technology of Beijing (Grant No. D121100004912002), Beijing Municipal Administration of Hospitals' Ascent Plan (Grant No. DFL20152201), and Beijing Municipal Health Bureau project (Grant No.2013-2-034).

Author Contributions

XW Song and J Li analyzed, interpreted the data, and drafted the manuscript. Y Hua and BB Liu analyzed the TCD data; ZY Zhang, CX Liu, CX Wang, and QN Zhao acquired the data and did some statistical work. XH Fang and J Wu conceived the study and proposed the data analysis plan, XH Fang supervised the whole study, and J Wu made the final revision of the manuscript.

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Supplemental Table 1. Demographics and risk factors comparison between subjects included and excluded

Variables (*n*, % or M ± SD)	Total (*n* = 6,906)	Inclusion (*n* = 3,678)	Exclusion (*n* = 3,228)	*p*-value
Age (year)	61 ± 14	62 ± 13	59 ± 15	< 0.001
Male	3,089 (44.7)	1,583 (43.0)	1,506 (46.7)	0.003
Risk factors				
Hypertension	3,653 (53.7)	2,127 (58.4)	1,526 (48.2)	< 0.001
Diabetes	1,260 (18.4)	816 (22.2)	444 (14.0)	< 0.001
Hyperlipidemia	3,178 (53.0)	2,235 (60.8)	943 (40.0)	< 0.001
Atrial filtration	114 (2.3)	85 (2.4)	29 (2.1)	0.409
CAD	530 (7.8)	333 (9.1)	197 (6.2)	< 0.001
Previous stroke history	585 (8.5)	330 (9.0)	255 (7.9)	0.110
Smoking	2,090 (33.1)	1,104 (30.0)	986 (33.1)	0.007
Drinking	1,960 (29.2)	968 (26.3)	992 (31.7)	< 0.001
BMI (kg/m^2)	25.57 ± 3.77	25.78 ± 3.83	25.26 ± 3.68	< 0.001

CAD: coronary heart disease

In summary, subjects included were much older (mean age 62 vs 59, $p < 0.05$),more likely to have hypertension (58.4% vs 48.2%, $p < 0.05$),diabetes (22.2% vs 14.0%, $p < 0.05$), hyperlipidemia (60.8% vs 40.0%, $p < 0.05$), and coronary disease (9.1% vs 6.2%, $p < 0.05$), but the proportion of male is much lower than in those excluded (43.0% vs 46.7%, $p < 0.05$), accordingly, the percentage of smoking (30.0% vs 33.1%) and drinking (27.0% vs 31.7%).

Several factors contribute to the unmatched difference. First, some risk factors are age-related, thus older subjects have a much higher percentage of risk factors; Second, subjects with more risk factor seems to more willing to participate the biochemistry testing and vascular assessment. Third, the risk factors diagnosis was based on self-reported medical history in the exclusion group, lack of laboratory test might possibly result in the underestimation of diagnosis, such as diabetes and hyperlipidemia. Finally, the gender difference between the two groups could explain part of the unbalance of smoking and drinking.