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Association of Intracranial Artery Calcification with Cognitive Impairment in Hemodialysis Patients

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Background: Chronic kidney disease (CKD) is one of risk factors for dementia and cognitive decline. Cardiovascular and dialysis-related factors might also be involved in the mechanism of cognitive impairment in hemodialysis patients. The objective of this study was to investigate whether cardiovascular risk factors including intracranial artery calcification and dialysis-related factors such as fibroblast growth factor 23 (FGF23) might be associated with cognitive impairment in hemodialysis patients.

Material/Methods: A cross-sectional observational study included patients receiving in-center hemodialysis over 6 months at our hospital. All patients underwent non-contrast computed tomography (CT) examinations. Internal carotid artery (ICA) calcium scores were measured using the Agatston method. The Korean version of the Montreal Cognitive Assessment was used for measurement of cognitive function at each study visit. Serum concentrations of FGF23, osteoprotegerin, and klotho were analyzed using commercial enzyme-linked immunosorbent assay kits.

Results: This study included 69 patients. Cognitive impairment was observed in 22 patients (31.9%), including 3 patients with dementia. ICA calcium score in patients with cognitive impairment was higher than that in those without cognitive impairment (177.3 versus 87.6, *P*=0.022). Intracranial artery calcification was significantly associated with cognitive impairment after adjusting for FGF23 and 25-OH vitamin D, but not significant after adjusting for age, FGF23, and 25-OH vitamin D. Low level of FGF23 was associated with cognitive impairment.

Conclusions: Intracranial artery calcification and low FGF23 could be associated with cognitive impairment in hemodialysis patients. Longitudinal studies are needed to investigate whether intracranial artery calcification and FGF23 could affect cognitive function of hemodialysis patients.

MeSH Keywords: Cognitive Science • Fibroblast Growth Factors • Hemodialysis Units, Hospital • Vascular Calcification

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Background

Individuals at all stages of chronic kidney disease (CKD) have higher risk of developing dementia and cognitive impairment than those without CKD [1]. In hemodialysis patients, the prevalence of cognitive impairment is 30–60% [2]. Many factors could be associated with cognitive impairment in CKD patients. It has been reported that vascular risk factors and dialysis-related factors are associated with deterioration of cognitive function in CKD patients [3,4]. One may hypothesize that direct paths in CKD could affect brain function and morphology and hence cognition. An alternative possibility is that risk factors shared by the brain and kidneys can lead to cognitive deficit, decline, and impairment [1,5,6]. This parallel risk factor model is appealing because both the kidney and brain are low-resistance end organs known to be exposed and re-exposed to high-volume blood flow though the cardiac cycle. Thus, the brain and kidney are very likely to share common risk factors for cognitive deficit and impairment.

Intracranial artery calcification might be an independent risk factor for ischemic stroke in the general population [7]. Although some studies have shown that intracranial artery calcification is predominant in hemodialysis patients [3,8], it is doubtful that intracranial artery calcification is a risk factor of cognitive impairment in hemodialysis patients. Fibroblast growth factor 23 (FGF23) is a circulating hormone that stimulates urinary phosphate excretion and decreases phosphorus absorption [9]. FGF23 is associated with left ventricular hypertrophy, coronary calcification, and mortality in hemodialysis patients [9–13]. Both klotho and FGF receptors are present in the brain. Drew et al. have suggested that high FGF23 levels are associated with cognitive impairment in hemodialysis patients [2]. The aim of our study was to investigate whether cardiovascular risk factors including intracranial artery calcification and dialysis-related factors such as FGF23 might be associated with cognitive impairment in patients with hemodialysis.

Material and Methods

Study population

In this cross-sectional observation study, patients receiving in-center hemodialysis over 6 months at our hospital were evaluated for study participation. Patients on prevalent hemodialysis in Soonchunhyang University Cheonan Hospital Artificial Kidney Center (Cheonan, South Korea) were recruited. All recruited patients were older than 18 years of age, had undergone thrice-weekly hemodialysis for at least 6 months, and had not been hospitalized for acute illness during the preceding month. Study patients with evident major stroke, those who were using benzodiazepine, those with uncontrolled malignancy or with confirmed dementia were excluded from this study. We obtained history, clinical examination reports, and laboratory investigations for all patients. The present study was approved by the Institutional Review Board of Soonchunhyang University Cheonan Hospital (201404008). Informed consent was obtained from all patients.

Calcium scoring of the intracranial internal carotid artery

All patients underwent computed tomography (CT) examinations with a 256-slice multidetector-row CT scanner (Brilliance iCT 256, Philips Healthcare, Best, The Netherlands) using a standardized non-contrast CT protocol (120 kVp; 280 mAs; collimation, 64×0.625 mm; table speed, 31.3 mm/sec; pitch, 0.39). Images were reconstructed with a field of view of 160 mm, matrix size of 512×512 mm, and slice thickness/increment of 0.8 mm/0.8 mm. Quantification of calcium burden was performed on a standard post-processing platform (Brilliance Workspace Portal v. 2.6.0.32, Philips Healthcare, Best, The Netherlands). Calcium scoring was carried out using the Agatston method [14]. By this method, ≥2 continuous pixels with CT density ≥130 Hounsfield units were automatically marked by the software. Because of the proximity of the arterial wall calcium and the adjacent sphenoid and temporal bone, a board-certificated neuroradiologist with 7 years of experience drew the region-of-interest (ROI) using a semi-automated method to extract the calcium score of intracranial internal carotid arteries (ICAs), but not bony structures. Calcium scores of all ROIs in each ICA were summed. Total Agatston score of the intracranial ICA was then calculated for each patient

Assessment of cognitive function

The Korean version of the Montreal Cognitive Assessment (K-MoCA, English version 7.1 available at www.mocatest.org) was used for the measurement of cognitive function at each study visit. The K-MoCA is a screening tool consisting of 30 points. Completion of this test needs approximately 10 minutes. It is highly sensitive in detecting mild cognitive impairment (MCI) [15–17]. The K-MoCA includes multiple area of cognition, which includes short-term memory, visuospatial abilities and executive function, language, attention, concentration and working memory, and time and place orientation. Delayed recall of 5 nouns is included after 2 learning trials, a clock-drawing and a 3-dimensional cube copy test, Trail Making B test, a phonemic fluency task, a verbal abstraction task, a sustained attention task, serial subtraction and digits forward and backward tasks, a naming task, repetition of complex sentences, and a fluency task. The education level of the participant is adjusted for by adding one point to the total score for participants with ≤12 years of formal education. Thirty-one is the possible maximum score on test. We defined MCI as a score ≤22 in our study. This level might be the reliable cutoff score

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to detect MCI [18]. The K-MoCA was scored by a researcher in accordance with the Korean version instructions.

Measurement of FGF23, osteoprotegerin, and klotho

Within 30 minutes after collection, blood samples were centrifuged at 3000 rpm for 15 minutes. The serum was extracted and stored at –70°C until analysis. Serum FGF23, klotho, and osteoprotegerin were analyzed using Human FGF-23 ELISA Kit (Merck Millipore, St. Louis, MO, USA), Human Soluble Alpha-klotho Assay Kit (Immuno-Biological Laboratories, Gunma, Japan), and Human Osteoprotegerin ELISA Kit (Abcam, Cambridge, UK) according to manufacturers' instructions. These were analyzed twice with intra- and inter-assay coefficients of variation <10%.

Statistical analysis

R version 3.4.0 (The R Foundation for Statistical Computing, Vienna, Austria) were used for all statistical analyses. Categorical variables are expressed as counts (percentage). Normally distributed continuous variables are expressed as means ± standard deviation (SD) while non-normally distributed continuous variables are expressed as medians (interquartile ranges). Differences between groups were tested by Kruskal-Wallis test or Mann-Whitney U test according to the number of groups. For selecting parameters for prediction model, univariable logistic regression analyses were performed, and covariates whose *P*-value was less than 0.1 were selected for further analysis. From all subset logistic regression models constructed by selected parameters, best fitted model was the logistic regression model that maximized prediction accuracy acquired by repeated 10-fold cross validation method. The model with the highest predictive accuracy and the second highest models were chosen, and they were also validated by receiver-operating characteristic (ROC) curve analysis. Two-tailed tests were performed in all hypothesis tests. *P*-value <0.05 was considered statistically significant.

Results

Study population at baseline

This study included 69 patients; 53.6% males and 46.4% females. The mean age was 55.3±11.4 years. Baseline characteristics of these patients are shown in Table 1. Hemodialysis vintage (length of time on hemodialysis) was 75 months. Twenty-four patients (34.8%) had diabetes. Twenty-two patients (31.9%) had cognitive impairment, including 3 patients with dementia. Age, urea nitrogen, creatinine, phosphorus, 25-OH vitamin D level, Kt/v, total ICA calcium score, and FGF23 level were statistically different between patients with cognitive impairment and those without such impairment. However, osteoprotegerin or klotho level was not significantly different between the 2 groups.

Relationship between intracranial calcification and cognitive function

ICA calcium score was higher in patients with cognitive impairment (Figure 1). To investigate the association of cognitive function with other biologic markers, logistic regression analysis was performed. In univariate analysis, 25-OH vitamin D, FGF23, and ICA calcium score showed statistically significant association with cognitive impairment (Table 2). However, osteoprotegerin or klotho level was not significantly associated with cognitive impairment. To search how these factors affected cognitive function, multivariable logistic regression analysis was performed using different models. Two models with high predictive accuracy for cognitive dysfunction were selected and further analyzed (Supplementary Table 1). In these multivariable logistic regression models, ICA calcium score was significantly associated with cognitive impairment after adjusting for FGF23 and 25-OH Vitamin D (model 1) (Table 3). However, after adjusting for age, FGF23, and 25-OH vitamin D, ICA calcium score was not significantly associated with cognitive function (model 2). Low level of FGF23 was associated with cognitive impairment. ROC analysis showed that FGF23, 25-OH vitamin D, ICA calcium score, and age were more effective than only ICA calcium score to predict cognitive impairment in hemodialysis patients (Figure 2).

Relationship between intracranial calcification and baseline factors

We also investigated which factors were correlated with ICA calcium scores (Figure 3). Age and osteoprotegerin level were correlated with ICA calcium score, whereas FGF23 and/or 25-OH vitamin D was not correlated with ICA calcium score.

Discussion

Our study showed that hemodialysis patients had a high prevalence of cognitive impairment. Our results suggested that cognitive impairment in hemodialysis patients could be associated with ICA calcium scores and FGF23 levels. However, ICA calcium score was not a predictive factor for cognitive impairment after adjusting for age. ICA calcium score was also well-correlated with age. Low level of FGF23 was an important factor to predict cognitive impairment.

Meta-analysis has confirmed poor cognitive performance in patients receiving hemodialysis [19]. A recent study showed that hemodialysis patients demonstrated significant cognitive decline [2]. Older age might be associated with greater decline in

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Table 1. Baseline demographics and clinical characteristics according to cognitive impairment.

	All patients (n=69)	Patients without cognitive dysfunction (n=47)	Patients with cognitive dysfunction (n=22)	*P*-value
Age, years	55.3±11.4	52.1±10.8	62.2±9.6	<0.001
Sex, male (%)	37 (53.6)	29 (61.7)	8 (36.4)	0.088
Diabetes, present	24 (34.8)	14 (29.8)	10 (45.5)	0.316
CAD, present	10 (14.5)	7 (14.9)	3 (13.6)	1.000
Vintage of HD, months	73.0 (37.0–125.0)	92.0 (32.5–135.5)	62.5 (40.5–109.8)	0.511
BMI, kg/m^2	22.3 (19.4–24.6)	22.3 (19.5–24.0)	22.1 (19.4–25.2)	0.467
Hemoglobin, g/dL	10.7±0.6	10.8±0.6	10.4±0.6	0.049
Urea nitrogen, mg/dL	58.2±11.5	60.5±11.9	53.4±9.2	0.016
Creatinine, mg/dL	9.5±2.6	10.2±2.6	8.1±1.9	0.001
Albumin, g/dL	3.95±0.25	4.00±0.22	3.84±0.28	0.388
Total cholesterol, mg/dL	141.3±30.7	142.0±30.6	140.0±31.5	0.805
Triglycerides, mg/dL	85.5 (63.3–127.0)	86.2 (63.1–131.0)	82.0 (66.4–121.3)	0.827
Uric acid, mg/dL	6.59±0.96	6.60±1.04	6.56±0.81	0.887
Calcium, mg/dL	9.10±0.54	9.15±0.58	9.00±0.41	0.265
Phosphorus, mg/dL	4.10 (3.64–4.73)	4.35 (3.81–4.97)	3.80 (3.31–4.05)	0.002
Intact PTH, pg/mL	214.4 (130.5–315.1)	251.0 (133.7–354.8)	202.9 (86.4–245.8)	0.078
25(OH)D, ng/mL	10.8 (8.9–14.6)	11.4 (9.3–14.9)	9.9 (8.3–11.3)	0.036
Ferritin, ng/mL	272.6 (180.1–414.9)	284.6 (182.2–406.9)	270.9 (186.0–410.8)	0.837
β2-microglobulin, mg/L	28.8 (23.5–31.9)	28.8 (25.3–32.6)	27.9 (21.1–30.2)	0.229
Kt/V	1.84±0.32	1.78±0.33	1.97±0.27	0.019
Total ICA calcium score	101.9 (5.9–312.0)	87.6 (1.5–194.9)	177.3 (59.2–381.0)	0.022
CA calcium score	109.7 (1.1–712.5)	251.0 (0.0–845.3)	51.4 (11.6–389.9)	0.615
FGF23, pg/mL	727.8 (159.1–4946.4)	897.6 (203.3–5085.2)	372.9 (147.2–768.5)	0.021
Klotho, pg/mL	182.6 (160.8–228.0)	182.6 (160.4–213.2)	186.5 (161.4–250.3)	0.709
Osteoprotegerin, pg/mL	201.9 (131.1–289.8)	200.4 (124.2–246.0)	244.9 (147.2–334.4)	0.137
K-MoCA	25.0 (21.0–26.0)	26.0 (25.0–27.0)	19.5 (13.5–20.0)	<0.001

Data are presented as mean ±SD, median (interquartile range), or count (%) as appropriate. *P*-values are calculated by Student's *t*-test for normally distributed continuous variables, Mann-Whitney U test for non-normally distributed continuous variables, and Pearson's chi-squared test for categorical variables. CAD – coronary artery disease; HD – hemodialysis; BMI – body mass index; PTH – parathyroid hormone; 25(OH)D – 25-hydroxyvitamin D; TIBC – total iron-binding capacity; ICA – internal carotid artery; CA – coronary artery; FGF – fibroblast growth factor.

cognitive function per year whereas sex, race, education level, stroke history, or cause of renal failure have not been associated with steeper decline [2]. Within the general population, steep decline has been reported predominantly within older individuals [20]. A comparison of 2 previous studies [2,20] found that the rate of deterioration of cognitive function in the same age group was faster in hemodialysis patients compared to the general population. Several factors might be involved in the high prevalence of cognitive impairment in and rapid deterioration of hemodialysis patients [21]. Vascular calcification is

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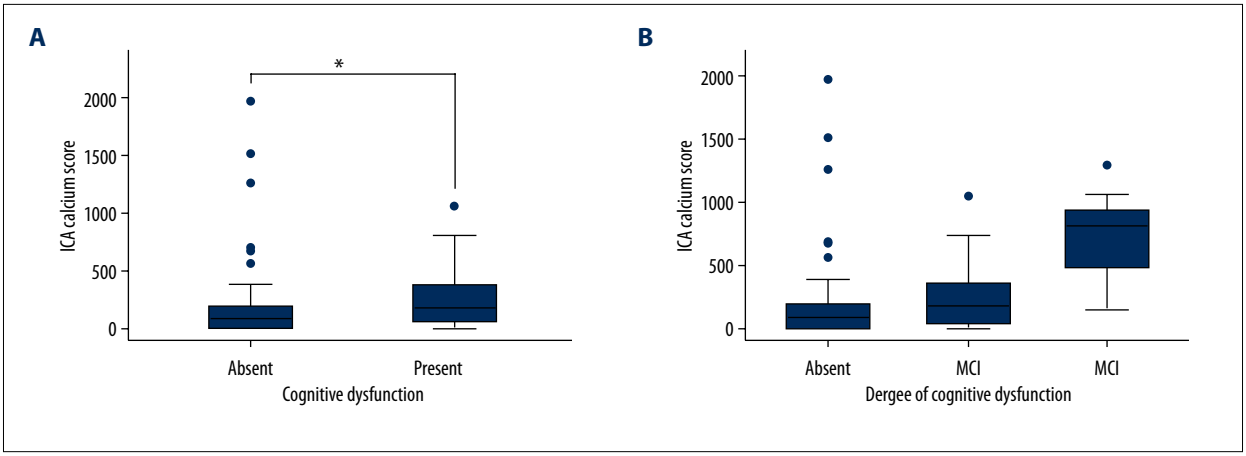

Figure 1. (**A, B**) Internal carotid artery (ICA) calcium score according to cognitive function: ICA calcium score is higher in hemodialysis patients with cognitive impairment than that in those without cognitive impairment.

Table 2. Univariable logistic regression analyses for predicting cognitive impairment in hemodialysis patients.

Variables	Univariable model	
	Odd ratio	P-value
Age, years	1.10 (1.04–1.18)	0.001
Sex	0.36 (0.12–0.99)	0.053
Vintage of HD, months	1.00 (0.99–1.01)	0.523
Hemoglobin, g/dL	0.40 (0.14–0.96)	0.056
Albumin, g/dL	0.07 (0.01–0.55)	0.017
Creatinine, mg/dL	0.68 (0.52–0.86)	0.003
Phosphorus, mg/dL	0.45 (0.22–0.82)	0.016
25(OH)D, ng/mL	0.87 (0.73–0.98)	0.054
ICA calcium score	4.06 (1.33–13.04)	0.015
FGF23, ng/mL	0.65 (0.44–0.88)	0.014
Klotho, pg/mL	1.00 (0.99–1.00)	0.726
Osteoprotegerin, pg/mL	1.00 (1.00–1.01)	0.109

HD – hemodialysis; ICA – internal carotid artery; FGF – fibroblast growth factor.

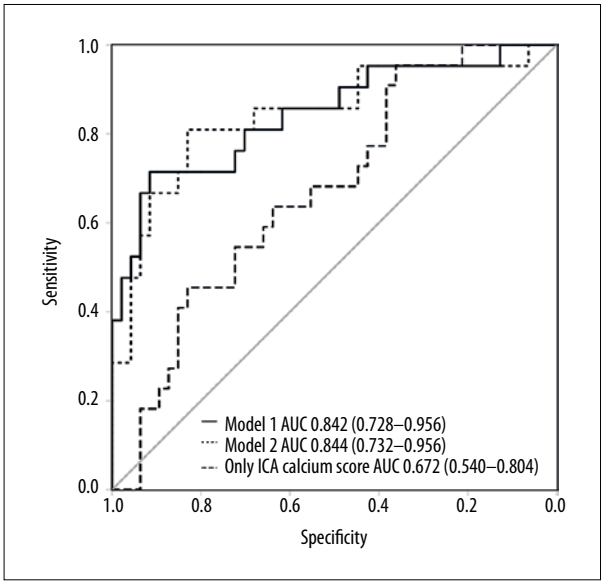

Figure 2. ROC curve plots for cognitive impairment in hemodialysis patients. Each ROC curve is used to predict cognitive impairment. Using model 1 or model 2 could predict cognitive impairment better than using only ICA calcium score. ROC – receiver-operating characteristic; ICA – internal carotid artery.

Table 3. Multivariable logistic regression analyses for predicting cognitive impairment in hemodialysis patient.

Variables	Multivariable model 1		Multivariable model 2	
	Odd ratio	*P*-value	Odd ratio	*P*-value
Age, years			1.05 (0.98–1.15)	0.173
25(OH)D, ng/mL	0.84 (0.69–0.98)	0.062	0.84 (0.68–0.99)	0.068
ICA calcium score	5.44 (1.40–25.27)	0.019	2.65 (0.49–16.04)	0.262
FGF23, ng/mL	0.56 (0.35–0.79)	0.005	0.60 (0.37–0.88)	0.019

ICA – internal carotid artery; FGF – fibroblast growth factor.

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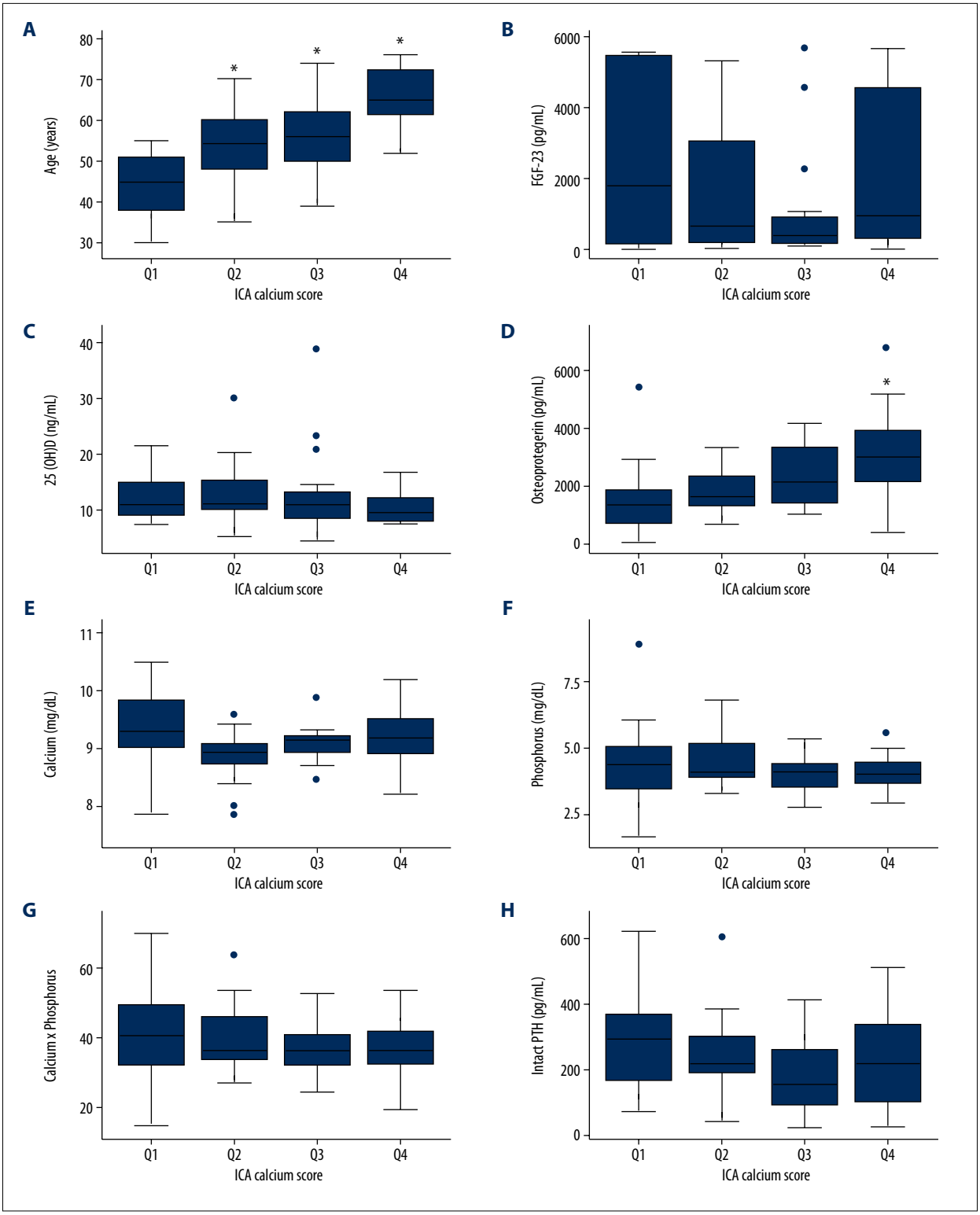

Figure 3. (**A–H**) Relationship between internal carotid artery (ICA) calcium score and each parameter.

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a well-known complication of CKD. It is one of the main predictors for increased cardiovascular events in these patients [22]. Compared with the general population, vascular calcification is a predominant feature in hemodialysis patients [22]. Our study showed that ICA calcium scores were correlated with age, suggesting that intracranial artery calcification could be an important factor affected by age. A much higher rate of intracranial artery calcification has been observed in hemodialysis patients than that in the general population [8]. Although intracranial artery calcification is an independent risk factor for ischemic stroke in the general population [7], one study has shown that intracranial artery calcification is not associated with acute ischemic stroke in hemodialysis patients [3]. Further study is needed to suggest the role of intracranial artery calcification in hemodialysis patients.

We investigated whether well-known uremic factors were associated with cognitive function in hemodialysis patients. FGF23, klotho, and osteoprotegerin levels are factors with a known association with vascular calcification [10,13,22]. FGF23 is related with many adverse outcomes, including left ventricular hypertrophy, cardiovascular morbidity, and mortality among CKD patients [9,11,13]. Although FGF23 is mainly expressed in the bone, FGF23 in the brain is also found in high concentration [23]. Although both klotho and FGF receptors are expressed in the brain, the role of FGF23 in the brain has not been revealed. Drew et al. showed that there was a modest association between higher serum FGF23 levels and lower cognitive function in a cohort of patients treated with maintenance hemodialysis [24]. Interestingly, our study showed that low FGF23 levels were associated with cognitive impairment. Although some experimental studies have suggested that FGF23 itself can affect hippocampus function, blood FGF23 levels were not shown to reflect the level in cerebrospinal fluid [9,25,26]. Further large and longitudinal study is needed to reveal the effect of FGF23 on cognitive function in hemodialysis patients and the relationship between serum FGF23 and brain damage.

This study had several limitations. First, this study had a cross sectional design. The causality between cognitive impairment and observational parameters remains unclear. Second, total number of participants was not large to adjust many confounding variables in the multivariable statistical models. Third, the number of hemodialysis patients with cognitive impairment was small. Third, given the observational nature of this study, there might be unmeasured factors and residual confounders.

Conclusions

Our study suggests that ICA calcium sore and low FGF23 could be correlated with cognitive impairment in hemodialysis. Longitudinal studies are needed to investigate whether intracranial artery calcification and FGF23 could affect cognitive function of hemodialysis patients.

Supplementary Table

Supplementary Table 1. Assessing the performance of logistic regression models predicting cognitive dysfunction.

	Variable included	C-statistics	K-fold cross validation*
Model 2	Age, ICA calcium score, FGF23, 25(OH)D	0.844	0.820
Model 1	ICA calcium score, FGF23, 25(OH)D	0.842	0.807
	Age, serum albumin, FGF23, 25(OH)D	0.855	0.805
	Age, sex, FGF23, 25(OH)D	0.850	0.799
	Age, sex, ICA calcium score, FGF23, 25(OH)D	0.845	0.799
	Age, sex, FGF23	0.826	0.798
	Age, serum creatinine, FGF23, 25(OH)D	0.843	0.796
	Age, 25(OH)D	0.786	0.793
	ICA calcium score, serum albumin, FGF23, 25(OH)D	0.853	0.791
	Age, ICA calcium score, serum albumin, FGF23, 25(OH)D	0.858	0.790

* The predicting abilities obtained by K-fold cross validation were presented as accuracy of prediction (%). ICA – internal carotid artery.

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