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Original Research Article

Association of Chronic Kidney Disease and Cerebral Small Vessel Disease with Cognitive Impairment in Elderly Patients with Type 2 Diabetes

Toshitaka Umemura[a] Takahiko Kawamura[b] Hiroyuki Umegaki[d] Naoko Kawano[d] Shinichi Mashita[c] Toshimasa Sakakibara[a] Nigishi Hotta[b] Gen Sobue[e]

Departments of [a]Neurology, [b]Diabetes and Endocrine Internal Medicine and [c]Radiology, Chubu Rosai Hospital, and Departments of [d]Geriatrics and [e]Neurology, Nagoya University Graduate School of Medicine, Nagoya, Japan

Key Words

Chronic kidney disease · Albuminuria · Glomerular filtration rate · Cerebral small vessel disease · Cognitive impairment · Elderly · Diabetes · Magnetic resonance imaging

Abstract

Background/Aims: In recent years, the relationship between chronic kidney disease (CKD) and cognitive impairment has been attracting attention. Cerebral small vessel disease (SVD) is also associated with an increased risk of cognitive impairment. However, it is still unknown whether CKD markers are associated with cognitive impairment independently of SVD in elderly diabetic patients. ***Methods:*** Seventy-nine type 2 diabetic patients (mean age, 76.0 years) were enrolled in the present study. CKD was defined as the presence of albuminuria and/or a low estimated glomerular filtration rate (eGFR <60 ml/min/1.73 m^2). SVD was evaluated by the presence and severity of silent brain infarcts (SBIs) and white matter lesions (WMLs) on brain magnetic resonance imaging. Neuropsychological tests were assessed using four validated cognitive instruments. ***Results:*** In multiple linear regression analyses, albuminuria was associated with worse modified Stroop Color Word scores (β = 0.284, p = 0.017) and low eGFR was associated with reduced Digit Symbol Substitution scores (β = –0.224, p = 0.026) after adjustment for age, sex, education years, diabetes duration, hypertension, multiple SBIs, and advanced WMLs. In contrast, there were no significant associations between CKD markers and Mini-Mental State Examination or Word Recall scores. ***Conclusion:*** Our findings suggest that albuminuria and low eGFR are associated with frontal lobe dysfunction independently of SVD in elderly type 2 diabetic patients.

Toshitaka Umemura, MD, PhD
Department of Neurology
Chubu Rosai Hospital
1-10-6 Komei, Minato-ku, Nagoya, Aichi 455-8530 (Japan)
E-Mail t.umemura@bg7.so-net.ne.jp

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Introduction

Chronic kidney disease (CKD) is defined as the presence of persistent albuminuria or a decreased estimated glomerular filtration rate (eGFR), which is a widely accepted risk factor for cardiovascular events. In addition to an increased incidence of stroke, CKD is associated with cognitive impairment and dementia. Although an association between CKD and cognitive impairment was reported in several previous studies [1–6], few studies have investigated the association between different CKD markers and cognitive impairment. In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study [7], albuminuria and low eGFR were complementary, but not additive, even though they were independently associated with incident cognitive impairment. Another recent study reported that faster eGFR decline and proteinuria were associated with an increased risk of vascular dementia [8]. A relationship between CKD and cognitive decline has been the focus of recent attention because of similarities in the histopathological appearance of small vessels in the brain and kidney [9–11].

In contrast, several studies have shown that the presence of small vessel disease (SVD) on brain magnetic resonance imaging (MRI), including silent brain infarcts (SBIs) and white matter lesions (WMLs), was associated with cognitive impairment [12–15]. SVD has been established as an important brain MRI marker for evaluating cognitive impairment. However, it is still poorly understood how SVD influences the relationship between CKD and cognitive impairment. In addition, several studies have shown that diabetes mellitus increases the risk of cognitive decline [16–18]. In the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) subanalysis [19], albuminuria and increased levels of cystatin C were associated with poor performance on a test of processing speed in patients with type 2 diabetes. For preventing future dementia in diabetic patients, it is important to elucidate the mechanism of the relationship between renal dysfunction and cognitive impairment. We sought to clarify whether CKD markers are associated with cognitive impairment independently of SVD in elderly patients with type 2 diabetes. This study examines vascular determinants of cognitive impairment in patients with type 2 diabetes but not in the general population.

Methods

Study Population

We reviewed our dementia study database for outpatients who visited the Diabetic Center of the Chubu Rosai Hospital between May 2006 and March 2009 and identified 90 type 2 diabetic patients aged >65 years. Before cognitive assessment in 2009, all patients underwent an MRI examination. Patients with a prior history of stroke or transient ischemic attack, severe renal dysfunction (creatinine value of ≥2.0 mg/dl) or on dialysis, severe retinopathy, atrial fibrillation, and probable Alzheimer's disease were excluded from the present study. Between registration and cognitive testing, 2 patients died of cancer and hemorrhagic stroke, and 7 patients were excluded due to refusal to conduct cognitive tests or no response to recontact. Neuropsychological tests were performed using four validated cognitive instruments in 2009. Mean interval between brain MRI and cognitive testing was 3.5 ± 3.0 months. Two patients with severe cognitive impairment [a Mini-Mental State Examination (MMSE) [20] score of <19 points] at baseline were also excluded. Finally, 79 patients (30 men and 49 women with a mean age of 76.0 ± 6.1 years) with type 2 diabetes were enrolled in the present study. Informed consent was obtained from all participants, and the study protocol was approved by the Ethics Committee of the Chubu Rosai Hospital. In addition, this study was conducted in accordance with the principles of the Declaration of Helsinki.

Assessment of Cardiovascular Risk Factors

Diabetes mellitus was defined as a fasting serum glucose level of ≥126 mg/dl, hemoglobin (Hb) A1c levels of ≥6.5%, or the use of antidiabetic drugs. HbA1c was measured using high-performance liquid chromatography (HLC-723G7; Tosoh, Tokyo, Japan). HbA1c (%) was estimated as the National Glycohemoglobin Standardization Program (NGSP) value (%) calculated by the formula HbA1c (%) = HbA1c (Japan Diabetes Society, JDS) (%) × 1.02 + 0.25 [21]. Hypertension was defined as a blood pressure of >140/90 mm Hg at three different time points or taking antihypertensive drugs (calcium channel blockers, angiotensin receptor blockers, and angiotensin-converting enzyme inhibitors). Dyslipidemia was defined as a fasting serum low-density lipoprotein cholesterol level of ≥140 mg/dl, a fasting serum triglyceride level of ≥150 mg/dl, a fasting serum high-density lipoprotein cholesterol level of <40 mg/dl, or the use of oral lipid-lowering drugs. Antithrombotic drugs were administered if the patients had ischemic heart disease, peripheral artery disease, or multiple plaques on carotid ultrasonography.

Measurement of eGFR and Albuminuria

Each patient's eGFR was calculated using the following three-variable Japanese equation: eGFR (ml/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ × 0.739 (if female) [22]. Decreased eGFR was defined as <60 ml/min/1.73 m^2. Albuminuria was determined from urinary albumin-to-creatinine ratios (UACRs) obtained from a first morning urine specimen. UACR was calculated from urinary albumin, which was estimated using the latex agglutination method and urinary creatinine concentration. Albuminuria was classified into one of the following three categories: normoalbuminuria: <30 mg/g of creatinine, microalbuminuria: 30–299 mg/g of creatinine, and macroalbuminuria: ≥300 mg/g of creatinine. CKD was defined as the presence of albuminuria (UACR of ≥30 mg/g of creatinine) and/or a decreased eGFR (<60 ml/min/1.73 m^2).

Magnetic Resonance Imaging

MRI was performed on a Signa Horizon 1.5-tesla system (GE Healthcare, Milwaukee, Wisc., USA). The imaging protocol consisted of T1-weighted spin echo [inversion recovery; repetition time/echo time (TR/TE) = 2,380/27.4 ms], T2-weighted fast spin echo (TR/TE = 4,017/103 ms), and fluid-attenuated inversion-recovery (FLAIR) (TR/TE = 8,002/146 ms) sequences in the axial plane with a slice thickness of 5 mm and a 2-mm interslice gap. We defined SBIs as focal hyperintense areas that were >3 mm in diameter on T2-weighted images, hypointense areas on T1-weighted images, and areas of hypointensity surrounded by a hyperintense rim on FLAIR images. Lesions of <3 mm in diameter or with a signal intensity similar to that of cerebrospinal fluid on FLAIR images were excluded because of the high possibility of enlarged perivascular spaces, even if hyperintensities on T2-weighted images and hypointensities on T1-weighted images were detected. The numbers of SBIs were divided into three categories: no SBIs, 1–3 SBIs, and >3 SBIs. Multiple SBIs were defined as >3 SBIs. The severity of WMLs was graded separately for periventricular and subcortical areas. Periventricular WMLs were classified as grades 1–3 as follows: grade 1 (mild), pencil-thin lining; grade 2 (moderate), smooth halo, and grade 3 (severe), large confluence. Subcortical WMLs were classified according to the following three grades in accordance with the Fazekas scale: grade 1 (mild), punctuate foci; grade 2 (moderate), early confluence, and grade 3 (severe), diffuse confluence [23, 24]. A grade of ≥2 was regarded as advanced periventricular or subcortical WMLs. A trained neurologist and a trained radiologist who were blinded to the patients' laboratory and clinical information assessed the presence of SBIs and WMLs. Each value of interrater reliability for the MRI findings, expressed as Cohen's κ, was within the range of 0.67–0.84.

Assessment of Cognitive Function

To determine global cognitive functioning, MMSE [20] was administered to all patients. Moreover, we selected the following standardized neuropsychological tests measuring cognitive function, as previously described [25, 26]. We administered the Word Recall test, a subtest of the Alzheimer's Disease Assessment Scale, with a score ranging from 0 to 10 to assess verbal memory [27]. Complex psychomotor skills were evaluated by the Digit Symbol Substitution (DSS) test, a subtest of the Wechsler Adult Intelligence Scale-Revised, with a score ranging from 0 to 93 [28]. We used the modified Stroop Color Word (mStroop) test to assess attention and executive function, in which the seconds to completion are recorded and the difference between the time required to read the word card and that required to read the dot card is calculated [29]. The DSS and mStroop tests were generally attributed to frontal lobe function, including processing speed, attention, and executive function. For each participant, we calculated the z scores (individual test score minus mean test score divided by the standard deviation) for the neuropsychological tests, except for MMSE. All tests were performed by a well-trained psychological tester.

Statistical Analysis

Each of the two kidney markers was treated as a dichotomized variable. Statistical analysis was performed using unpaired t tests or Mann-Whitney U tests to compare continuous variables, and the χ^2 test or Fisher exact test was used to assess categorical variables. Since the levels of UACR and immunoreactive insulin were not normally distributed, differences were tested by nonparametric statistical procedures (Mann-Whitney U test) and the results were shown as medians (interquartile range, 25–75%). We also examined a possible association between CKD markers and cognitive testing scores by analysis of covariance, which was adjusted for age, sex, education years, and diabetes duration. To determine whether CKD markers are associated with cognitive impairments independently of SVD in the type 2 diabetic population, we used multiple linear regression analyses with age, sex, education years, diabetes duration, hypertension, and MRI markers of cerebral SVD as covariates. All tests were two-tailed, and a p value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS 11.0 software (SPSS Inc., Chicago, Ill., USA).

Results

Characteristics of the Study Population Stratified by CKD Markers

The characteristics of the study population according to eGFR and UACR levels are summarized in table 1. Patients with a low eGFR (<60 ml/min/1.73 m^2) compared to those without a low eGFR were more likely to be older, have less education years, and a longer diabetes duration. Patients with albuminuria (UACR of ≥30 mg/g of creatinine) compared to those without albuminuria were more likely to be older and have a longer diabetes duration, and they were more likely to use antithrombotic drugs. CKD was observed in 43 (54.4%) diabetic patients. Of the 79 patients, 49 (62.0%) used oral hypoglycemic agents and 14 (17.7%) were being treated with insulin.

Prevalence of Cerebral SVD according to eGFR and UACR Levels

The prevalence of cerebral SVD according to eGFR and UACR levels is shown in table 2. SBIs were observed in 50 (63.3%) patients and 20 (25.3%) patients had multiple SBIs. Periventricular and subcortical WMLs were observed in 56 (70.9%) patients and advanced WMLs were observed in 25 (31.6%) patients. Patients with albuminuria had a higher prevalence of SBIs and advanced WMLs than those without albuminuria. There were no significant differ-

Table 1. Characteristics of the study population stratified by eGFR and UACR levels

	Diabetic patients (n = 79)					
	eGFR (ml/min/1.73 m^2)			UACR (mg/g of creatinine)		
	≥60 (n = 54)	<60 (n = 25)	p value	<30 (n = 50)	≥30 (n = 29)	p value
Age, years	74.6±5.3	79.0±6.7	0.002	74.6±5.7	78.4±6.0	0.007
Men	20 (37.0)	10 (40.0)	0.800	15 (30.0)	15 (51.7)	0.074
Education, years	9.6±1.9	8.7±2.1	0.049	9.6±2.0	8.9±2.1	0.113
Diabetes duration, years	16.0±7.3	20.0±9.9	0.046	15.7±7.8	20.1±8.8	0.023
Hypertension	36 (66.7)	18 (72.0)	0.636	32 (64.0)	22 (75.9)	0.388
Hyperlipidemia	36 (66.7)	14 (56.0)	0.360	32 (64.0)	18 (62.1)	0.864
Systolic blood pressure, mm Hg	138±19	144±19	0.193	138±17	144±21	0.143
Diastolic blood pressure, mm Hg	78±9	76±8	0.376	77±9	77±10	0.958
Fasting blood glucose, mg/dl	132±35	123±25	0.250	129±28	130±39	0.978
HbA1c, %	6.7±0.7	6.5±0.9	0.254	6.6±0.6	6.8±0.9	0.266
Immunoreactive insulin, μU/ml	5.1 (4.1–6.5)	8.0 (3.3–10.0)	0.147	5.6 (4.1–8.5)	5.3 (3.7–9.1)	0.910
Serum creatinine, mg/dl	0.7±0.1	1.2±0.8	<0.0001	0.7±0.2	1.0±0.8	0.010
eGFR, ml/min/1.73 m^2	73.5±13.5	44.4±11.7	<0.0001	67.8±16.0	58.2±21.8	0.029
UACR, mg/g of creatinine	23 (14–36)	32 (18–135)	0.061	18 (13–23)	73 (45–413)	<0.0001
Insulin	8 (14.8)	6 (24.0)	0.320	7 (14.0)	7 (24.1)	0.255
Oral hypoglycemic agents	34 (63.0)	15 (60.0)	0.801	32 (64.0)	17 (58.6)	0.635
Calcium channel blockers	21 (29.6)	12 (48.0)	0.445	18 (36.0)	15 (51.7)	0.172
Angiotensin receptor blockers	16 (29.6)	12 (48.0)	0.112	16 (32.0)	12 (41.4)	0.401
Angiotensin-converting enzyme inhibitors	8 (14.8)	5 (20.0)	0.745[a]	8 (16.0)	5 (17.2)	0.326[a]
Antithrombotic drugs	6 (11.1)	8 (32.0)	0.053[a]	5 (10.0)	9 (31.0)	0.030[a]
Lipid-lowering drugs	18 (33.3)	12 (48.0)	0.212	16 (32.0)	14 (48.3)	0.151

Values are expressed as means ± SD, medians (interquartile range, 25–75%), or as n (%). Comparisons of the two groups were evaluated by the unpaired t test or Mann-Whitney U test. The χ^2 test for independence was used where appropriate. [a] The Fisher exact test was used.

ences in the prevalence of multiple SBIs when patients were divided into the two groups according to eGFR and UACR levels.

Comparison of Differences in Cognitive Function Scores according to eGFR or UACR Levels

Raw scores of the cognitive testing according to eGFR or UACR levels are shown in table 3. Patients with a low eGFR had worse DSS scores compared to those without a low eGFR. Patients with albuminuria had worse mStroop scores compared to those without albuminuria. Figure 1 compares differences in cognitive testing scores in four groups stratified by eGFR and UACR levels. Raw scores were standardized into z scores per domain, except for MMSE. After adjustment for age, sex, education years, and diabetes duration, patients with albuminuria but without a low eGFR had significantly worse mStroop scores compared to those without a low eGFR and albuminuria [0.55 ± 0.38 vs. –0.34 ± 0.10 (values are given as mean ± SE), p = 0.032]. Cognitive testing scores were also evaluated by the presence or absence of multiple SBIs or advanced WMLs. After adjustment for age, sex, education years, and diabetes duration, patients with multiple SBIs had significantly worse mStroop scores compared to those without multiple SBIs (0.62 ± 0.27 vs. –0.15 ± 0.12, p = 0.025). Patients with advanced WMLs had significantly worse DSS scores compared to those without advanced WMLs (DSS; –0.72 ± 0.20 vs. 0.31 ± 0.12, p = 0.044). However, there were no significant differences in MMSE and Word Recall scores between patients with and without multiple SBIs or advanced WMLs (data not shown).

Table 2. Prevalence of cerebral SVD according to eGFR and UACR levels

Brain MRI findings	Diabetic patients (n = 79)					
	eGFR (ml/min/1.73 m^2)			UACR (mg/g of creatinine)		
	≥60 (n = 54)	<60 (n = 25)	p value	<30 (n = 50)	≥30 (n = 29)	p value
SBIs	31 (57.4)	19 (76.0)	0.111	26 (52.0)	24 (82.8)	0.006
Multiple SBIs	11 (20.4)	9 (36.0)	0.137	11 (22.0)	9 (31.0)	0.373
WMLs	35 (64.8)	21 (84.0)	0.081	32 (64.0)	24 (82.8)	0.077
Advanced WMLs	14 (25.9)	11 (44.0)	0.108	11 (22.0)	14 (48.3)	0.016

Values are expressed as n (%). The χ^2 test for independence was used where appropriate.

Table 3. Cognitive function according to eGFR and UACR levels

	Diabetic patients (n = 79)					
	eGFR (ml/min/1.73 m^2)			UACR (mg/g of creatinine)		
	≥60 (n = 54)	<60 (n = 25)	p value	<30 (n = 50)	≥30 (n = 29)	p value
Global cognitive function						
MMSE	26 (22–28)	23 (20–25)	0.166	26 (23–28)	23 (20–27)	0.196
Neuropsychological tests						
Word Recall	7 (5–8)	5 (4–8)	0.345	7 (6–8)	5 (4–6)	0.069
DSS	33 (29–41)	29 (20–32)	0.004	34 (28–42)	30 (24–34)	0.266
mStroop	20 (16–25)	22 (19–28)	0.647	19 (16–24)	24 (17–30)	0.048

Raw scores are expressed as medians (interquartile range, 25–75%). Comparisons of the two groups were evaluated by the Mann-Whitney U test. A higher score indicates worse performance on the mStroop test. p values are shown after adjustment for age by analysis of covariance.

Association of CKD Markers and Cerebral SVD with Cognitive Domains

Multiple linear regression analysis was used to examine the association of CKD markers and cerebral SVD with four cognitive domains. Albuminuria was associated with worse mStroop scores (β = 0.284, 95% CI 0.10–1.04, p = 0.017) and low eGFR with reduced DSS scores (β = –0.224, 95% CI –0.90 to –0.06, p = 0.026) after controlling for age, sex, education years, diabetes duration, hypertension, multiple SBIs, and advanced WMLs. No significant associations between CKD markers and MMSE or Word Recall scores were found in the multiple linear regression models. In addition, multiple SBIs were associated with worse DSS (β = –0.314, 95% CI –1.24 to –0.30, p = 0.002) and mStroop scores (β = 0.349, 95% CI 0.33–1.39, p = 0.002) after controlling for age, sex, education years, diabetes duration, hypertension, low eGFR, and albuminuria. Furthermore, advanced WMLs were associated with worse DSS (β = –0.373, 95% CI –1.22 to –0.40, p < 0.001), mStroop (β = 0.292, 95% CI 0.14–1.11, p = 0.012), and MMSE scores (β = –0.259, 95% CI –1.01 to –0.10, p = 0.020) after controlling for age, sex, education years, diabetes duration, hypertension, low eGFR, and albuminuria (table 4).

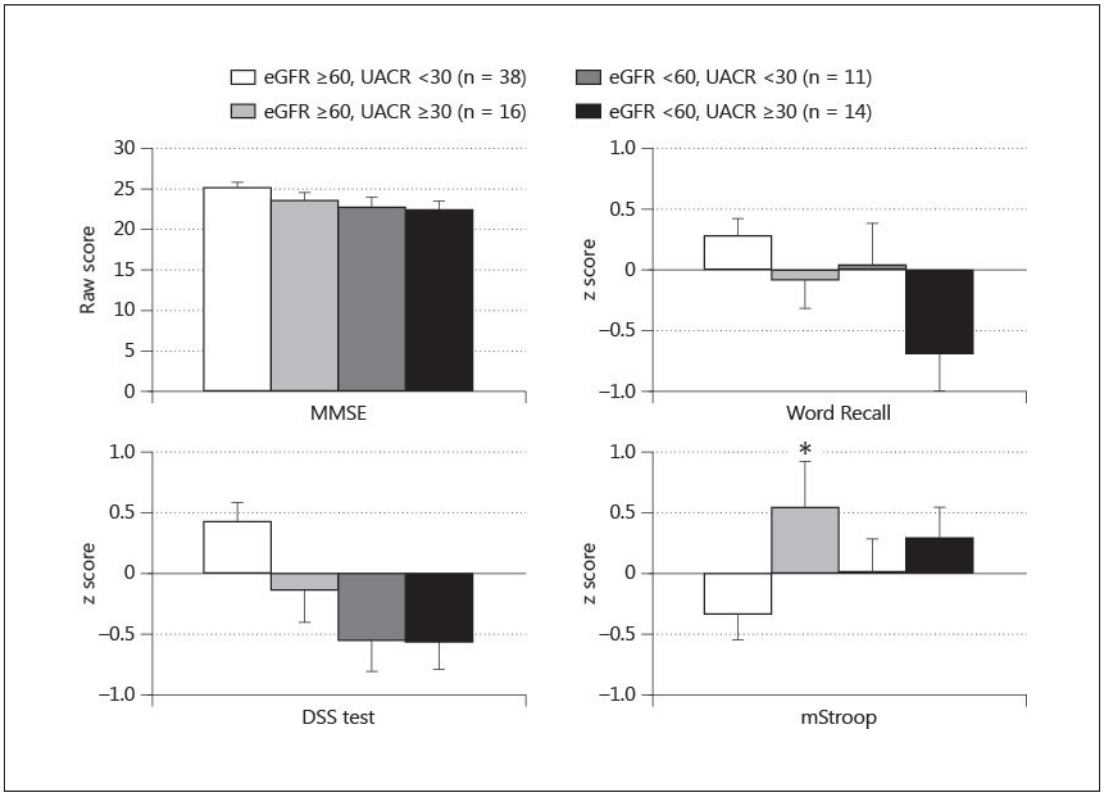

Fig. 1. Comparison of differences in cognitive performance scores according to eGFR or UACR levels. Raw scores were standardized into z scores per domain, except for MMSE. Values are expressed as means ± SE. Bar charts represent comparison of differences in cognitive testing scores between the occurrence of low eGFR and albuminuria. The comparison of the four groups was conducted after adjustment for age, sex, education years, and diabetes duration. A higher score indicates worse performance on the mStroop test. * $p < 0.05$ vs. eGFR ≥60 ml/min/1.73 m^2 and UACR <30 mg/g of creatinine.

Discussion

This cross-sectional hospital-based study showed that albuminuria and low eGFR were associated with frontal lobe dysfunction independently of SVD in elderly patients with type 2 diabetes. Our findings provide new insights into the cognitive interaction between brain and kidney.

In recent years, the association between CKD and cognitive impairment has received much attention, and there is greater research targeting individual CKD markers. Moreover, there have been some studies analyzing the association between a decreased eGFR and cognitive impairment [1, 3, 4, 6] as well as the association between albuminuria and cognitive decline [2, 5, 30–32]. However, there have been only few studies examining the association between different CKD markers and cognitive impairment, and results from studies that have been indicated are conflicting [7, 8]. Additionally, it has been noted that methodological differences between studies, such as patient selection, study design, and cognitive screening instruments, can affect the results. Furthermore, albuminuria is considered a better early CKD marker than low eGFR, and the importance of evaluating microalbuminuria has been emphasized because it reflects vascular endothelium dysfunction. This is supported by the results of a meta-analysis concerning cardiovascular events [33]. Therefore, it is very likely

Table 4. Association of CKD markers and cerebral SVD with different cognitive domains

Independent variables		MMSE β (95% CI)	Word Recall β (95% CI)	DSS test β (95% CI)	mStroop β (95% CI)
Low eGFR	model 1	−0.180 (−0.88 to 0.12)	−0.126 (−0.76 to 0.23)	−0.233 (−0.97 to −0.03)*	0.034 (−0.46 to 0.60)
	model 2	−0.165 (−0.82 to 0.12)	−0.119 (−0.75 to 0.24)	−0.224 (−0.90 to −0.06)*	0.026 (−0.45 to 0.56)
Albuminuria	model 1	−0.098 (−0.66 to 0.27)	−0.208 (−0.87 to 0.03)	−0.156 (−0.75 to 0.13)	0.271 (0.07 to 1.02)*
	model 2	−0.034 (−0.52 to 0.39)	−0.223 (−0.91 to 0.01)	−0.108 (−0.63 to 0.20)	0.284 (0.10 to 1.04)*
Multiple SBIs	model 1	−0.092 (−0.78 to 0.32)	−0.173 (−0.96 to 0.11)	−0.268 (−1.16 to −0.16)*	0.294 (0.18 to 1.27)*
	model 2	−0.123 (−0.83 to 0.23)	−0.211 (−1.05 to 0.01)	−0.314 (−1.24 to −0.30)**	0.349 (0.33 to 1.39)**
Advanced WMLs	model 1	−0.287 (−1.08 to −0.14)*	−0.204 (−0.91 to 0.04)	−0.401 (−1.29 to −0.45)***	0.325 (0.22 to 1.18)**
	model 2	−0.259 (−1.01 to −0.10)*	−0.175 (−0.85 to 0.10)	−0.373 (−1.22 to −0.40)***	0.292 (0.14 to 1.11)*

Multiple linear regression analysis with cognitive domains as dependent variables was used. Model 1 was adjusted for age, sex, education years, and diabetes duration. Model 2 was additionally adjusted for hypertension, low eGFR (<60 ml/min/1.73 m^2), albuminuria (UACR of ≥30), multiple SBIs (>3), and advanced WMLs (grade 2 or 3). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

that changes in the incidence of microalbuminuria observed in diabetic patients are more important than slight decreases in eGFR from the perspective of long-term prognosis (not just concerning cardiovascular events but also cognitive impairment).

An association between cognitive decline and SVD, including SBIs and WMLs, has been indicated in several studies [12–15]. In this regard, the Rotterdam Scan Study found an association between SBI and decline in psychomotor speed as well as between WML severity and subsequent cognitive decline [12, 15]. Furthermore, a cross-sectional study of a population without a history of stroke or cognitive impairment noted an association between albuminuria and increased WML volume or deterioration in executive function [31]. Another cross-sectional study on a general population reported an association between decreased eGFR and frontal lobe dysfunction independently of subclinical lacunar infarction [6]. Although their subjects were different, the findings of these studies are consistent with the present study in demonstrating that CKD markers are associated with frontal lobe dysfunction. Several studies have also revealed an association between albuminuria and decreased eGFR and SVD [34–36]. Interestingly, similar microvessel structures in the kidney and brain may be linked to the pathogenesis between CKD and SVD.

The Leukoaraiosis and Disability Study (LADIS) showed that diabetes was associated with WML prevalence and progression as well as cognitive decline [17]. A cross-sectional study of type 2 diabetics reported an association between WMLs and frontal lobe dysfunction [37, 38]. Additionally, we have previously reported an association between SVD progression and frontal lobe dysfunction in type 2 diabetic patients [25]. Furthermore, an autopsy study demonstrated that diabetic individuals with dementia had more microvascular infarcts and activation of neuroinflammation as compared to those without dementia [39]. In diabetic patients, increased oxidative stress and advanced glycation end-product may promote progression of endothelial dysfunction, raising the possibility that vascular factors are major contributors of incident dementia [40]. In this regard, levels of soluble intercellular adhesion molecule-1, a marker of endothelial dysfunction, were associated with SVD progression and subsequent decline in psychomotor speed in a 6-year longitudinal study of type 2 diabetes [26]. Another prospective study reported that higher soluble intercellular adhesion molecule-1 levels were strongly associated with increasing urinary albumin excretion or development of new microalbuminuria [41]. Therefore, prospective studies should attempt to determine whether CKD and cognitive decline are associated with vascular endothelial and inflammatory markers.

Several limitations of the present study should be addressed. First, cognitive function evaluation was based on a cross-sectional analysis, which precludes the assessment of causality. Regarding this point, a prospective study of the same subjects is currently ongoing. Second, patients with probable Alzheimer's disease were excluded from the study population, but we did not specifically evaluate the presence of medial temporal lobe atrophy using detailed brain imaging. Third, we were unable to evaluate the association of CKD markers and brain MRI findings with neuropsychological tests in nondiabetic subjects because of the small sample size. Finally, the present study only enrolled outpatients from a single center; therefore, a large-scale prospective study will be necessary to confirm the present results.

In summary, our findings suggest that albuminuria and decreased eGFR are associated with frontal lobe dysfunction independently of SVD in elderly patients with type 2 diabetes. The former is linked with attention and executive function deficit and the latter with decline in psychomotor speed. It is possible that different CKD markers are involved in the pathogenesis of the brain-kidney connection for cognitive function. Therefore, prospective interventional research is needed to determine whether improvement of CKD marker can prevent cognitive decline in elderly individuals with type 2 diabetes.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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