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Investigation of Possible Correlation Between Retinal Neurovascular Biomarkers and Early Cognitive Impairment in Patients With Chronic Kidney Disease

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Purpose: To investigate the association between retinal neurovascular biomarkers and early cognitive impairment among patients with chronic kidney disease (CKD).

Methods: Patients with CKD stage ≥3 were evaluated using the standardized Mini-Mental State Examination (MMSE). Patients were classified as having a low (<24), middle (24 to 27), and high (>27) MMSE level. Retinal nerve fiber layer thickness, ganglion cell complex (GCC) thickness, GCC global loss volume, and GCC focal loss volume were measured using optical coherence tomography (OCT). Superficial vascular plexus vessel density, deep vascular plexus vessel density (DVP-VD), and size of the foveal avascular zone were obtained by OCT angiography.

Results: The study enrolled 177 patients with a mean ± SD age of 64.7 ± 6.6 years. The mean ± SD MMSE score was 27.25 ± 2.30. Thirteen, 65, and 99 patients were classified as having a low, middle, and high MMSE level, respectively. The patients with a high MMSE level were younger, had more years of education, had less severe CKD, and had higher DVP-VD than patients with a low MMSE level. The multivariable regression revealed that age (coefficient, 0.294; 95% confidence interval [CI], 0.195–0.393; $P = 0.041$), years of education (coefficient, 0.294; 95% CI, 0.195–0.393; $P < 0.001$), estimated glomerular filtration rate (coefficient, 0.019; 95% CI, 0.004–0.035; $P = 0.016$), and DVP-VD (coefficient, 0.109; 95% CI, 0.007–0.212; $P = 0.037$) were independent factors associated with MMSE score.

Conclusions: Retinal DVP-VD was associated with early cognitive impairment among patients with CKD.

Translational Relevance: DVP-VD measured by OCT angiography may facilitate early detection of cognitive impairment.

Introduction

Dementia continues to be a prevalent disease worldwide. Although the age-specific incidence has fallen because of improvements in education, nutrition, and health care, the number of people living with dementia is still increasing due to increased life expectancy and population aging.[1,2] Some patients may experience mild cognitive impairment (MCI), which is characterized by objective impairment in cognitive function that is not sufficiently severe to require help with usual daily living activities.[3] Annually, the conditions of approximately 8% to 15% of these patients may

progress to dementia,[4] but 16% to 30% of patients could revert to normal function.[5,6] Coping with modifiable risk factors could prevent or delay dementia in approximately 40% of patients.[1,2] Therefore, identifying patients in the early stage of cognitive impairment is important for the prevention of devastating outcomes.[1,5,6]

Retinal neurovascular biomarkers measured through optical coherence tomography (OCT) and OCT angiography (OCTA) have recently been associated with both Alzheimer disease (AD) and MCI.[7–16] Considering the fact that expensive and invasive tests (e.g., magnetic resonance imaging, positron emission tomography, cerebrospinal fluid study) are usually required for the diagnoses of AD, it would be useful if retinal biomarkers obtained through noninvasive and rapid modalities could be used for early detection or for monitoring progression in these patients.[3,17] However, an important unsolved question is how systemic comorbidities may influence the validity of these retinal biomarkers. Systemic comorbidities such as diabetes mellitus (DM), hypertension, and chronic kidney disease (CKD) are common among the aged population.[18,19] However, major systemic comorbidities have been excluded in most relevant studies.[8–12] These diseases could have significant impacts on the metrics of retinal biomarkers even before clinically detectable retinopathy occurs.[20,21] Those retinal biomarkers require validation under different systemic comorbidities to generalize the aforementioned findings to a wider population.

CKD is a highly prevalent systemic disease among the aged population and could affect 44% of adults aged ≥65 years.[18] It could be a common systemic disease among patients attending ophthalmologic clinics. Patients with CKD had a substantially increased risk of cognitive impairment.[22,23] The prevalence of MCI among patients with CKD ranges from 27% to 62%.[23] The incidence of dementia was much higher among individuals with end-stage renal disease (ESRD) than those without (10.73 vs. 1.40 cases per 1000 years).[24] It would be promising if ophthalmic diagnostic tools could help to identify susceptible patients at early stages of cognitive impairment. The purpose of this study was to evaluate the association between retinal neurovascular biomarkers and cognitive function among patients with CKD.

Methods

A prospective cross-sectional study was conducted between August 2018 and July 2019 at the Department of Nephrology and the Department of Ophthalmology of our hospital. This study was approved by the Chang Gung Memorial Hospital Institutional Review Board and followed the tenets of the Declaration of Helsinki.

CKD was diagnosed by a nephrologist on the basis of the presence of kidney structural or functional abnormalities for >3 months and an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2. CKD was classified into stage 3 (eGFR, 30–59 mL/min/1.73 m^2), stage 4 (eGFR, 15–29 mL/min/1.73 m^2), stage 5 (eGFR <15 mL/min/1.73 m^2), and ESRD (undergoing hemodialysis or peritoneal dialysis).

The inclusion criteria for patients in this study were (1) regular follow-up at our nephrology department for >1 year, (2) CKD stage ≥3 (including ESRD), (3) age ≥50 years, and (4) no visual symptoms. The exclusion criteria were (1) a prior diagnosis of AD, vascular dementia, depression, or other psychological disorders; (2) education level below elementary school; (3) significant ocular media opacity; (4) inadequate quality of OCT (signal strength index, <40) or OCTA (quality score <6 or presence of significant artifacts); (5) axial length of <22 mm or ≥26 mm; or (6) a prior diagnosis of glaucoma, optic nerve disease, or a major retinal disease such as diabetic retinopathy, retinal vein occlusion, macular pucker, or neovascular age-related macular degeneration.

Demographic data and information on medical histories, medications, and years of education were collected using a standardized questionnaire. All patients underwent unattended automated office blood pressure measurement after resting for 15 minutes in a blood pressure suite. A standardized Chinese version of the Mini-Mental State Examination (MMSE) was administered by a single experienced evaluator. The MMSE covers the cognitive domains of registration, orientation, recall, attention, calculation, naming, repetition, comprehension, writing, and construction. The maximum score is 30. Patients were classified in the low, middle, or high MMSE level if they had MMSE scores of <24, 24 to 27, or >27, respectively.

A complete ocular examination was performed on the date of enrollment. Intraocular pressure was measured using a noncontact tonometer (NT-3000; Nidek, Tokyo, Japan). Axial length was measured using an IOL Master (Carl Zeiss Meditec, Jena, Germany). OCT and OCTA images were acquired using AngioVue (Optovue RTVue XR Avanti; Optovue, Inc., Fremont, CA, USA). If both eyes were eligible for this study, the eye with the better OCTA image quality would be chosen.

The retinal neurovascular biomarkers evaluated in this study included retinal nerve fiber layer

thickness (RNFLt, in μm), ganglion cell complex (GCC) thickness (GCCt, in μm), GCC global loss volume (GLV, percentage), GCC focal loss volume (FLV, percentage), parafoveal superficial vascular plexus (SVP) vessel density (VD, percentage), parafoveal deep vascular plexus (DVP) VD (percentage), and size of foveal avascular zone (FAZ, in mm^2). All of the values were automatically calculated by the machine software (AngioVue version A2017.1.0.151; Optovue, Inc.).

The RNFLt was measured over a 3.45-mm-diameter circle around the optic nerve head. A GCC scan measured a 7-mm^2 region centered on a point 1 mm temporal to the fovea. A 304-pixel × 304-pixel OCTA image of each eye was acquired over an area of 3 × 3 mm^2 centered on the fovea. FAZ was measured in the full inner retinal layer OCTA image. The default of the SVP includes the vasculature between the internal limiting membrane and 10 μm above the inner plexiform layer. The default of the DVP includes the vasculature between 10 μm above the inner plexiform layer and 10 μm below the outer plexiform layer. VD was defined as the percentage area occupied by all vascular components within the region of interest. The parafoveal region was defined as a 1-mm-wide circular annulus centered on the fovea.

The demographic data and clinical characteristics between low- and high-level MMSE groups were compared using the χ^2 test for categorical variables and the independent sample *t*-test for continuous variables. Simple linear regression models were used to evaluate the association of retinal neurovascular biomarkers and systemic variables with MMSE score after adjustment for years of education. Then, 4 major retinal neurovascular biomarkers (RNFLt, GCCt, SVP-VD, and DVP-VD) and 7 systemic variables (age, sex, eGFR, DM, hypertension, dyslipidemia, and years of education) were entered into a multivariable linear regression model to determine whether these factors were associated with MMSE score. Partial correlation was used to determine whether blood pressure parameters were correlated with MMSE score (after adjustment for age, sex, eGFR, DM, and years of education) and retinal microvascular biomarkers (after adjusting for age, gender, eGFR, and DM). All the data were analyzed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). A two-tailed *P* value of <0.05 was considered statistically significant.

Results

This study included 177 patients with CKD. The mean ± SD age of patients was 64.7 ± 6.6 years. The mean ± SD MMSE score was 27.25 ± 2.30. Thirteen (7%), 65 (37%), and 99 (56%) patients were classified in the low-, middle-, and high-level MMSE groups, respectively. Table 1 summarizes patients' demographic data and clinical characteristics. The patients with a high MMSE level were younger ($P = 0.032$), had more years of education ($P < 0.001$), had a less severe CKD stage ($P = 0.027$), had a higher eGFR ($P = 0.003$), and had a higher DVP-VD ($P = 0.036$) than those with a low MMSE level. No significant difference was noted in sex, smoking history, DM, hypertension, dyslipidemia, systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure, intraocular pressure, RNFLt, GCCt, GCC GLV, GCC FLV, SVP-VD, and FAZ size between the high- and low-level MMSE groups.

Table 2 shows the results of the simple and multivariable linear regression models for the association of retinal neurovascular biomarkers and MMSE. Years of education was associated with MMSE score in both simple (coefficient, 0.308; $P < 0.001$) and multivariable linear regression models (coefficient, 0.294; $P < 0.001$). Age (coefficient, −0.052; $P = 0.031$), male sex (coefficient, −0.693; $P = 0.030$), and DVP-VD (coefficient, 0.115; $P = 0.013$) were associated with MMSE score after adjustment for years of education. In the multivariable regression model, age (coefficient, 0.053; $P = 0.041$), eGFR (coefficient, 0.019; $P = 0.016$), and DVP-VD (coefficient, 0.109; $P = 0.037$) were associated with MMSE score. No significant correlations were observed between other neurovascular biomarkers and MMSE scores. The proportion of patients taking different categories of antihypertensive drug is listed in Supplementary Table S1. None was associated with MMSE score. Two representative cases with normal and low MMSE scores are illustrated in Figure 1 and Figure 2, respectively.

Table 3 shows the partial correlation between blood pressure parameters, MMSE score, and retinal microvascular biomarkers. MMSE score was correlated with SBP (coefficient, 0.170; $P = 0.026$) and pulse pressure (coefficient, 0.178; $P = 0.019$). SVP-VD was correlated with SBP and DBP (coefficient, 0.173; $P = 0.023$; coefficient, 0.295; $P < 0.001$, respectively). DVP-VD was also correlated with SBP and DBP (coefficient, 0.176; $P = 0.021$; coefficient, 0.198; $P = 0.009$, respectively).

Discussion

Our results showed that DVP-VD measured with OCTA, age, years of education, and eGFR were

Table 1. Demographic Data and Ocular Characteristics

Characteristic	All Patients ($n = 177$)	MMSE Level			
		Low (Score <24) ($n = 13$)	Middle (Score 24–27) ($n = 65$)	High (Score >27) ($n = 99$)	Low vs. High *P* Value[a]
Age, y	64.7 ± 6.6 (50–80)	67.8 ± 7.4 (54–77)	65.6 ± 6.7 (50–80)	63.7 ± 6.3 (50–80)	**0.032**
Sex, female/male, *n* (%)	73/104 (41/59)	3/10 (23/77)	26/39 (40/60)	44/55 (44/56)	0.142
Years of education	9.9 ± 3.2 (6–18)	6.7 ± 1.3 (6–9)	9.2 ± 3.0 (6–16)	10.7 ± 3.2 (6–18)	**<0.001**
MMSE score	27.25 ± 2.30 (19–30)	21.62 ± 1.33 (19–23)	25.95 ± 1.14 (24–27)	28.85 ± 0.72 (28–30)	**<0.001**
Ever-smoker, *n* (%)	27 (15)	2 (15)	11 (17)	14 (14)	0.904
Diabetes mellitus, *n* (%)	76 (43)	7 (54)	27 (42)	42 (42)	0.435
Hypertension, *n* (%)	149 (84)	12 (92)	52 (80)	85 (86)	0.521
Dyslipidemia, *n* (%)	73 (41)	4 (31)	28 (43)	41 (41)	0.462
CKD stage, *n* (%)					
Stage 3	95 (54)	2 (15)	39 (60)	54 (55)	**0.027**
Stage 4	27 (15)	4 (31)	9 (14)	14 (14)	
Stage 5/ESRD	55 (31)	7 (54)	17 (26)	31 (31)	
eGFR, mL/min/1.73 m^2	30.7 ± 20.7 (3–68)	16.5 ± 14.2 (4–40)	32.6 ± 20.3 (3–68)	31.3 ± 21.1 (3–67)	**0.003**
SBP, mm Hg	131.5 ± 20.6 (75–199)	129.7 ± 18.9 (105–162)	128.6 ± 21.7 (75–181)	133.5 ± 20.0 (98–199)	0.514
DBP, mm Hg	71.8 ± 11.7 (33–109)	68.7 ± 6.7 (61–81)	71.0 ± 12.7 (33–102)	72.8 ± 11.6 (50–109)	0.212
Pulse pressure, mm Hg	59.6 ± 12.7 (33–99)	60.0 ± 17.1 (43–99)	57.6 ± 12.7 (33–87)	60.7 ± 12.0 (38–93)	0.938
Axial length	23.83 ± 0.95 (22.01–25.99)	23.53 ± 0.76 (22.18–24.55)	23.80 ± 0.98 (22.01–25.96)	23.88 ± 0.95 (22.21–25.99)	0.197
IOP, mm Hg	15.0 ± 2.5 (10.0–23.0)	15.9 ± 2.9 (13.0–21.8)	14.9 ± 2.6 (10.0–23.0)	14.9 ± 2.5 (10.2–21.1)	0.222
RNFLt, µm	95.8 ± 10.4 (52–119)	92.5 ± 7.6 (83–106)	94.7 ± 12.2 (58–119)	96.9 ± 9.3 (52–117)	0.107
GCCt, µm	92.4 ± 7.5 (65–114)	89.7 ± 4.9 (84–98)	92.1 ± 7.9 (70–107)	92.9 ± 7.6 (65–114)	0.139
GCC GLV, µm	5.24 ± 5.03 (0.03–29.11)	6.74 ± 3.48 (1.09–11.21)	5.70 ± 5.40 (0.03–24.93)	4.74 ± 4.92 (0.04–29.11)	0.160
GCC FLV, µm	1.63 ± 1.79 (0–10.70)	1.89 ± 1.54 (0.19–4.75)	1.72 ± 1.70 (0.00–7.18)	1.54 ± 1.88 (0.00–10.70)	0.524
SVP-VD, %	46.9 ± 4.4 (26.0–55.1)	45.9 ± 3.4 (38.8–52.8)	46.7 ± 4.0 (33.0–51.9)	47.1 ± 4.8 (26.0–55.1)	0.375
DVP-VD, %	51.6 ± 3.4 (41.7–59.4)	49.8 ± 3.9 (41.7–54.6)	51.5 ± 3.3 (43.2–57.5)	51.9 ± 3.4 (42.0 –59.4)	**0.036**
FAZ size, mm^2	0.335 ± 0.117 (0.113–0.696)	0.313 ± 0.123 (0.126–0.522)	0.328 ± 0.128 (0.113–0.696)	0.343 ± 0.109 (0.117–0.678)	0.354

Data are expressed as mean ± standard deviation (range) unless otherwise indicated. IOP, intraocular pressure.
[a]Comparison between low MMSE level group and high MMSE level group. Bold values indicate $P < 0.05$.

independent factors associated with MMSE score in patients with CKD. The associations between other retinal neurovascular biomarkers (GCC, RNFLt, and SVP-VD) and MMSE score were not significant. MMSE score was partially correlated with SBP and pulse pressure. Additionally, SVP-VD and DVP-VD were partially correlated with SBP and DBP.

Many recent studies showed promising results in associating OCTA parameters with MCI,[7,8] preclinical AD,[10,11] and AD.[7–9,12] The rationale for

Table 2. Linear Regression Models for MMSE Score

Characteristic	Simple Linear Regression Model[a]			Multivariable Linear Regression Model[b]		
	Coefficient	95% CI	*P* Value	Coefficient	95% CI	*P* Value
Years of education	0.308	0.212 to 0.404	**<0.001**	0.294	0.195 to 0.393	**<0.001**
Age	−0.052	−0.099 to 0.005	**0.031**	−0.053	−0.103 to 0.002	**0.041**
Sex (male)	−0.693	−1.319 to 0.067	**0.030**	−0.520	−1.203 to 0.163	0.134
eGFR	0.011	−0.004 to 0.026	0.141	0.019	0.004 to 0.035	**0.016**
Diabetes mellitus	−0.081	−0.709 to 0.547	0.798	−0.249	−0.939 to 0.440	0.477
Hypertension	0.210	−0.641 to 1.06	0.627	0.657	−0.210 to 1.525	0.137
Dyslipidemia	0.142	−0.486 to 0.771	0.656	0.021	−0.610 to 0.653	0.947
RNFLt	0.020	−0.010 to 0.050	0.185	0.011	−0.039 to 0.062	0.659
GCCt	0.027	−0.014 to 0.067	0.202	0.038	−0.035 to 0.111	0.306
SVP-VD	0.022	−0.049 to 0.093	0.538	−0.073	−0.160 to 0.014	0.100
DVP-VD	0.115	0.025 to 0.205	**0.013**	0.109	0.007 to 0.212	**0.037**

CI, confidence interval.
[a]Apart from years of education, the *P* values for all other parameters were calculated using a linear regression model after adjustment for years of education. Bold values indicate $P < 0.05$.
[b]The *P* values were calculated by multivariate linear regression models by entering all of the following variables: years of education, age, sex, eGFR, diabetes mellitus, hypertension, dyslipidemia, RNFLt, GCCt, SVP-VD, and DVP-VD. Bold values indicate $P < 0.05$.

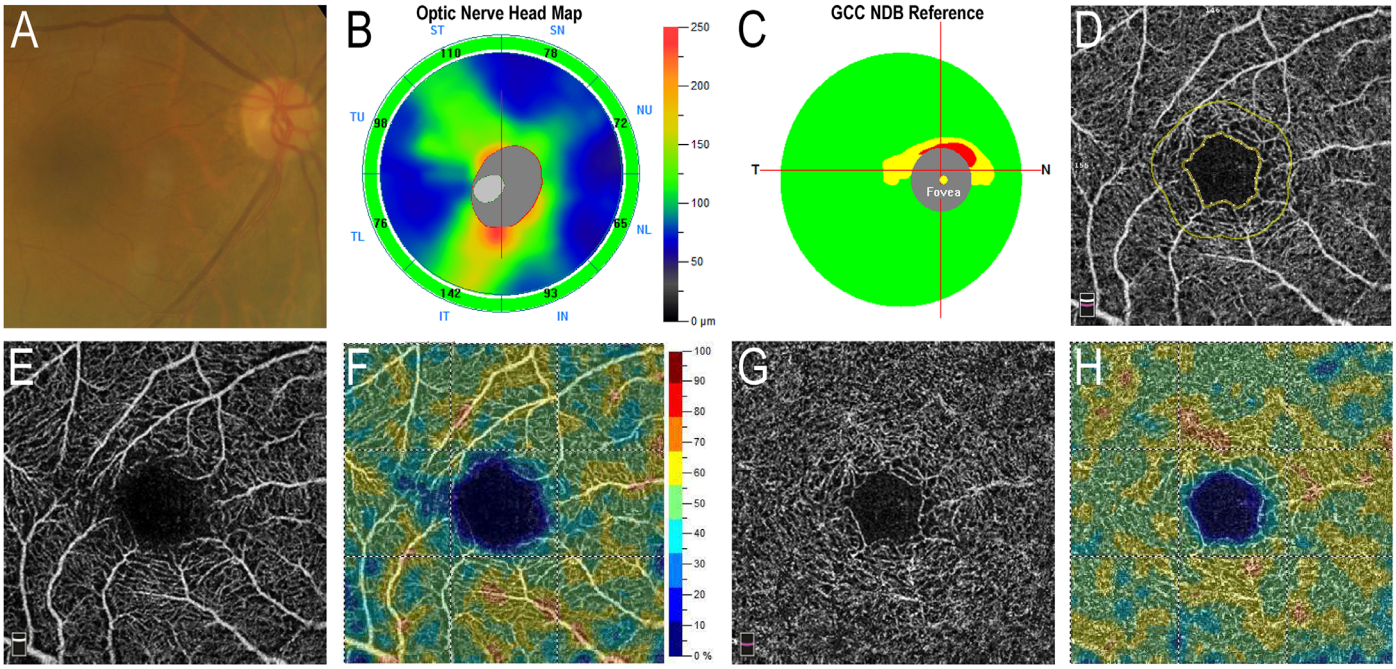

Figure 1. Images of a 70-year-old woman with a high MMSE score (28) and normal DVP-VD. (A) Color fundus photo. (B) Optic nerve head map showing normal retinal nerve fiber layer thickness. (C) Ganglion cell complex layer was generally intact. (D) OCTA of full inner retinal layer showing the foveal avascular zone (*inner yellowish line*). (E) OCTA of SVP. (F) SVP-VD map. (G) OCTA of DVP. (H) DVP-VD map. The size of the foveal avascular zone and the percentage of parafoveal SVP-VD and parafoveal DVP-VD were 0.337 mm^2, 52.3%, and 55.2%, respectively.

using retinal microvascular changes as biomarkers for neurologic diseases is based on the highly similar vasculature of the eye and brain.[25] Retinal microvascular changes might provide insight into brain vessels and thus could be associated with cerebrovascular or neurologic diseases.[17,26]

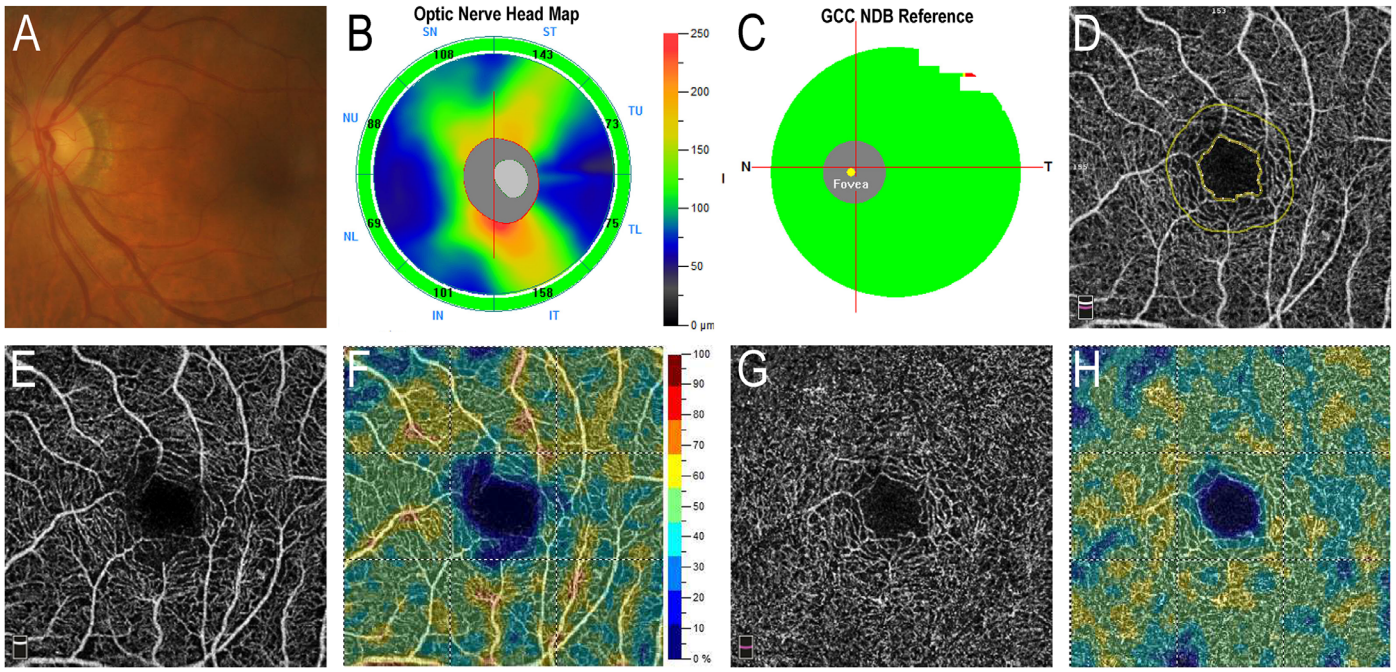

Figure 2. Images of a 69-year-old male patient with low MMSE score (24) and DVP-VD. (A) Color fundus photo. (B) Optic nerve head map showing normal retinal nerve fiber layer thickness. (C) Ganglion cell complex layer was generally intact. (D) OCTA of full inner retinal layer showing the foveal avascular zone (*inner yellowish line*). (E) OCTA of the SVP. (F) SVP-VD map. (G) OCTA of DVP. (H) DVP-VD map. The size of the FAZ and percentage of parafoveal SVP-VD and parafoveal DVP-VD were 0.244 mm^2, 51.9%, and 49.1%, respectively.

Table 3. Partial Correlation between Blood Pressure, MMSE Score, and Retinal Microvascular Biomarkers

	MMSE Score[a]		SVP-VD[b]		DVP-VD[b]	
Characteristic	Coefficient	*P* Value	Coefficient	*P* Value	Coefficient	*P* Value
SBP	0.170	**0.026**	0.173	**0.023**	0.176	**0.021**
DBP	0.107	0.163	0.295	**<0.001**	0.198	**0.009**
Pulse pressure	0.178	**0.019**	0.010	0.900	0.104	0.175

[a]The *P* values were calculated by partial correlation after control for age, sex, eGFR, diabetes mellitus, and years of education. Bold values indicate $P < 0.05$.

[b]The *P* values were calculated by partial correlation after control for age, sex, eGFR, and diabetes mellitus. Bold values indicate $P < 0.05$.

Researchers have suggested that chronic cerebral hypoperfusion could be part of the pathogenesis of AD and that disrupted cerebral blood flow can serve as a biomarker for predicting the conversion of MCI to AD.[27] In patients with CKD, cerebrovascular diseases could be a major cause of cognitive impairment.[22] Aortic stiffness may determine cognitive function in CKD and ESRD.[28] Intradialytic cerebral blood flow reduction is also correlated with cognitive dysfunction.[29] Our study also revealed that SBP and pulse pressure were correlated with MMSE score. SVP-VD and DVP-VD were also correlated with SBP and DBP. With consideration of all this evidence, it is possible that the low DVP-VD observed in our study might represent compromised cerebral perfusion and might increase the risk of early cognitive impairment.

However, controversy remains regarding which retinal layer(s) would have the highest correlation with early cognitive impairment.[7,8] Chua et al.[7] found a reduced VD in SVP but not in DVP among patients with MCI. On the contrary, Wu et al.[8] found a reduced VD in DVP but not in SVP in patients with MCI. The discrepancy between these studies could result from the continuum of cognitive decline, or it may reflect that patients with different characteristics or severities may have been enrolled on the basis of different inclusion criteria. The results could also be influenced by different defaults for retinal layer segmentation in different OCTA machines.

Our results showed that DVP-VD was significantly associated with MMSE score in patients with CKD. A trend of progressively increasing SVP-VD from low- to high-level MMSE groups was observed, but results of a related statistical analysis were nonsignificant. The exact mechanism is still unclear. In vivo study showed that the SVP and DVP may each have different feeder vessels, anatomic structures, and autoregulation.[30] Therefore, they would respond differently to systemic physiologic[31,32] and pathologic changes.[21,33–35] It has been speculated that the vessels within DVP are smaller than those within SVP, thus making them perhaps more vulnerable than SVP in microvascular diseases.[8,34,35] For instance, Carnevali et al.[35] found that vessel density of DVP, not SVP, decreased significantly in patients with type 1 DM without diabetic retinopathy. Thangamathesvaran et al.[34] found a lower DVP-VD in patients with sickle cell disease. This might possibly explain why DVP-VD is associated with early cognitive changes.

The results of our study support that the selected retinal microvascular biomarker could be associated with early cognitive impairment in patients with CKD. However, whether the association exists in other systemic comorbidities is yet to be determined. The pathogenesis of dementia is multifactorial, including both vascular neuronal injury and nonischemic neuronal death due to neurodegeneration.[36] Molecular mechanisms may involve hypoxia, oxidative stress, mitochondrial bioenergetics, neuroinflammation, neurodegeneration, and blood–brain barrier alteration.[37] Each pathologic pathway may have different roles in different systemic diseases.[36,37] For example, cerebral vascular diseases, atherosclerosis, and global hypoperfusion are thought to cause vascular dementia in patients with hypertension.[36] On the other hand, diabetic microangiopathy and macroangiopathy, lacunar infracts, and accumulation of amyloid-β and τ may contribute to mixed dementia in patients with DM.[36] For patients with dyslipidemia, carotid atherosclerosis may cause cerebral hypoperfusion or embolism, leading to cognitive impairment.[38] Due to different pathologic pathways, a biomarker useful in one systemic disease might not necessarily be valid in another.

Even with the same disease, biomarkers might contribute differently at different disease stages. For instance, uremic metabolites or toxins may build up as CKD advances in severity, but they would be removed after the initiation of dialysis in ESRD. These uremic metabolites or toxins might influence brain activity

but could have no relation to retinal microvascular biomarkers. Further large-scale or population-based investigations are necessary for the validation of different retinal biomarkers for different systemic comorbidities and different disease severity.

Decreased RNFLt and GCCt measured by OCT had been shown in patients with MCI or AD.[13–16] Although trends of increased RNFLt and GCCt as well as decreased GCC GLV and GCC FLV could be found with a higher MMSE score, the related statistical analysis results were nonsignificant in this study. This may be due to relatively good cognitive function of our study population. Patients with a prior diagnosis of AD or vascular dementia were excluded. Only 13 patients (7%) had MMSE scores of <24. The RNFLt and GCCt changes may not have been as obvious as they would have been in those with more advanced diseases.

Alternatively, the discrepancy could also be attributed to different pathogeneses involved in different diseases. Although patients with CKD could have a higher risk of AD,[39] some other mechanisms of cognitive impairment also play important roles in CKD. Accumulation of extracellular β-amyloid plaques and intracellular τ filaments in the brain are the hallmarks of AD.[3] However, cerebrovascular diseases and uremic metabolites may be the important pathologies in CKD-associated cognitive impairment.[22,23] Retinal ganglion cell loss and widespread axonal degeneration in the optic nerves had been identified postmortem in the retinas of patients with AD.[40–42] However, the effects of cerebrovascular diseases and uremic metabolites on RNFLt and GCC are unclear. Therefore, whether RNFLt and GCCt could be useful biomarkers for CKD-associated cognitive impairment still requires further investigation.

Our study found that older age and lower education level were associated with a lower MMSE score. This is compatible with a prior study showing that the prevalence of MCI increases with age and lower level of education.[43] DM has been suggested to be associated with cognitive impairment.[44] Forty-three percent of our patients had DM. However, DM was not a significant variable in our multivariable regression model. Education level and severity of CKD could be more important factors for cognitive impairment among patients with CKD.

Our results suggest that physicians should be more alert to evaluate cognitive function in patients with low DVP-VD, particularly in those with a low education level and poor renal function. Cognitive impairment may present in 10% to 40% of patients with CKD and is an increasingly recognized major cause of chronic disability in such patients.[22,23,45] It causes not only lower quality of life and higher health care use[45] but also increased all-cause mortality and cardiovascular mortality.[46,47] However, patients in an early stage of cognitive impairment, such as MCI, could be independent in their daily living activities.[3] Thus, they may not seek medical help intentionally. Early filtering of these patients and providing appropriate interventions could be beneficial to them.[22]

This study had several limitations. First, our study was limited by a small sample size. Therefore, further analysis of the individual domains of cognitive function and systemic comorbidity subgroups was difficult. Most patients with CKD were taking multiple medications, and it is possible that some medications might influence mental status. However, it would be difficult to make meaningful statistical analysis of these medications with the current sample size. Second, there was a lack of etiologic biomarkers such as neuroimaging or cerebrospinal fluid tests. Thus, the exact etiology of cognitive impairment is unclear. Third, blood pressure is a dynamic variable that may have significant diurnal and day-to-day variations. Whether it can represent the brain perfusion status require further investigation. Finally, MMSE scores only have moderate accuracy in diagnosing dementia and predicting conversion to overt dementia.[48] Further long-term longitudinal studies are necessary to confirm the role of DVP-VD in the development of overt dementia in these patients.

In conclusion, our study found that retinal DVP-VD measured by OCTA, age, years of education, and eGFR were associated with MMSE score in patients with CKD. We suggest that physicians should pay more attention to signs of early cognitive impairment in patients with CKD with low DVP-VD, especially patients with old age, low education level, and poor renal function. It is also noteworthy that many systemic comorbidities such as obesity, hypertension, DM, heart failure, chronic lung disease, and carotid stenosis may also affect the oxygenation of brain and cognitive status. Further similar studies of biomarkers and cognitive tests in patients with the above comorbidities but without CKD are necessary to confirm whether our result in the present study is specific to the CKD group investigated.

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