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The observation of enlarged perivascular spaces and white matter hyperintensities in patients with type 2 diabetic nephropathy based on MRI

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Abstract

Background & Objective: Diabetic nephropathy (DN) is one of the common complications of diabetes, and cerebral small vessel disease is associated with cognitive deficits and functional impairment. This study aims to explore the correlation between enlarged perivascular spaces (EPVS) and white matter hyperintensities (WMH) with different stages of type 2 DN, and to evaluate the relationship of diabetes-related parameters with EPVS and WMH. *Methods:* A total of 213 type 2 diabetic participants with possible DN underwent 3T MRI and laboratory analysis. The participants were grouped according to the urinary albumin-to-creatinine ratios (UACR) or estimated glomerular filtration rate (eGFR), respectively. EPVS number and grade were rated on MRI in the centrum semiovale (CSO-EPVS) and basal ganglia (BG-EPVS). Periventricular and deep WMH (PWMH and DWMH) were also graded on MRI. The logistic regression analysis was performed to evaluate the association of risk factors with EPVS and WMH. *Results:* eGFR was associated with the severity of BG-EPVS (p=0.033), DWMH and PWMH (both p<0.001), and UACR was associated with the severity of BG-EPVS (p=0.010) and DWMH (p<0.001). HbA1c (p=0.013 for DWMH, p=0.024 for PWMH), I2/I0 (p=0.032 for BG-EPVS and DWMH, p=0.014 for PWMH) and CysC (p=0.002 for DWMH, p=0.043 for PWMH) showed associations with the severity of WMH.
Conclusions: Our study indicated the close correlation of kidney function related parameters (eGFR and UACR) and cerebral small vessel diseases (mainly EPVS and WMH) in patients with DN. HbA1c, I2/I0 and CysC may be the risk indicators of WMH in this population.

Keywords: Enlarged perivascular spaces, white matter hyperintensities, diabetic nephropathy, glomerular filtration rate, urine albumin-to-creatinine ratio

INTRODUCTION

The incidence rate of type 2 diabetes mellitus (T2DM) is rising alarmingly around the world. Diabetic nephropathy (DN) is one of the common complications in the diabetes who have had the disease for more than ten years, accounting for approximately 25% of all diabetes[1] and 40% in T2DM.[2] Characterized by progressive albuminuria and declining glomerular filtration rate (eGFR), DN imposes a great burden on patients, not only physically and psychologically but also financially.

Cerebral small vessel disease (CSVD) refers to diseases of the small arteries, arterioles, veins, and capillaries of the brain, and is closely associated with conditions including cognitive impairment, dementia, ischemic stroke and depression.[3] CSVD manifests on MRI as enlarged perivascular spaces (EPVS), cerebral white matter hyperintensities (WMH), cerebral microbleeds (CMBs), asymptomatic lacunar infarcts (ALI) and cerebral atrophy[4,5], and among these, EPVS and WMH are two of the most common neuroradiological signatures

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of CSVD. However, the definitive etiology of CSVD remains incompletely understood.

According to the previous studies, both T2DM and chronic kidney disease (CKD) have been associated with CSVD.[6,7] In addition to the characteristics of diabetes and CKD, DN has its unique effects. DN is considered as an inflammatory disease, and its inflammatory process is initiated by poor glycemic control and/or high level of albuminuria. Meanwhile, DN is also characterized by the activation of renin–angiotensin system (RAS), activated components of which are proved to be harmful.[8] Previous study has shown that overexpression of the RAS leads to upregulation of organ oxidative stress affecting CSVD, exacerbating insulin resistance and promoting CKD progression.[9] Besides, advanced glycosylation products cause inflammation of CSVD[9], and many reports have shown systemic inflammation plays a critical role in the pathophysiology of CSVD.[10,11] Inflammation involved in the development of both DN and CSVD, thus we speculate that there is correlation between them. Previous studies have only concerned CKD or diabetes on CSVD, and no study has focused on CSVD in patients with DN at different stages. In this research, we aim to investigate the relationship between EPVS and WMH with DN at different stages, and assess the associations of diabetes-related parameters with EPVS and WMH, so as to provide early prevention or treatment strategies for individuals at risk of CSVD.

METHODS

Study population

From Jan 2023 to July 2023 in the Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, China, this study consecutively enrolled subjects who visited the department of endocrinology or nephrology and were diagnosed with type 2 diabetes, simultaneously presented with one or more of the following clinical symptoms: changes in urine volume (polyuria, oliguria, or anuria), foamy urine, localized or generalized edema, anemia, pruritus, and osteoporosis. Patients with the following conditions were excluded from our study: (1) history of stroke, traumatic brain injury, cognitive decompensation, neurological or psychiatric disease, and history of systemic, metabolic or immune-related diseases that may severely affect the brain (hypothyroidism, hyperthyroidism, severe liver damage, systemic lupus erythematosus or other serious somatic disease); (2) history of tumor, craniocerebral surgery, demyelinating disease, overt cardiovascular disease and radiotherapy; (3) presence of T1DM, ketoacidosis, infectious diseases, hypertensive kidney diseases, chronic glomerulonephritis, nephrotic syndrome and other types of kidney disease. The protocol was approved by our institutional ethical review board and conformed to the Declaration of Helsinki, and informed consent from participants was waived due to the retrospective design. Fig.1 showed the participants screening workflow in our research.

Measurements

Baseline assessment

We recorded clinical characteristics including age, sex, height, weight, time since diagnosis of diabetes, history of ischemic heart disease, actual blood pressure (BP) values (including systolic blood pressure [SBP] and diastolic blood pressure [DBP]), actual total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL) and high-density lipoprotein (HDL), hypertension and dyslipidemia. Hypertension was defined as SBP > 140 mmHg or DBP > 90 mmHg or use of antihypertensive medication. Dyslipidemia was defined as fasting serum TC ≥ 200 mg/dL, triglyceride ≥ 150 mg/dL, LDL ≥ 130 mg/dL, HDL < 40 mg/dL (for men) and HDL < 50 mg/dL (for women) or use of antidyslipidemic agents.[12]

Measurement of kidney function related parameters

At the baseline, two frequently used kidney parameters were examined. the enzymatic method was used to measure the serum creatinine level of estimated glomerular filtration rate (eGFR), and the first morning void specimen was used to determine the urine albumin-to-creatinine ratio (UACR), which is measured in mg/g. Greater kidney damage is indicated by lower eGFR and higher UACR. eGFR (ml/min/1.73m^2) was classified as follows: Group A (normal)= >90; Group B (mild)= 60 to 90; Group C (moderate)= 30 to 60; Group D (severe)= 15 to 30; Group E (kidney failure)= < 15. UACR (mg/g) was classified as follows: Group 1 (no to mild)= < 30; Group 2 (moderate)= 30–300; Group 3 (severe)= > 300.[13]

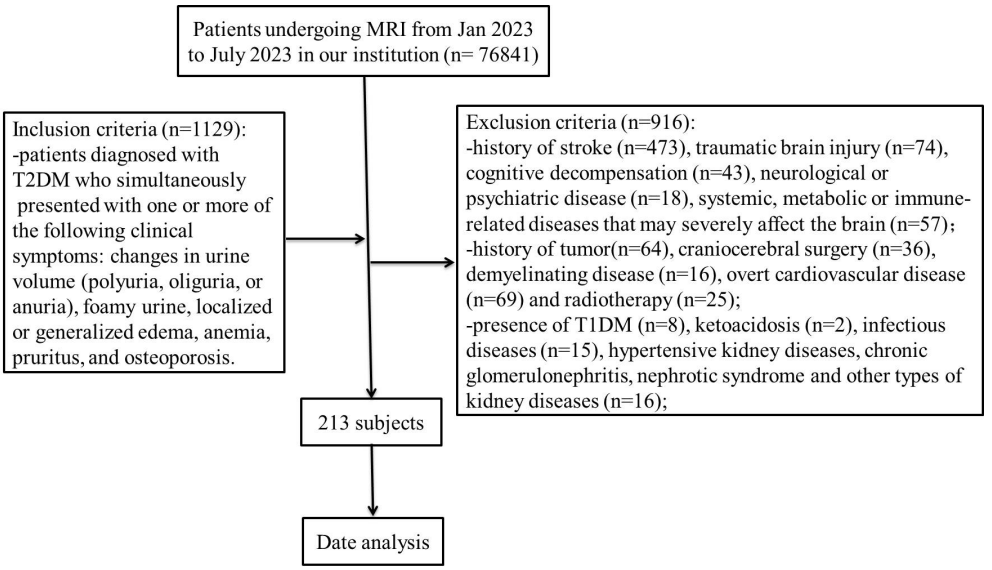

Figure 1. Participants screening workflow in our research.

Measurement of diabetes related parameters

Some other laboratory variables were collected: cystatin C (CysC), fasting blood glucose (FBG), glycated hemoglobin (HbA1c), fasting insulin (I0), 2 hour insulin (I2), fasting C-peptide (C0) and 2 hour C-peptide (C2). I2 or C2 represents insulin or C-peptide level at 120 minutes after an oral glucose tolerance test (OGTT). Venous blood samples were drawn from all subjects in the early morning after 8 hours of fasting. All biochemical determinations were performed in the same laboratory using standard laboratory methods.

Magnetic Resonance Imaging

MR scans were performed using the uniform 3T MRI scanning protocol (Magnetom Verio, Siemens Healthcare, Germany). The MRI scanning protocol included axial T1-weighted, axial T2-weighted, axial FLAIR, axial DWI and sagittal T1-weighted sequences, and the scanning parameters were as follows:

(1) T1-weighted: TR = 2100 ms, TE = 10 ms, flip angle = 150°, matrix = 384 × 384 pixels, FOV = 250 mm × 250 mm, slice thickness = 5 mm.
(2) T2-weighted: TR = 6000 ms, TE = 10 ms, flip angle = 150°, matrix = 384 × 384 pixels, FOV = 250 mm × 250 mm, slice thickness = 5 mm.
(3) FLAIR: TR = 8400 ms, TE = 98 ms, flip angle = 150°, matrix = 256 × 180 pixels, FOV = 250 mm × 250 mm, slice thickness = 5 mm.
(4) DWI: TR = 5500 ms, TE = 96 ms, flip angle = 150°, matrix = 162 × 162 pixels, FOV = 250 mm × 250 mm, b-values = 0, 1000 s/mm^2, slice thickness = 5 mm, intersection gap = 1.8 mm.

WMH were assessed using the Fazekas rating scale.[14] PWMH and DWMH were selected for analysis based on previous experience. PWMH were graded as follows: 0= absent; 1 = cap; 2 = smooth halo; or 3 = irregular and extending into the subcortical white matter. DWMH were graded as follows: 0 = absent; 1 = punctate foci; 2 = early-confluent; or 3 = confluent. A Fazekas score ≥ 2 was regarded as severe for PWMH and DWMH, respectively.

EPVS were defined as round, ovoid, or linear lesions with a CSF-like signal (hypointense on T1/flair and hyperintense on T2) that were located along the penetrating arteries. According to previous experience, EPVS were identified and graded at the level of the centrum semiovale (CSO) and basal ganglia (BG). We selected the largest number of unilateral brain regions for counting. For both of these areas, the EPVS rating scores applied were as follows: 0 = no EPVS;1 = 1-10 EPVS; 2 = 11-20 EPVS;3 = 21-40 EPVS; 4 = 40 or more EPVS.[15] A score ≥ 2 was regarded as severe CSO-EPVS or BG-EPVS, respectively.[16]

The MRI results were evaluated by an experienced neuroradiologist blinded to the clinical data. The intraclass correlation coefficient (ICC) was used to determine the interobserver

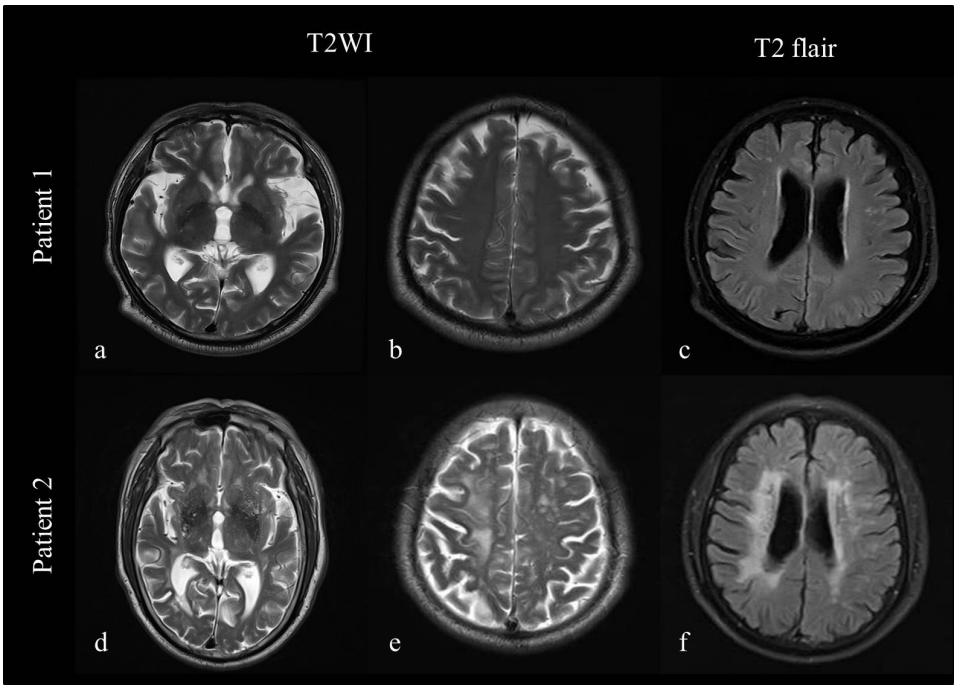

Figure 2. The MR imaging of two typical type 2 diabetes patients with early or late diabetic nephropathy. Patient 1, a 60-year-old male patient, eGFR= 80.76 ml/min/1.73m^2 (Group B, mild), UACR= 16.24 mg/g (Group 1, no to mild), BG-EPVS=grade 1 (a), CSO-EPVS=grade 0 (b); DWMH=grade 1, PWMH= grade 1 (c). Patient 2, a 67-year-old male patient, eGFR=26.16 ml/min/1.73m^2 (Group D, severe), UACR= 736.2 mg/g (Group 3, severe), BG-EPVS=grade 4 (d), CSO-EPVS=grade 3 (e); DWMH=grade 3, PWMH= grade 3 (f).

reliability for WMH and EPVS, as evaluated on a random sample of 100 subjects with a four-week interval between the first and second image assessments. Fig. 2 shows the MR imaging of two typical type 2 diabetes patients with early or late diabetic nephropathy, displaying their WMH and EPVS grades, as well as their personal information and diabetes-related parameters.

Statistical analysis

All statistical tests were performed by the SPSS Statistics for Windows software (version 26.0, IBM, Armonk, NY, USA). For continuous variables, data are expressed as mean (±standard deviation), and for categorical variables as frequencies (percentage). The t-test or analysis of one-way ANOVA was used to compare the continuous variables among each disease group, and the chi-square test was used to compare qualitative variables of participant demographics and to analyze the eGFR and UACR of the participants with or without severe WMH or EPVS. The logistic regression analyses were applied to estimate the association between eGFR, UACR, laboratory variables and WMH, EPVS, respectively. $p<0.05$ were considered statistically significant.

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. The final study population consisted of 213 participants. According to the eGFR level, they were divided into Group A (42 people), Group B (42 people), Group C (48 people), Group D (40 people) and Group E (41 people). According to the UACR level, they were divided into Group 1 (72 people), Group 2 (69 people) and Group 3 (72 people). There were no differences in age, sex, body Mass Index (BMI), diabetes duration, hypertension, dyslipidemia, ischemic heart disease, DBP, cholesterol ratio, FBG, HbA1c or I2/I0 among the groups (all $p>0.05$). SBP differed among eGFR groups ($p<0.05$). There were statistical differences

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

Characteristics	eGFR (ml/min/1.73m^2)						UACR (mg/g)			
	Group A (n=42)	Group B (n=42)	Group C (n=48)	Group D (n=40)	Group E (n=41)	*P value*	Group 1 (n=72)	Group 2 (n=69)	Group 3 (n=72)	*P value*
Age [years]	67.1±8.1	69.±7.8	68.9±6.7	69.9±8.9	67.2±7.3	0.309	69.8±7.2	68.4±7.6	67.4±8.4	0.180
Male n, (%)	28 (66.7)	22 (52.4)	29 (60.4)	21 (52.5)	30 (73.2)	0.226	45(62.5)	42(60.9)	43(59.7)	0.943
BMI [kg/m^3]	23.8±3.3	24.2±2.9	24.4±3.0	24.3±3.8	23.7±3.6	0.834	23.8±3.0	24.2±3.3	24.2±3.5	0.712
Diabetes duration [years]	11.9±10.7	11.4±9.2	14.4±9.1	14.2±7.9	16.2±8.3	0.085	12.0(14.0)	14.0(16.0)	11.5(11.0)	0.882
Hypertension n, (%)	31 (73.8)	33 (78.6)	41 (85.4)	36(90.0)	36(87.8)	0.250	57(79.2)	58(84.1)	62(86.1)	0.521
Dyslipidemia n, (%)	7 (16.7)	5 (11.9)	9 (18.8)	9(22.5)	2(4.9)	0.200	14(19.4)	6(8.7)	12(16.7)	0.181
Ischemic heart disease n, (%)	10(23.8)	9(21.4)	17 (35.4)	17 (42.5)	10 (25.0)	0.172	24(33.3)	18(26.5)	21(29.2)	0.669
SBP [mmHg]	138.3±21.0	136.6±16.3	139.6±26.8	144.4±23.4	142.4±31.9	0.033	136.8±20.4	143.4±23.4	140.5±28.6	0.272
DBP [mmHg]	81.7±11.0	76.5±10.4	77.4±13.9	76.9±13.1	75.9±14.7	0.319	78.4±11.8	79.2±11.8	75.6±14.4	0.208
Cholesterol ratio[a]	4.1±1.2	3.8±1.1	4.4±1.4	3.9±1.2	4.4±1.6	0.097	3.62(1.0)	4.2(2.0)	4.0(2.0)	0.320
FBG [mg/dl]	8.0±2.5	7.1±2.1	8.0±3.1	7.3±2.0	7.8±2.8	0.380	7.4±2.4	8.2±2.7	7.4±2.6	0.103
HbA1c [%]	7.4±1.4	7.5±1.6	8.0±2.3	7.0±1.4	7.2±1.4	0.096	7.4±1.5	7.6±1.8	7.3±1.8	0.696
eGFR [ml/min/1.73 m $^{2]}$	94.0(5.3)	75.8(12.9)	50.0(6.7)	25.7(7.2)	5.9(5.8)	**<0.001**	75.6±39.5	62.8±61.3	18.9±23.7	**<0.001**
UACR [mg/g]	30.3(36.4)	26.1(71.6)	34.3(271.6)	332.9(581.0)	2704.2(5215.8)	**<0.001**	14.2±11.2	78.5±99.6	1255.4±3488.4	**<0.001**
Cys C [nmol/L]	0.8(0.2)	1.0(0.3)	1.4(0.4)	2.4(0.8)	5.7(2.1)	**<0.001**	1.0±0.7	1.3±1.1	3.3±3.7	**<0.001**
I2/I0	4.1(4.0)	3.5(5.0)	3.9(4.0)	3.8(8.0)	2.7(3.0)	0.681	3.9(4.0)	3.9(5.0)	2.8(6.0)	0.276
C2/C0	2.4(2.0)	2.2(2.0)	2.2(2.0)	1.6(1.0)	1.7(1.0)	**0.003**	2.5±1.3	2.2±1.1	2.0±1.2	**0.021**

*Continuous variables are presented as mean (SD) or median (IQR). Categorical variables are presented as number of subjects (%). The p values that are statistically significant are in bold.
[a]Cholesterol ratio= total cholesterol/HDL.

Abbreviation: eGFR= estimated glomerular filtration rate; UACR= urinary albumin-to-creatinine ratios; BMI= body Mass Index; SBP= systolic blood pressure; DBP= diastolic blood pressure; FBG= fasting blood glucose; HbA1c= glycated hemoglobin; Cys C= cystatin C. I2/I0=2 hour insulin/fasting insulin; C2/C0=2 hour C-peptide/fasting C-peptide.

in CysC and C2/C0 among eGFR groups and UACR groups (both $p<0.05$). Furthermore, there were also significant differences in eGFR and UACR among eGFR groups and UACR groups (both $p<0.05$).

Lower eGFR or higher UACR associated with more severe degree of BG-EPVS but not CSO-EPVS

The excellent reliability of the EPVS and WMH scores was demonstrated by an ICC of 0.960 (95% CI: 0.939–0.974, $p<0.001$) for inter-observer reliability. The prevalence of EPVS according to eGFR and UACR levels was shown in Table 2. UACR was associated with the degree of CSO-EPVS ($p=0.04$), but the association attenuated after adjustment for age, sex, BMI, diabetes duration, hypertension, dyslipidemia and ischemic heart disease ($p=0.058$). Both eGFR and UACR were associated with the degree of BG-EPVS ($p=0.01$ and $p=0.028$, respectively), and after adjustment for confounding factors above, individuals with lower eGFR or higher UACR had more severe degree of BG-EPVS ($p=0.033$ and $p=0.010$, respectively).

Lower eGFR and higher UACR differentially affecting severity of WMH

The prevalence of WMH according to eGFR and UACR levels was also shown in Table 2. eGFR was associated with the degree of DWMH and PWMH (both $p<0.001$). After adjustment for confounding factors, people with lower eGFR had more severe degree of DWMH and PWMH (both $p<0.001$). UACR was associated with the degree of DWMH ($p=0.001$). After adjustment for confounding factors, people with higher UACR had more severe degree of DWMH ($p<0.001$). Further details were presented in Table 2.

HbA1c, I2/I0 and CysC identified as the risk indicators of WMH

After adjustment for confounding factors, HbA1c ($p=0.013$ for DWMH, $p=0.024$ for PWMH), I2/I0 ($p=0.032$ for DWMH, $p=0.014$ for PWMH) and CysC ($p=0.002$ for DWMH, $p=0.043$ for PWMH) showed close associations with the severity of WMH. Further details were presented in Table 3 and Figure 3.

DISCUSSION

In this study, we assessed the associations

Table 2: The relationship between eGFR and UACR with EPVS and WMH, respectively

Brain MRI findinds		eGFR (ml/min/1.73m^2)						UACR (mg/g)			
		Group A (n=42)	Group B (n=42)	Group C (n=48)	Group D (n=40)	Group E (n=41)	*P* value	Group 1 (n=72)	Group 2 (n=69)	Group 3 (n=72)	*P* value
CSO-EPVS	A	35(83.3)	35(83.3)	43(89.6)	34(85.0)	41(100)	0.095	59(81.9)	66(95.7)	63(87.5)	**0.040**
	B	1(referent)	0.888(0.266-2.969)	1.773(0.485-6.489)	1.327(0.359-4.901)	259518836.2 (0.000-)	0.866	1(referent)	4.918(1.282-18.868)	1.917(0.699-5.259)	0.058
BG-EPVS	A	15(35.7)	26(61.9%)	30(62.5)	27(67.5)	29(70.7)	**0.010**	38(52.8)	37(53.6)	52(72.2)	**0.028**
	B	1(referent)	2.710(1.063-6.909)	2.873(1.152-7.161)	3.466(1.279-9.393)	4.377(1.611-11.891)	**0.033**	1(referent)	1.098(0.534-2.257)	2.987(1.388-6.429)	**0.010**
DWMH	A	17(40.5)	30(71.4)	37(77.1)	36(90.0)	38(92.7)	**<0.001**	43(59.7)	52(75.4)	63(87.5)	**<0.001**
	B	1(referent)	4.309(1.550-11.978)	5.907(2.103-16.593)	16.148(4.262-61.190)	24.668(5.684-107.053)	**<0.001**	1(referent)	2.513 (1.099-5.748)	7.822(2.960-20.670)	**<0.001**
PWMH	A	7(16.7)	22(52.4)	30(62.5)	28(70.0)	30(73.2)	**<0.001**	35(48.6)	37(53.6)	45(62.5)	0.237
	B	1(referent)	6.009(1.982-18.222)	10.455(3.471-31.490)	15.471(4.642-51.565)	16.285(4.948-53.604)	**<0.001**	1(referent)	1.0289(0.618-2.687)	2.462(1.154-5.255)	0.057

*A: The Chi-square tests were used for univariate analysis. B: The logistic regression analyses were used for multivariate analysis after adjustment for age, sex, BMI, diabetes duration, hypertension, dyslipidemia and ischemic heart disease. The p values that are statistically significant are in bold.
Abbreviation: eGFR= estimated glomerular filtration rate; UACR= urinary albumin-to-creatinine ratios; CSO-EPVS= enlarged perivascular spaces in centrum semiovale; BG-EPVS= enlarged perivascular spaces in basal ganglia; DWMH=deep white matter hyperintensities; PWMH= periventricular white matter hyperintensities.

Table 3: The relationship between diabetes-related parameters with EPVS and WMH

Brain MRI findinds	FBG		HbA1c		I2/I0		C2/C0		CysC	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
CSO-EPVS	0.959(0.783-1.175)	0.687	1.252(0.872-1.798)	0.223	1.038(0.909-1.185)	0.582	0.941(0.588-1.505)	0.800	1.483(0.964-2.284)	0.073
BG-EPVS	0.964(0.849-1.094)	0.569	1.052(0.858-1.291)	0.624	1.100(1.008-1.201)	**0.032**	0.761(0.560-1.034)	0.081	1.187(0.987-1.427)	0.068
DWMH	0.964(0.817-1.137)	0.661	1.459(1.084-1.964)	**0.013**	1.157(1.012-1.323)	**0.032**	0.898(0.616-1.308)	0.574	1.641(1.204-2.236)	**0.002**
PWMH	1.050(0.916-1.205)	0.482	1.309(1.036-1.653)	**0.024**	1.121(1.024-1.227)	**0.014**	0.734(0.532-1.013)	0.060	1.203(1.006-1.440)	**0.043**

*The logistic regression analyses were used for multivariate analysis after adjustment for age, sex, BMI, diabetes duration, hypertension, dyslipidemia and ischemic heart disease. The *p* values that are statistically significant are in bold.

Abbreviation: CSO-EPVS= enlarged perivascular spaces in centrum semiovale; BG-EPVS= enlarged perivascular spaces in basal ganglia; DWMH=deep white matter hyperintensities; PWMH= periventricular white matter hyperintensities; FBG= fasting blood glucose; HbA1c= glycated hemoglobin; Cys C= cystatin C; I2/I0=2 hour insulin/fasting insulin. C2/C0=2 hour C-peptide/fasting C-peptide.

of DN and diabetes-related parameters with EPVS and WMH, and after adjusting for confounding factors, our study found that eGFR was associated with the severity of BG-EPVS, DWMH and PWMH, and UACR was associated with the severity of BG-EPVS and DWMH. Additionally, HbA1c, I2/I0 and CysC showed associations with the severity of WMH. These findings indicated the significant relationship between DN and CSVD (EPVS and WMH).

In the current literature, the relationship between eGFR and WMH remains under debate. A study of Japanese community dwellers showed no clear association between eGFR and WMH.[17] Conversely, another prospective observational study of stroke in young patients showed that lower eGFR within the normal range was associated with the presence of moderate to severe WMH.[18] Our study results showed that eGFR was associated with WMH in DN, and the association was confirmed after adjusting for confounding factors. Analyzing the reasons, patients with DN have activated RAS and inflammation process, which may contribute to the association between eGFR and WMH.

Only one prior study demonstrated that BG-EPVS was the most strongly associated markers in relation to microalbuminuria.[19] In our study, a high degree of BG-EPVS was associated with severe UACR. Because the vascular systems of the brain and kidney display similar anatomical and hemodynamic features, they may share similar pathogenesis.[20] UACR is a marker of glomerular endothelial dysfunction[19], so we speculate that it is also the marker of endothelial dysfunction of the cerebral small vessels, which leads to the generation of EPVS. Meanwhile, both eGFR and UACR were associated with BG-EPVS but not with CSO-EPVS after adjusting for confounding factors, probably for the reason that the blood supply to the basal ganglia regions is predominantly from the middle cerebral artery (MCA)[21], and the geometry and local haemodynamics of MCA are believed to contribute to atherosclerosis on the vascular wall[22], especially for the DN patients with hyperglycemia and renal disorders. This may be the cause of why the basal ganglia are more susceptible to EPVS than the centrum semiovale. It is also the reason that the basal ganglia is the most prone to spontaneous intracerebral hemorrhage.

Previous studies have reported that UACR was associated with WMH[23,24], while we further found that UACR was associated with

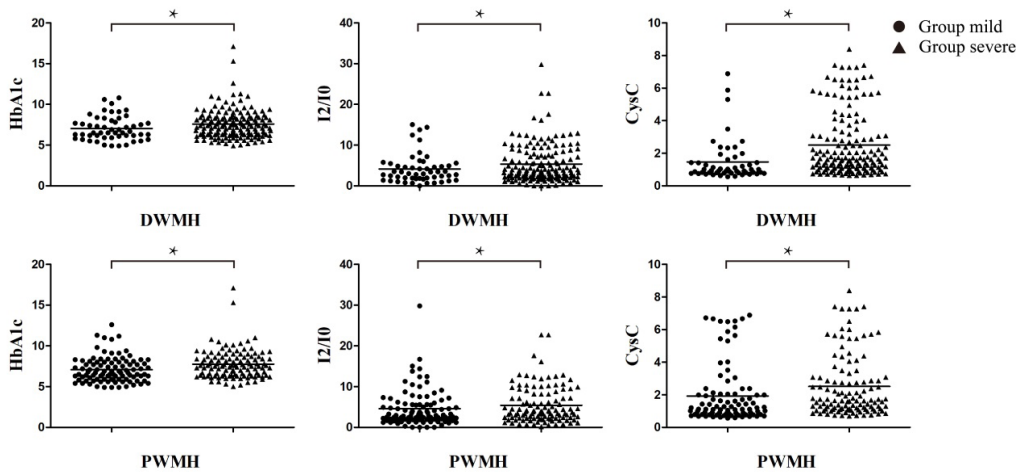

Figure 3. Differences in HbA1c, I2/I0, CysC between individuals with mild and severe DWMH or PWMH. *$p \leq 0.05$.

DWMH but not with PWMH in our study. The pathogenesis of DWMH and PWMH is different. PWMHs are mainly attributed to the damage of veins due to the dysfunction of the glymphatic pathway, while DWMHs can be affected by both ischemia-hypoperfusion and dysfunction of the glymphatic pathway.[25] DWMHs have also been shown to be influenced by small vessel atherosclerosis and endothelial activation, resulting in the endothelial dysfunction.[26] Albuminuria, as measured by UACR levels, is a risk factor for macro- and microvascular complications of T2DM[27], and is associated with maladaptive arterial remodeling and impaired arterial flow-mediated vasodilation, which are also related to endothelial dysfunction.[28,29] Thus, we speculate that UACR is more associated with DWMH than with PWMH in our research.

Several studies have reported that high levels of HbA1c are associated with a high WMH burden in young diabetes patients.[30,31] In our study, we came to a consistent conclusion in patients with DN. HbA1c represents the 3-month average plasma glucose concentration and is regarded as one of the markers of glucose control. Meta-analytic evidence confirms that inflammatory process is involved in metabolic disorders, which include glucose disorders.[32,33] Inflammatory process is one of the mechanisms of WMH formation. Therefore, we speculated that the inflammatory process acted as a mediator to correlate glucose disorders with WMH formation.

To our knowledge, no previous studies have investigated the relationship between 2h-insulin level (I2) with WMH or EPVS. Previous study has shown that impaired insulin secretion and insulin resistance are important pathological mechanisms of T2DM, and elevated I2 is closely related to the risk of T2DM.[34] Meanwhile, Previous study of Altuve *et al.* showed that people with the metabolic syndrome have significantly greater insulin levels than marathon runners at all the stages of the oral glucose tolerance test (OGTT)[35], confirming the value of I2 in assessing insulin resistance and the risk of T2DM. In our research, we found that I2/I0 was positively associated with WMH burden in T2DM patients with DN, and this might be because there was a strong relationship between insulin resistance and vessel atherosclerosis.[36,37] Additionally, we speculated that I2 was more representative of independent predictor of prediabetes than I0.

Previous studies have reported that serum CysC concentration was closely associated with the degree of WMH.[38,39] In our study, we came to the same conclusion. The mechanisms underlying the association between CysC and WMH are not clear. First, inflammation is one of the risk factors of WMH. CysC affects inflammation by interfering with granulocyte phagocytosis and chemotaxis.[40] Secondly, as the cysteine proteinase inhibitor, CysC is crucial for controlling the activity of vascular wall protease-antiproteases.[41] An imbalance between the expression of cysteine cathepsins and CysC could lead to vascular wall remodeling.

It has proved that C-peptide is secreted in an

equimolar amount to insulin from the pancreatic β cells into the circulation.[42] C-peptide enters the endothelial cells and increases nitric oxide release from endothelial nitric oxide synthase (eNOS), which can reduce endothelial cell dysfunction and impaired vasodilatation.[43] Therefore, it has renoprotective effects[42,44] and can reduce the risk of microvascular complications.[45,46] Based on the above, it is speculated that C-peptide may be negatively correlated with WMH or EPVS. However, our study concluded that these was no statistically significant association between C-peptide and WMH or EPVS. There might be two reasons for this. First, our study population mainly consists of T2DM patients with different stages of DN. Expanding the participants scope of our research, such as including patients with diabetes or even prediabetes, might lead to different conclusion. Second, the imaging manifestations of CSVD are irreversible, so even when the C2 level is elevated in the body, it can only protect the kidney but cannot improve WMH or EPVS, which aligns with our findings. Additionally, we interestingly found that diabetes-related parameters (HbA1c, I2/I0, CysC) had a stronger correlation with WMH than with EPVS. Perhaps these parameters can better predict the occurrence of WMH, and the underlying mechanisms need further investigation.

Our study should be interpreted in light of following limitations. First, we used validated visual rating scales to assess EPVS and WMH, which are rater-dependent and may have ceiling or floor effects. Instead, the computationally derived EPVS and WMH metrics (total volume and count, individual size, length, and width) should be used for a more precise evaluation of EPVS and WMH. Secondly, although traditional cardiovascular risk factors such as hypertension, dyslipidaemia, ischemic heart disease were included in the analysis model, the existence of unmeasured confounding variables cannot be fully ruled out. Finally, this is a cross-sectional study which precludes the assessment of causality. Future large-scale longitudinal studies are warranted to address these issues.

In conclusion, our study demonstrated that eGFR was associated with the severity of BG-EPVS and WMH, and UACR was associated with the severity of BG-EPVS and DWMH, indicating the correlation of kidney function related parameters and cerebral small vessel diseases. Additionally, HbA1c, I2/I0 and CysC were identified as the risk indicators of WMH. Therefore, for patients with diabetic nephropathy, as well as those with diabetes or prediabetes, the most important thing is to prevent the deterioration of renal function. It is also advisable to consider eGFR, UACR, HbA1c, I2/I0, and CysC as routine clinical laboratory examination. If diabetic patients present with abnormality of these parameters, brain MRI scans can be considered to detect CSVD at early stage.

DISCLOSURE

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