Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2018, Vol. 46(12) 5040–5051

DOI: 10.1177/0300060518789299
journals.sagepub.com/home/imr
SAGE

Positive correlation between cognitive impairment and renal microangiopathy in patients with type 2 diabetic nephropathy: a multicenter retrospective study

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Abstract

Objective: This study was performed to explore the correlation between cognitive impairment and renal microangiopathy in patients with type 2 diabetic nephropathy (T2DN) by detecting changes in cognitive function and cerebral metabolism in these patients with different stages of T2DN.

Methods: Prospectively maintained databases were reviewed from 2006 to 2017. Blood biochemical indexes and the urinary albumin excretion rate (UAER) were measured in all

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participants. Cognitive function was assessed by the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment Scale (MoCA). Cognitive impairment was the primary endpoint. Renal microangiopathy was the secondary endpoint. Pearson correlation analysis was used to assess correlations.

Results: Two hundred sixteen patients with type 2 diabetes mellitus (T2DM) were divided into three groups according to their UAER: T2DM without nephropathy (n=72), early T2DM with nephropathy (n=74), and the clinical stage of early T2DM with nephropathy (n=70). Healthy participants were selected as the normal control group (n=70). Pearson correlation analysis demonstrated that the total MMSE and MoCA score was negatively correlated with the UAER (r=−0.327) and positively correlated with the estimated glomerular filtration rate (r=0.428) in patients with T2DN.

Conclusions: The present study showed a positive correlation between cognitive impairment and renal microangiopathy in patients with T2DN.

Keywords

Diabetic nephropathy, cognitive impairment, renal microangiopathy, correlation, glomerular filtration rate, urinary albumin excretion rate

Date received: 30 April 2018; accepted: 26 June 2018

Introduction

Type 2 diabetic nephropathy (T2DN) is a common microvascular complication of diabetes mellitus (DM), and many studies have shown that T2DN is closely related to cognitive function in patients with DM.[1–4] T2DN is a major health issue worldwide because of its progressive course and risk of adverse outcomes.[1] Previous research has proven that T2DN in patients of advanced age is a risk factor for cognitive impairment or dementia.[5] Among patients with T2DN, those with cognitive impairment have a higher risk of cardiovascular accidents and death than those without cognitive impairment.[6,7] Recent research suggests that T2DN may be closely related to cognitive impairment and serves as indirect evidence of cognitive impairment.[8,9] To date, no studies have shown a correlation between T2DN and cognitive impairment among patients with different stages of type 2 DM (T2DM).

Although several factors have been hypothesized to contribute to diabetes-related cognitive impairment, few studies have involved measurement of cognitive decline in a large sample of patients with T2DN. Therefore, the present retrospective study was performed to explore the correlation between cognitive impairment and renal microangiopathy in patients with T2DN by detecting the changes in cognitive function and cerebral metabolism in patients with different stages of T2DN.

Materials and methods

Study population and endpoints

This study was approved by the Medical Ethics Committees of the First Hospital, Hebei Medical University (249165) and the

First Affiliated Hospital, Sun Yat-sen University (2017461). Additionally, two informed consent exemptions were obtained from our responsible Investigational Ethics Review Board. The study included all patients with T2DN followed at the participating centers from February 2006 to March 2017. The patients were divided into three groups according to their urinary albumin excretion rate (UAER): T2DM without nephropathy (Group DW, UAER of <20 μg/min), early T2DN (Group DN-III, UAER of 20 to <200 μg/min), and clinical T2DN (Group DN-IV, UAER of ≥200 μg/min). Healthy volunteers served as normal controls (NC group). All enrolled patients were managed according to standard guidelines, including treatment with renin–angiotensin system inhibitors. The estimated glomerular filtration rate (eGFR) was measured at least twice during a ≥6-month follow-up. Centralization testing was performed in two medical centers. The inclusion criteria were an age range of 40 to 75 years, diagnosis of T2DM according to the 1999 criteria of the World Health Organization,[10] patients with T2DN who had undergone renal biopsy, no history of renin–angiotensin system inhibitor use, a glycated hemoglobin A1c (HbA1c) concentration of 7% to 10%, a fasting blood glucose concentration of 6 to 15 mmol/L, no severe hypoglycemia or hyperglycemia, a negative urine ketone test, an Activity of Daily Living Scale score of ≤26 points, a Global Deterioration Scale score of ≤3 points, and a Hamilton Depressive Scale score of ≤7 points. The exclusion criteria were type 1 DM, diabetic ketoacidosis, hypertonic diabetes or severe hypoglycemia, dementia or depression, a history of cerebrovascular disease (including hemorrhagic and ischemic cerebrovascular disease), congenital dementia, mental retardation, epilepsy, unhealed or planned surgery, severe infection, traumatic brain injury, Alzheimer's disease or other neurological disease, hypothyroidism, hyperthyroidism, severe liver or kidney damage or other serious somatic disease that may affect cognitive function, alcohol dependence or psychotropic substance abuse, current treatment with medications that affect cognitive or renal function, severe visual and hearing impairment affecting cognitive function tests, metallic material in the body that cannot be examined by magnetic resonance imaging (MRI), and a primary or secondary nephropathy other than T2DN.

Definitions of main descriptive variables

The hypoglycemic, lipid-lowering, and antihypertensive drugs used in each group were matched. Age, sex, education level, and history of macrovascular disease (heart disease and/or hypertension) were also matched. Each participant received a general survey to complete. The participants' height, weight, blood pressure, and body mass index were measured. Fasting venous blood sampling, a glucose oxidase assay for fasting blood glucose, and high-performance liquid chromatography for detection of HbA1c were performed in all participants. An automated biochemical analysis was performed to measure the serum concentrations of total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, alanine aminotransferase, and aspartate aminotransferase. The mean UAER was measured for 2 weeks in all participants. A UAER of <20 μg/minute was normal, a UAER of ≥20 to <200 μg/minute was considered to indicate microalbuminuria, and a UAER of ≥200 μg/minute was consistent with macroalbuminuria. Patients with a UAER of ≥20 μg/minute were considered to have T2DN. The eGFR was determined as described by Levey et al.[9] The participants had no changes in their diet throughout the study. Each patient was placed in the supine position with the kidney at

the center of the visual field. A forearm bolus-type intravenous injection of 1 mL of ^{99m}diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) was administered, and dynamic collection was then performed for 20 minutes. The acquisition matrix was $64 \times 64 \times 16$. After the collection was completed, the empty syringe was again counted for 1 minute and the radioactivity count per minute that was injected into the body was calculated. Using the region of interest technique to map the kidney profile and background, the ^{99m}Tc-DTPA radioactivity counts and the patient's window width and window position were entered, and the eGFR was obtained by computerized quantitative molecular software. In this way, the body surface area was standardized.

Examination of cognitive impairment

Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment Scale (MoCA) assessments were performed simultaneously by experts. The maximum MoCA score is 30 points. A score of $\leq$26 points is considered to indicate cognitive impairment. In the present study, if the participant's length of education was $\leq$12 years, 1 point was added to the measurement result to correct for education bias. All enrolled participants were assessed on the MMSE and MoCA scales separately, and repeated assessments were not performed. Assessments were completed by the same group of personnel who were trained and skilled in the practice of standardization. The evaluation process was performed strictly in accordance with the instructions and steps of the scale. Before the assessment, each participant's blood glucose concentration was tested, and the impact of hypoglycemia on cognition was excluded. Finally, the MMSE and MoCA scores were added together.

Examination of brain metabolism

Functional MRI can detect early brain cell dysfunction before the appearance of morphological abnormalities of brain cells. Proton magnetic resonance spectroscopy (^{1}H-MRS) was used to observe the peaks of different metabolites. Using a Siemens Sonata 1.5T superconducting MRI system, conventional cranial MRI scans were performed, including cross-sectional T1- and T2-weighted imaging, sagittal T2-weighted imaging, coronal inclination angles, and vertical scanning of the hippocampus. The position of the bilateral hippocampal head and basal ganglia was used as the region of interest. The MRI scans were completed by a specialist in the radiology department. ^{1}H-MRS was used to observe the resonance peaks and the area of the peaks of different metabolites [N-acetyl aspartate (NAA), choline (Cho), and creatine (Cr)]; the NAA/Cr and Cho/Cr ratios were calculated separately. NAA, which has anabolic activity transmitted along the axon, is mainly found in the neuronal mitochondria and exhibits the highest peak in ^{1}H-MRS in the normal human brain; thus, it is a preferred marker for nerve cells. NAA can also be a sensitive indicator of neuronal damage or mitochondrial dysfunction. The Cr peak represents the total amount of creatine and phosphocreatine. Cho is an integral part of the cell membrane phospholipids and myelin in brain tissue; hence, changes in the Cho level indicate disruption of the cell membrane or myelin sheath.

Statistical analysis

Categorical variables are expressed as counts and percentages and were analyzed using the χ^2 test or the Mann–Whitney U-test. Continuous numerical variables are expressed as mean and standard deviation and were analyzed using Student's t-test. Multivariate analysis of categorical

variables was performed using logistic regression analysis. Pearson correlation coefficients were obtained to determine the strengths of linear relationships among the variables involved in the analyses. The correlation between cognitive impairment and renal microangiopathy was calculated by Pearson correlation analysis. Data were analyzed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA). A P-value of <0.05 was considered statistically significant.

Results

In total, 438 patients were assessed for study eligibility, and 216 patients met the inclusion criteria (Group DW: n=72, mean age of 53.3±15.52 years; Group DN-III: n=74, mean age of 55.1±14.49 years; and Group DN-IV: n=70, mean age of 54.1±15.84 years) (Figure 1). The NC group comprised 70 healthy volunteers. Table 1 compares the patient demographics among the groups. The mean duration of the study at the primary analysis cut-off date was 67 months (interquartile range, 53.6–73.4) among the four groups.

Comparison of MMSE scores

All patients enrolled in this study were evaluated using the MMSE. The MMSE scores in all four groups were >24 points and failed to reach the level consistent with dementia. No statistically significant difference in the MMSE scores was present among the groups (NC group, 27.63 ±1.27; DW group, 27.43±1.16; DN-III group, 27.37±1.75; and DN-IV group, 27.21±1.33).

Comparison of MoCA scores

All patients enrolled in this study were assessed using the MoCA, and their total scores and sub-item scores were obtained. Compared with the NC group, there were no statistically significant differences between the total scores of the MoCA and the sub-item scores in the DW group. In the DN-III and DN-IV groups, the scores of the MoCA and sub-items (attention, visuospatial/executive function, delayed recall, language, abstraction, etc.) were significantly decreased, and these differences were statistically significant ($P<0.05$). In a comparison of the three groups of patients with T2DM, we found differences in abstraction, delayed recall scores, and total MoCA scores. The score in the DN-IV group was significantly lower than that in the DM or DN-III group, and the score in the DN-III group was significantly lower than that in the DM group (all $P<0.05$). There was no statistically significant difference in visuospatial/executive function, attention, naming, orientation, or language (Table 2).

Comparison of NAA, Cho, Cr, NAA/Cr, and Cho/Cr in the bilateral hippocampus between the DW and DN groups

^{1}H-MRS was performed in patients with T2DM, including 55 patients in the DW group and 56 patients in the DN group (both the DN-III and DN-IV groups). The level of left NAA (LNAA) was significantly lower and the level of left Cho (LCho) was significantly higher in the DN than DW group (both $P<0.05$). However, no significant difference was detected in RNAA, RCho, LCr, or RCr. When Cr was used as a reference for error correction, a statistically significant difference was only noted in LCho/Cr ($P<0.05$); no statistically significant difference was found in the bilateral NAA/Cr or RCho/Cr (Table 3).

MoCA score and Pearson correlation analysis of UAER and eGFR

The patients' MoCA scores were analyzed with UAER and eGFR, respectively, using linear correlation. The MoCA scores were

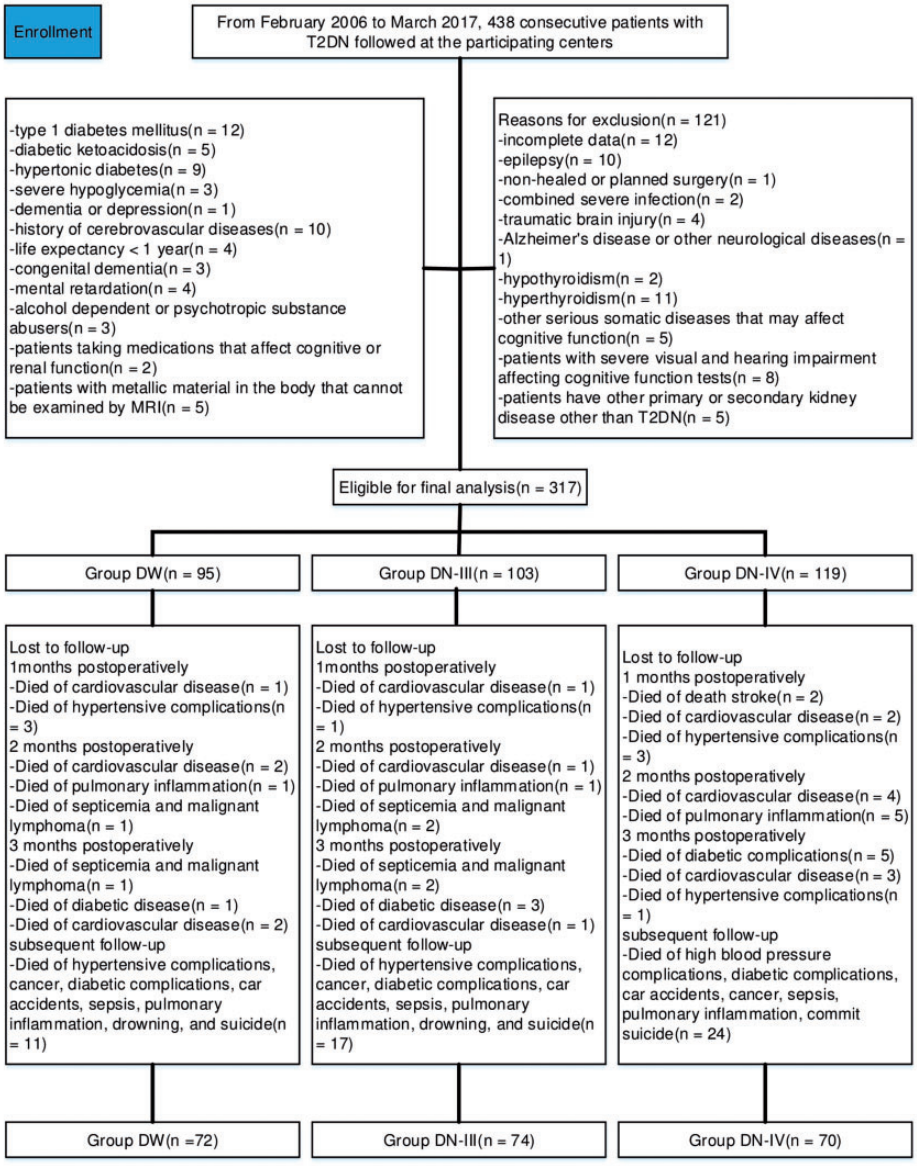

Figure 1. Flow diagram demonstrating methods of identification of studies to explore the correlation between cognitive impairment and renal microangiopathy in patients with type 2 diabetic nephropathy (T2DN). Changes in cognitive function and cerebral metabolism were detected in patients with different stages of T2DN using cognitive impairment as the primary endpoint.

Table 1. Patient demographics among the study groups

Variable	NC (n=70)	DW (n=72)	DN-III (n=74)	DN-IV (n=70)	*P*-value
Age at onset (y)					0.117[a]
40–49	20	18	22	24	
50–59	36	39	40	35	
60–69	14	15	12	11	
Sex (M/F)	36/34	37/35	39/35	35/35	0.216[b]
Educational level	12.1±3.21	11.6±3.53	11.8±2.76	11.7±3.75	0.112[c]
BMI (kg/m^2)	24.6±2.81	25.1±3.36	24.8±2.92	24.2±3.62	0.316[c]
SBP (mmHg)	143.9±17.42	145.6±15.71	144.2±14.70	145.2±17.22	0.436[c]
DBP (mmHg)	90.3±9.47	89.8±10.28	91.4±17.32	91.5±16.76	0.633[c]
FPG (mmol/L)	4.8±0.75	11.2±7.23*	11.5±6.73*	11.7±8.01*	<0.05*,[c]
HbA1c (%)	5.3±0.90	9.1±2.42*	9.2±3.50*	9.5±3.54*	<0.05*,[c]
TC (mmol/L)	4.3±1.12	4.2±1.71	4.6±1.34	4.5±1.52	0.265[c]
TG (mmol/L)	1.9±0.62	2.0±0.13	1.9±0.71	2.1±0.26	0.137[c]
HDL-C (mmol/L)	1.2±0.33	1.1±0.74	1.1±0.62	1.1±0.95	0.447[c]
LDL-C (mmol/L)	2.4±0.66	2.3±0.59	2.4±0.28	2.5±0.13	0.241[c]
UAER (μg/min)	9.8±5.67	9.9±4.93	118.3±47.14*,#	1479.2±486.49*,#,&	<0.05*,[c]
eGFR (ml/min/1.73 m^2)	98.2±27.44	97.9±29.61	88.3±30.07*,#	70.3±26.87*,#,&	<0.05*,[c]

Data are presented as number of patients or mean ± standard deviation. *P<0.05 compared with NC group, #P<0.05 compared with DW group, &P<0.05 compared with DN-III group. [a]Analyzed using the Mann–Whitney test, [b]Analyzed using the chi-square test, [c]Analyzed using an independent-samples t-test. NC: normal control group, DW: type 2 diabetes mellitus without nephropathy, DN-III: early nephropathy, DN-IV: clinical nephropathy, M: male, F: female, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, HbA1c: glycated hemoglobin, TC: total cholesterol, TG: triglycerides, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, UAER: urinary albumin excretion rate, eGFR: estimated glomerular filtration rate (according to the Schwartz formula).

Table 2. Comparison of MoCA scores among the study groups

Variable	NC (n=70)	DW (n=72)	DN-III (n=74)	DN-IV (n=70)	*P*-value
Attention	5.12±0.34	5.01±1.13	4.87±1.21*	5.24±0.47*	<0.05*,[a]
Visuospatial/Executive	4.22±1.24	3.95±1.01	3.47±0.93*	3.56±0.75*	<0.05*,[a]
Delayed recall	3.21±1.27	2.86±1.53	2.15±0.78*,#	1.76±0.92*,#,&	<0.05*,[a]
Language	1.26±0.73	1.12±0.64	1.09±0.58*	1.02±0.35*	<0.05*,[a]
Abstraction	1.74±0.28	1.33±0.57	1.01±0.42*	0.76±0.28*	<0.05*,[a]
Naming	2.78±0.97	2.71±0.23	2.98±0.64*,#	2.74±0.27*,#,&	<0.05*,[a]
Orientation	5.65±0.94	5.42±0.62	5.45±0.24	5.62±0.46	>0.05[a]
MoCA score	24.93±2.76	24.34±2.47	22.48±2.31*,#	21.03±2.35*,#,&	<0.05*,[a]

Data are presented as mean ± standard deviation. *P<0.05 compared with NC group, #P<0.05 compared with DW group, &P<0.05 compared with DN-III group. [a]Analyzed using an independent-samples t-test. NC: normal control group, DW: type 2 diabetes mellitus without nephropathy, DN-III: early nephropathy, DN-IV: clinical nephropathy, MoCA: Montreal Cognitive Assessment.

Table 3. Analysis of bilateral hippocampal spectrum in the DW and DN groups

Variable	DW (n=55)	DN (n=56)	*P*-value
LNAA	200.64±78.59	135.22±61.63	<0.05*,[a]
LCho	223.13±42.37	280.01±34.68	<0.05*,[a]
LCr	185.12±60.49	184.87±69.31	>0.05[a]
RNAA	203.36±56.26	201.73±45.39	>0.05[a]
RCho	211.43±57.09	209.15±54.21	>0.05[a]
RCr	176.61±73.15	178.02±52.16	>0.05[a]
LNAA/Cr	1.13±0.17	1.10±0.56	>0.05[a]
LCho/Cr	1.02±0.35	1.84±0.69	<0.05*,[a]
RNAA/Cr	1.29±0.78	1.31±0.24	>0.05[a]
RCho/Cr	1.26±0.48	1.28±0.62	>0.05[a]

*Statistically significant. [a]Analyzed using an independent-samples t-test. DW: type 2 diabetes mellitus without nephropathy, DN: diabetic nephropathy (both early and clinical nephropathy groups), LNAA: left N-acetyl aspartate, LCho: left choline, LCr: left creatine, RNAA: right N-acetyl aspartate, RCho: right choline, RCr: right creatine.

Table 4. Multifactorial non-conditional logistic regression analysis of patients with type 2 diabetes mellitus

Influencing factors	β	SE	OR	95% CI	X^2	*P*-value
Level of education	−0.721	0.579	1.45	1.16–2.93	3.276	0.012*[a]
FPG (mmol/L)	1.281	0.638	7.83	1.15–9.64	10.324	0.002*[a]
HbA1c (%)	1.749	0.327	5.39	1.92–7.85	8.057	0.005*[a]
UAER (μg/min)	2.395	0.408	6.49	2.76–8.38	9.073	0.001*[a]
eGFR (ml/min/1.73 m^2)	1.402	0.932	5.21	1.37–7.81	8.325	0.020[a]

*Statistically significant. [a]Analyzed using Pearson correlation analysis. FPG: fasting plasma glucose, HbA1c: glycated hemoglobin, UAER: urinary albumin excretion rate, eGFR: estimated glomerular filtration rate (according to the Schwartz formula), SE: standard error, OR: odds ratio, CI: confidence interval.

negatively correlated with the UAER (r=−0.327, *P*=0.04) and positively correlated with the eGFR (r=0.428, *P*=0.01).

Multivariate correlation analysis of cognitive impairment

Fourteen study factors were assigned and encoded. T2DN combined with cognitive impairment as the dependent variable and the 14 study factors (sex, age, education level, body mass index, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, HbA1c, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, UAER, and eGFR) as independent variables were analyzed using logistic regression. The final variables were education level, fasting plasma glucose, HbA1c, UAER, and eGFR, suggesting that an increased UAER and decreased eGFR were still independent risk factors for cognitive impairment in these patients with T2DN (Table 4).

Discussion

The most important finding in the present study was the positive correlation between cognitive impairment and renal microangiopathy in patients with T2DN.

Our findings are consistent with those reported by Rodriguez-Sanchez et al.[11]

Other studies of non-diabetic nephropathy and cognitive impairment have shown that chronic nephropathy is considered a risk factor for cognitive decline in patients of middle age and advanced age.[6] Ciudin et al.[12] suggested that T2DN may be closely related to diabetic cognitive impairment and may be used as indirect evidence of diabetic cognitive impairment. No report has described the relationship between T2DN and cognitive impairment at different stages of T2DM. The current study showed significant differences in the MoCA scores, attention, visuospatial/executive function, delayed recall, language, and abstraction between the DN and NC groups (all $P<0.05$). There were significant differences in abstraction, delayed recall score, and total MoCA score between the DN groups in different periods. The score was significantly lower in the DN-IV group than in the DW and DN-III groups (all $P<0.05$). The score in the DN-III group was significantly lower than that in the DW group ($P<0.05$). Correlation analysis showed that the MoCA score was negatively correlated with the UAER and positively correlated with the eGFR in patients with T2DN complicated by cognitive impairment. Multiple-factor regression analysis also indicated that an increased UAER and decreased eGFR were independent risk factors for cognitive impairment in patients with T2DM.

T2DN is closely associated with diabetic cognitive impairment, which can be explained by a variety of mechanisms.[13–16] One possibility is that brain and kidney damage are characterized by similar microvascular lesions.[17,18] The microvascular structure shows many similarities between kidney tissue affected by microangiopathy and brain tissue affected by cognitive impairment, such as thickening of the capillary basement membrane, narrowing of the lumen, and increased vascular permeability.[19] Damage to vascular endothelial function can manifest as a defect in the blood–brain barrier, lacunar cerebral infarction, and white matter change.[20,21] When renal function is damaged, the concentration of nitric oxide inhibitor increases, which affects the cerebral microcirculation and blood–brain barrier; this in turn affects the cerebral vascular endothelium and causes cognitive impairment.[22,23] In addition, β-amyloid plays an important role in the pathological process of cognitive decline, and its main clearance pathway is likely the kidney.[1,15,24]

Diabetic cognitive impairment is a multifactor, multi-link comprehensive pathogenic process.[8,16,20] In addition to microvascular disease, abnormal neurotransmitters may also participate in the pathogenesis of diabetic cognitive impairment.[3,7,17] Local analysis of the brains of diabetic mice demonstrated that the enhanced activity of acetylcholinesterase (also known as acetylhydrolase), a hydrolase that hydrolyses the neurotransmitter acetylcholine in the amygdala, thalamus, and hippocampus of diabetic mice, decreases enzyme activity in the cholinesterase system and affects the synthesis and release of acetylcholine.[25–27] Acetylcholinesterase is found mainly at neuromuscular junctions and cholinergic brain synapses, where its activity serves to terminate synaptic transmission.[27] In previous studies, the activity of choline acetyltransferase and the synthesis of acetylcholine in the cerebral cortex and hippocampus of patients with Alzheimer's disease were significantly decreased and were closely related to the degree of cognitive impairment.[28,29] In the present study, ^{1}H-MRS was used to evaluate the changes in bilateral hippocampal metabolism in patients with T2DM, and the results showed that the LNAA level in the DN group was significantly lower than that in the DW group. This finding may indicate that the nerve cells in the DN group were more severely damaged, the number of nerve cells significantly declined,

or the activity notably decreased. In addition, the LCho level in the DN group was significantly higher than that in the DW group. The increase in the LCho level may reflect the accelerated catabolism of the nerve cell membrane; it is also a compensatory manifestation of cognitive impairment.[26,29] Cho is a precursor of acetylcholine.[10,14] Increased cholinesterase activity in patients with DM who have mild cognitive impairment may contribute to increased Cho levels, thereby reducing compensatory impairment of cholinergic nerve cell function and loss of integrity.[30,31] Our study showed no differences in the RNAA or Cho levels between the DW and DN groups. This may be due to the functional asymmetry of the left and right hemispheres; metabolic abnormalities in the left hippocampus are more closely related to language memory impairment. It may also be related to the relatively small sample size of the study.

This study has several limitations. First, the retrospective nature of the present study limits the level of confidence in our conclusions. Second, potential selection bias may have contributed to over-categorization in some cases and may reduce the strength of our findings. Because this was a retrospective study, real-time clinical examination was not available at the time of the review. Nevertheless, this influence might be limited because a high participation rate was achieved in the current study. Finally, every attempt was made to adjust for all potential confounders, but other unmeasured factors may also be relevant.

In conclusion, the pathogenesis of and risk factors for cognitive impairment in patients with T2DN remain controversial. This study showed a positive correlation between cognitive impairment and renal microangiopathy in patients with T2DN, and cognitive impairment showed an increasing trend with the severity of renal damage. Biological indicators that reflect renal function, such as the UAER and eGFR, can be used for early detection of diabetic cognitive impairment to provide clinical support for early intervention.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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