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White matter impairment in type 2 diabetes mellitus with and without microvascular disease

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ABSTRACT

Background and objective: Type 2 diabetes mellitus (T2DM) is a serious public health problem, and the phenomenon of T2DM occurring in younger people has directed more attention to functional changes in the brain. In this study, the microstructural integrity of white matter (WM) was evaluated in three groups of middle-aged subjects: healthy controls (HCs) and T2DM patients with and without peripheral microvascular complications (T2DM-C and T2DM-NC patients, respectively).

Methods: Diffusion tensor imaging (DTI) and related clinical examinations were performed in 66 subjects, including 20 T2DM-C patients, 20 T2DM-NC patients, 26 age- and sex-matched HCs. Magnetic resonance imaging (MRI) at 3 T was used to perform DTI; then, FSL and tract-based spatial statistics (TBSS) software were used to assess differences in the fractional anisotropy (FA) and mean diffusivity (MD) among the groups. The use of the FA and MD as parameters was evaluated by receiver operating characteristic (ROC) curve analysis.

Results: There were no significant differences in sex or age among the groups, and the clinical data of the groups met the experimental requirements. There was no significant difference in the FA values between the HCs and T2DM-NC groups. Compared with the HCs, the T2DM-C patients showed decreased FA values and increased MD values in the corpus callosum, bilateral anterior limb of the internal capsule, right retrolenticular part of the internal capsule, bilateral posterior thalamic radiation, right superior longitudinal fasciculus, bilateral superior corona radiata and left middle frontal gyrus ($P < .01$). Compared with the T2DM-NC patients, the T2DM-C patients showed decreased FA values and increased MD values in the corpus callosum, bilateral fornix, right retrolenticular part of the internal capsule, middle cerebral peduncle, right superior longitudinal fasciculus, right posterior thalamic radiation, and left middle frontal gyrus ($P < .01$).

Conclusions: This study indicates that WM impairment is present in T2DM patients and may be related to microvascular complications. More importantly, this study also shows that such impairment may be diagnosed using the DTI mode of functional MRI before it can be diagnosed clinically.

1. Introduction

With high morbidity and mortality, type 2 diabetes mellitus (T2DM) is a serious chronic disease globally. It was reported that China, the largest developing country, will have 42.3 million patients with diabetes in 2030 (Boutayeb and Boutayeb, 2005; Yang et al., 2016). Moreover, T2DM is occurring in increasingly younger individuals, such as middle-aged adults, and even in children and adolescents (Tieh and Dreimane, 2014). This trend indicates that more attention should be directed toward diabetes-related complications, especially in young patients.

T2DM is a metabolic disease that can adversely affect tissues and

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organs in the body, including the kidneys, eyes, and brain. Brain damage caused by T2DM is associated with mild cognitive decline (Zimmet et al., 2001; Biessels et al., 2006). White matter (WM) impairment can be detected by diffusion tensor imaging (DTI), a non-invasive magnetic resonance imaging (MRI) sequence with high sensitivity. DTI characteristic parameters, including fractional anisotropy (FA) and mean diffusivity (MD), are related to microstructural changes in WM. Decreased FA or increased MD values suggest damage to WM microstructures and neurological disorders (Falvey et al., 2013), both of which are difficult to detect using other conventional MRI sequences.

Some previous studies have compared the WM of healthy people and patients with T2DM. DTI parameters can be used to distinguish T2DM patients with and without cognitive impairment, indicating that DTI can be used to detect early-stage cognitive decline, before clinical diagnosis is possible (Xiong et al., 2016; Zhang et al., 2014). Tan et al. found that the damaged WM regions in T2DM patients were similar to those in patients with Alzheimer's disease, as determined using tract-based spatial statistics (TBSS), such as the default mode network, which helped to further explain the neuropathological process of T2DM (Tan et al., 2016). Hoogenboom et al. researched cerebral WM abnormalities and disrupted functional connectivity in the default mode network in patients with T2DM, these early diagnoses may help to provide a rational solution for clinical treatment and facilitate patient recovery (Hoogenboom et al., 2014). The above studies have shown that the integrity of WM is altered in patients with T2DM, and that the combination of DTI and TBSS support early diagnosis.

In this study, we further divided dementia-free T2DM subjects into two groups according to the presence or absence of microvascular complications (T2DM patients with and without peripheral microvascular complications, T2DM-C and T2DM-NC group, respectively). DTI images were analyzed using FSL and TBSS software to detect the cerebral WM integrity in T2DM patients compared with that in healthy controls (HCs). We aimed to analyze the WM bundle differences among the three groups (T2DM-C group, T2DM-NC group and HCs group), so that we could diagnose T2DM by using DTI images, and even diagnose the presence of microvascular complications.

2. Methods

2.1. Subjects

This was a cross-sectional, observational, and case-control cohort study. All participants were recruited between October 2016 and June 2017, and all T2DM patients admitted to the Shanghai General Hospital inpatient service were screened for participation. We recruited patients who were diagnosed with T2DM and were > 18 years old (to avoid any effects of hyperglycemia on brain maturation) and < 60 years old. We recruited and excluded subjects according to our previously reported criteria (Fang et al., 2018). We recruited 26 healthy people as controls, with age and sex matching the disease group. Participants underwent a widely-used cognitive test, the Mini-Mental State Examination (MMSE) (Folstein et al., 1975). Subjects who obtained full marks (30 points) on the MMSE were considered to be dementia-free and were recruited into the study. All subjects provided written informed consent to participate in the study, which was approved by the Shanghai General Hospital Ethics Committee.

2.2. Microvascular complications assessment

The diagnostic criteria for microvascular complications were the same as those applied in our previous study (Fang et al., 2018). Patients with at least one microvascular complication (i.e., retinopathy, nephropathy, or diabetic peripheral neuropathy) were assigned to T2DM-C group. Patients without any of the above microvascular complications were assigned to the T2DM-NC group.

2.3. MRI acquisition

DTI scans were performed on a 3-T system (Ingenia, Philips Healthcare, Best, the Netherlands) with a sixteen-channel phased-array head coil. Sponges were used to restrict head movement as much as possible, and headphones suitable for the MRI configuration were used to reduce scanner noise. During the MRI scan, subjects were asked to try to stay still. The scanning parameters were as follows: flip angle = 90°; echo time (TE) = 89 ms; repetition time (TR) = 9240 ms; field of view (FOV) = 224 × 224 × 150 mm; thickness = 2 mm; slices = 75; gap = 0; acquisition voxel size = 2 × 2 × 2 mm^3; b value = 1000 s/mm^2; sequence scan time = 6 min30 s.

2.4. FSL and TBSS

DTI image pre- and postprocessing were performed using FSL software (www.fmrib.ox.ac.uk/fsl). Voxel-wise statistical analysis of the DTI images was performed using TBSS Smith et al., 2006. First, we used the brain extraction tool (BET) to extract brain tissue from the image with a b value equal to 0 (Smith, 2002). Eddy current correction was used to adjust the DTI images in gradient coils. All images were aligned to the FA standard template by nonlinear registration after using the Functional Magnetic Resonance Imaging of the Brain (FMRIB) toolbox (Jbabdi et al., 2007). FA and MD maps were output using the DTIFIT toolbox (Behrens et al., 2003).

Based on the above postprocessing procedure, we created FA data from a diffusion study and then registered the data as high-resolution FMRIB58_FA images so that all FA images were aligned to a standard space of 1 × 1 × 1 mm. All brain images were linearly and nonlinearly registered using the FLIRT and FNIRT tools, respectively. After registration, the images of all subjects were aligned to the standard MNI152 space (1 × 1 × 1 mm), and these images were combined into a 4D image file. The mean of all FA images was determined, and these images were input into the FA skeletonization program. We set the skeleton threshold to be lower than 0.2 to prevent the extreme variability of crossover subjects and the extreme case of poor nonlinear registration. The Threshold-Free Cluster Enhancement (TFCE) option for randomization was chosen to analyze the differences between the HCs and T2DM groups ($P < .01$). In addition to the FA analysis, the FSL Randomize tool was used to identify differences in the MD images among the groups.

2.5. ROC curve analysis

Bivariate logistic regression was used for the ROC curve analysis; the dichotomous criterion variable was the patient condition (T2DM-C or T2DM-NC), and the dichotomous predictor variables were the FA and MD values. The probability (P_0) was calculated according to the following formula: $P_0 = \exp.(a_0 + a_1FA + a_2MD)/[1 + \exp.(a_0 + a_1FA + a_2MD)]$, where a_0 is a constant, and a_1 and a_2 are the regression coefficients for FA and MD, respectively.

2.6. Statistical analysis

All quantitative values are given presented as the mean ± standard deviation (SD), including age, body mass index (BMI), education, FA and MD values and blood glycated hemoglobin (HbA1c), uric acid, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) levels. The quantitative values among the three groups were compared by one-way analysis of variance (ANOVA) statistical analysis. If there was a significant difference among the three groups, then the t-test was used for further statistical analysis of each pair of groups.

Qualitative data, including sex, hypertension, retinopathy, microalbuminuria, and statin treatment, were evaluated using Chi-squared

Table 1
Demographics and clinical characteristics of subjects.

Characteristics	HCs (n = 26)	T2DM-NC (n = 20)	T2DM-C (n = 20)	p value
Age	42.5 ± 10.4	41.7 ± 9.5	47.3 ± 8.2	0.130
Sex (F/M)	10/10	7/13	10/10	0.203
BMI (kg/m^2)	23.3 ± 3.6	26.1 ± 3.6	25.2 ± 3.5	0.033
Presence of hypertension	2 (7.7%)	8 (40%)	11 (55%)	0.002
Stage 1	2 (7.7%)	1 (5%)	3 (15%)	
Stage 2	0 (0%)	4 (20%)	5 (25%)	
Stage 3	0 (0%)	3 (15%)	3 (15%)	
Duration (months)	–	24 ± 1.216	60 ± 1.240	0.127
UACR	–	15.7 ± 24.294	19.7 ± 26.159	0.018
HbA1c	5.6 ± 0.2	10.5 ± 1.9	9.6 ± 2.9	< 0.001
Uric acid	292.5 ± 72.7	335.7 ± 92.8	342.5 ± 100.2	0.157
Statin use	0 (0%)	4 (20%)	5 (25%)	0.030
Total cholesterol	5.06 ± 1.1	4.51 ± 1.11	4.69 ± 1.51	0.374
Triglycerides	0.97 (0.39, 2.78)	1.65 (0.86, 6.29)	1.24 (0.91, 7.33)	0.013
HDL-C	1.49 ± 0.35	1.01 ± 0.22	1.08 ± 0.30	< 0.001
LDL-C	3.42 ± 0.88	2.83 ± 0.89	3.01 ± 1.03	0.128

UACR: Urinary albumin-to-creatinine ratio. HDL-C: high-density lipoprotein cholesterol. LDL-C: low-density lipoprotein cholesterol. HbA1c: glycated hemoglobin.

test. The duration of diabetes was analyzed using the Kruskal-Wallis test.

3. Results

3.1. Demographic and clinical analysis

We recruited 66 participants in this study, including HCs and T2DM-NC and T2DM-C patients. All participants were middle-aged, and the mean age was 43 years (23–59 years). The HCs group consisted of 10 males and 16 females, aged 42.5 ± 10.4 years (mean ± SD). The T2DM-NC group consisted of 13 males and 7 females, aged 41.7 ± 9.5 years. The T2DM-C group consisted of 10 males and 10 females, aged 47.3 ± 8.2 years. Table 1 shows that there were no significant differences among the groups in age (p value = .130), sex (p value = .203), or uric acid (p value = .157), TC (p value = .374), or LDL-C (p value = .128) concentration. Additionally, there was no difference in the diabetes duration between the T2DM-NC and T2DM-C groups (p value = .127).

Table 1 indicates that there were significant differences among the groups in BMI (p value = .033), the presence of hypertension (p value = .002), and the concentrations of HbA1c (p value < .001), TG (p value = .013), and HDL-C (p value < .001). There was an obvious significant difference between the T2DM-NC and T2DM-C groups in the presence of microvascular complications (p value < .001). In addition, T2DM-C contained more patients undergoing statin treatment than did the T2DM-NC group (p value = .030). Post-Hoc analysis showed that T2DM patients had a higher mean level of triglyceride (T2DM-NC vs. HCs, p = .001; T2DM-C vs. HCs, p = .011) and lower mean level of high density lipoprotein cholesterol (T2DM-NC vs. HCs, p < .001; T2DM-C vs. HCs, p < .001), higher prevalence of hypertension (T2DM-NC vs. HCs, p = .008; T2DM-C vs. HCs, p < .001) and higher statin usage (T2DM-NC vs. HCs, p = .017; T2DM-C vs. HCs, p = .007). However, there was no significant difference between T2DM-NC and T2DM-C groups in either demographic or clinical characteristics by Post-Hoc analysis.

3.2. FA image analysis

Fig. 1 showed that the FA values were decreased in the corpus callosum, bilateral anterior limb of the internal capsule, right retrolenticular part of the internal capsule, bilateral posterior thalamic radiation, right superior longitudinal fasciculus, bilateral superior corona radiata and left middle frontal gyrus in the T2DM-C group compared with the HCs group (p value < .01). The FA values were decreased in the corpus callosum, bilateral fornix, right retrolenticular part of the internal capsule, middle cerebral peduncle, right superior longitudinal fasciculus, right posterior thalamic radiation, and left middle frontal gyrus in the T2DM-C group compared with the T2DM-NC group (p value < .01). No significant decrease in FA values was observed between the HCs and T2DM-NC groups (p value < .05).

3.3. MD image analysis

Fig. 2 shows that the MD values were increased in the corpus callosum, bilateral anterior limb of the internal capsule, right retrolenticular part of the internal capsule, bilateral posterior thalamic radiation, right superior longitudinal fasciculus, bilateral superior corona radiata and left middle frontal gyrus in the T2DM-C group compared with the HCs group (p value < .01). The MD values were increased in the corpus callosum, bilateral fornix, right retrolenticular part of the internal capsule, middle cerebral peduncle, right superior longitudinal fasciculus, right posterior thalamic radiation, and left middle frontal gyrus in the T2DM-C group compared with the T2DM-NC group (p value < .01). No significant increase in the MD values was observed between the HCs and T2DM-NC groups (p value > .05). However, the degree of change was less for the MD values than for the FA values.

3.4. ROC curve analysis

FA and MD values were used to investigate two groups of subjects (i.e., T2DM-C and T2DM-NC groups) by ROC curve analysis. We measured the values of DTI parameters in the corpus callosum of all subjects. As shown in Fig. 3, the area under the curve (AUC) for FA was 0.872 (95% confidence interval: 0.716–0.947), while the AUC for MD was 0.751 (95% confidence interval: 0.611–0.835). The sensitivity and specificity of FA values for detecting WM bundle injury were higher than those of MD values in patients with T2DM.

4. Discussion

Noncommunicable chronic diseases have become the main cause of death and social burden worldwide. With improvements in living standards and changes in eating habits in China, the number of T2DM patients has grown continuously over recent years, creating a serious burden on the working population (Yang et al., 2010). Diabetes has become a social health problem, and the early and comprehensive detection of diabetes and its complications facilitates early clinical treatment, which may help improve patients' quality of life.

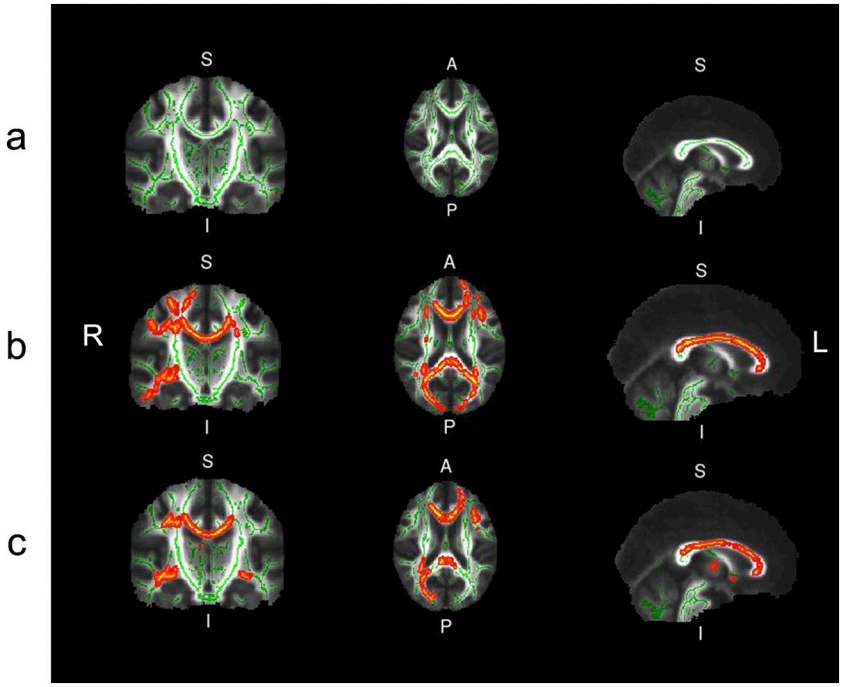

Fig. 1. a: there was no difference in FA between the HCs and T2DM-NC groups. b: the FA values were decreased in the corpus callosum, bilateral anterior limb of the internal capsule, right retrolenticular part of the internal capsule, bilateral posterior thalamic radiation, right superior longitudinal fasciculus, bilateral superior corona radiata and left middle frontal gyrus in the T2DM-C group compared with the HCs group. c: the FA values were decreased in the corpus callosum, bilateral fornix, right retrolenticular part of the internal capsule, middle cerebral peduncle, right superior longitudinal fasciculus, right posterior thalamic radiation, and left middle frontal gyrus in the T2DM-C group compared with the T2DM-NC group. All results were obtained by FSL-TBSS analysis. A standard MNI152-T1 1-mm brain space was used as a background image (grayscale). Red-yellow: a colourmap corresponding to thresholding the results at p value < .01. Green: FA skeleton with a threshold of 0.2 highlighting the fibers used in the comparison.

In the brain WM occupies a very important structural position and constitutes an integral part of the distributed neural network. Human cognition depends on the neuron connection and activity of cortical neurons, WM disorders have been investigated and found to be inextricably linked with neurological dysfunction (Roth and Dicke, 2005; Filley and Fields, 2016). In this study, we found that the integrity of the WM in the corpus callosum, bilateral anterior limb of the internal capsule, right retrolenticular part of the internal capsule, bilateral posterior thalamic radiation, right superior longitudinal fasciculus, bilateral superior corona radiata, left middle frontal gyrus, bilateral fornix, and middle cerebral peduncle was injured. There was a significant difference not only between the T2DM-C patients and HCs, but also between T2DM patients with and without microvascular complications, indicating that microvascular disease may increase T2DM-related WM damage.

Some previous studies have investigated WM changes in T2DM patients. Zhang et al. have suggested that there is widespread WM impairment in T2DM patients compared with HCs, including in the corpus callosum and external capsule, which is consistent with our experimental results (Zhang et al., 2014). The significant changes of DTI parameters in Zhang J's study involved increased FA, decreased MD and increased radial diffusivity (λ_{23}). Zhang et al. reported decreased FA values in T2DM patients in the corpus callosum, hippocampus, cingulate fasciculus, and other areas (Zhang et al., 2016). Van Bloemendaal et al. found that only the axial diffusivity (λ_1) was significantly different and that there were no significant differences in FA

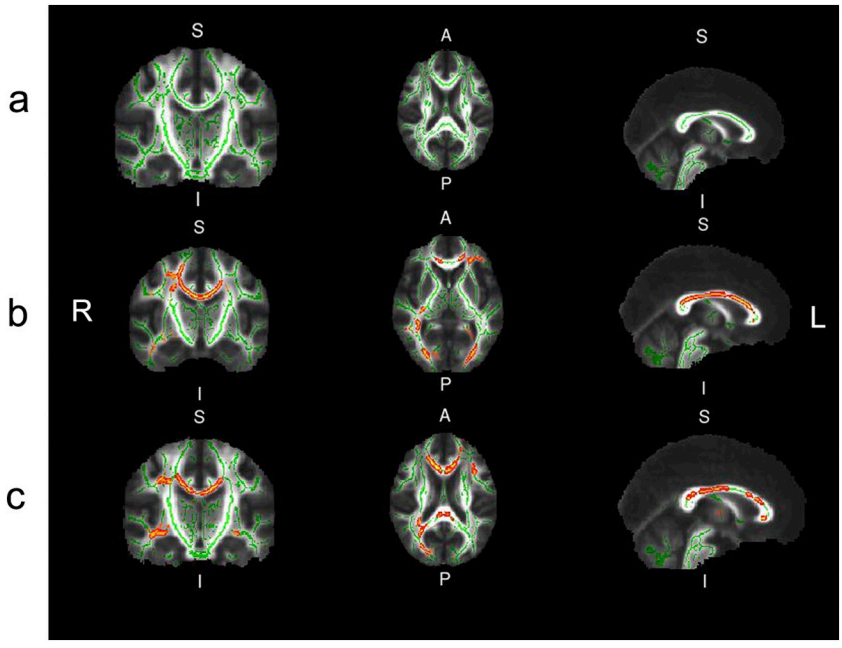

Fig. 2. a: there was no difference in MD between the HCs and T2DM-NC groups. b: the MD values were increased in the corpus callosum, bilateral anterior limb of the internal capsule, right retrolenticular part of the internal capsule, bilateral posterior thalamic radiation, right superior longitudinal fasciculus, bilateral superior corona radiata and left middle frontal gyrus in the T2DM-C group compared with the HCs group c: the MD values were increased in the corpus callosum, bilateral fornix, right retrolenticular part of the internal capsule, middle cerebral peduncle, right superior longitudinal fasciculus, right posterior thalamic radiation, and left middle frontal gyrus in the T2DM-C group compared with the T2DM-NC group. All results were obtained by FSL-TBSS analysis. A standard MNI152-T1 1-mm brain space was used as a background image (grayscale). Red-yellow: a colourmap corresponding to thresholding the results at p value < .01. Green: FA skeleton with a threshold of 0.2 highlighting the fibers used in the comparison.

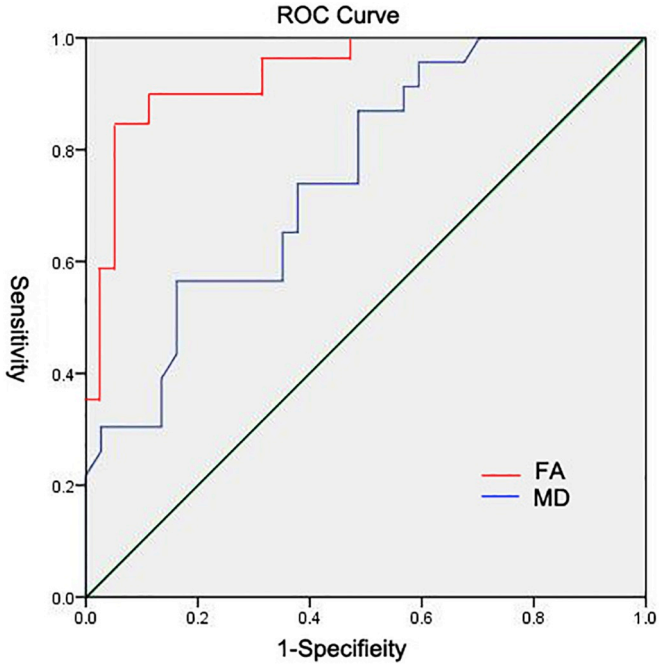

Fig. 3. ROC curves of FA (in red) and MD (in blue) for distinguishing T2DM-C and T2DM-NC patients.

or MD among T2DM patients and obese or lean HCs, but this result was further explained by the Body Mass Index (BMI), rather than T2DM (van Bloemendaal et al., 2016). In addition, other studies have shown WM microstructural damage in T2DM patients (Tan et al., 2016; Hsu et al., 2012; Sun et al., 2018). However, in the above research, the subjects were all elderly people; in our study, the subjects were all middle-aged people. Thus, our research may be more meaningful for solving public health problems. With the continuous development of imaging technology, MRI may be used to diagnose diabetes mellitus with WM bundle injury. This may help clinicians to take appropriate measures to actively prevent diabetes complications such as some mental disorders. Rofey et al. performed a pilot study and revealed that the microstructural integrity of WM was significantly different among adolescents with T2DM, obese adolescents and normal HCs Rofey et al., 2015. In our study, the ROC curve analysis further confirmed that FA and MD values may be helpful to determine the presence of microvascular complications in T2DM patients.

Few previous studies have further grouped T2DM patients according to the presence of microvascular complications and compared them in terms of WM integrity. Metabolic disorders in T2DM patients can cause a series of vascular conditions, such as retinopathy, nephropathy, and diabetic peripheral neuropathy (DeFronzo et al., 2015). In our study, we found that the integrity of the WM was compromised in T2DM patients with microvascular complications compared to patients without microvascular complications, and the integrity of the WM was not significantly different between T2DM-NC and HC groups. Microvascular lesions may cause impairment of the WM bundles. Other studies have confirmed the relationship between microvascular disease and cognitive dysfunction in diabetes (Manschot et al., 2007; McCrimmon et al., 2012), thus we can further infer that there may be a correlation between microvascular complications and cognitive dysfunction.

In conclusion, our results suggest that WM impairment is present in working-aged T2DM patients and that the integrity of the WM in T2DM patients with microvascular complications is compromised compared to that in patients without microvascular complications. However, this study also has some shortcomings, including that patients with T2DM-C have hypertension which may be one of the causes of the results. We believe that after further experimental studies, WM injury in T2DM patients may be clinically diagnosed by functional MRI mode, providing new basis for early diagnosis and treatment.

Declaration of Competing Interest

The authors report no conflicts of interest.

Acknowledgments

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