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Association between microstructural white matter abnormalities and cognitive functioning in patients with type 2 diabetes mellitus: a diffusion tensor imaging study

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Abstract

Background: Diffusion tensor imaging (DTI) technique is important for exploring more sensitive imaging-based biomarkers in prevention and early treatment of cognitive dysfunction induced by type 2 diabetes mellitus (DM).

Objectives: To predict early cognitive dysfunction and detection of microstructural white matter changes in patients with type 2 DM by diffusion tensor imaging.

Patients and methods: A case-control study included thirty patients aged ≥ 18 years old of both sexes with type 2 DM and 30 controls. All subjects underwent to Montreal Cognitive Assessment (MoCA) "Arabic version": to detect mild cognitive impairment (MCI) and diffusion tensor imaging study (DTI).

Results: Mild cognitive impairment is related to type 2 DM (56.7% of diabetic group), reduced fractional anisotropy (FA) values, and elevated mean diffusivity (MD) values were related to cognitive impairment evaluated through Montreal Cognitive Assessment (MoCA) in patients with type 2 DM.

Conclusion: The integrity of the white matter measured using DTI vary in MCI diabetics compared with non-MCI diabetics. Such changes have major implications on the cognitive function.

Keywords: Type 2 DM, Mild cognitive impairment, Diffusion tensor imaging

Introduction

Diabetes mellitus (DM) afflicts nearly 382 million people worldwide, a number that is predicted to reach more than 592 million by the year 2035 [1]. Many studies have also raised concerns about the long-term consequences of poor glycemic control on the impairment of cognitive function [2, 3]. Its effects on higher mental functions are frequently ignored because of the lack of obvious signs and the lack of standard evaluation techniques [4]. Many studies have reported a cognitive impairment in T2DM [5]. And that type 2 diabetes is associated with around a 1.5- to 2.5-fold increase in dementia risk [6, 7]. Bruce et al. found that about 17% of the elderly patients with diabetes had moderate to serious impairments in everyday life tasks, 11% had a cognitive impairment [8]. This cognitive impairment can be due to cerebral white matter conditions, related to cerebrovascular lesions such as lacunar infarctions, hyperintensities of white matter (WMHs), and microstructural lesions [9, 10].

Neuroimaging with diffusion tensor imaging (DTI). It is a process for describing microstructural changes or differences with neuropathology and gives details about the quality of the white matter tracts. DTI calculates the

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fractional anisotropy [FA], which is a measure of the diffusion directionality and the mean diffusivity [MD], which is a directionally averaged measure of diffusion, FA, and MD values vary from 0 to 1 [11].

Diffusion tensor imaging (DTI) is sensitive for measuring the development of the microstructure and integrity of white matter (WM) fiber tracts during the asymptomatic stage of AD [12, 13]. Fractional anisotropy (FA) and mean diffusivity (MD) describes fiber density, axonal diameter, and myelination in white matter (WM) based on quantitative measure of the degree of diffusion anisotropy [9]. The decreased FA and increased MD in mild cognitive impairment (MCI) are signs of the disruption of WM [14, 15]. Thus, DTI technique is important for exploring more sensitive imaging-based biomarkers in the prevention and early treatment of cognitive dysfunction induced by type 2 DM.

Aim of the work

To estimate the frequency of early cognitive dysfunction and to detect changes in microstructural white matter in patients with type 2 DM by means of diffusion tensor imaging.

Patients and methods

This case-control study was carried out in the Neurology Outpatient Clinic, Neurology Department and MRI unit, Diagnostic and Interventional Radiology Department of Suez Canal University Hospital, Ismailia, Egypt. Thirty adult patients aged ≥ 18 years old of both sexes with type 2 DM were included. Patients with type 1 DM, hypertension, history of cerebrovascular accidents, and dementia were excluded. Another 30 healthy subjects matched by ages and sex were included as a control group.

All the patients and control subjects had undergone the following:

History taking

History taking includes age, type of DM, the duration of DM, and type of treatment.

General examination and full neurological evaluation for identification of focal neurological deficit in patients.

Investigations

A fasting and post prandial blood sugar to confirm diagnosis of diabetes mellitus (FPG ≥ 126 mg/dl (7.0 mmol/l), while post prandial 2-h plasma glucose ≥ 200 mg/dl (11.1 mmol/l) [16]. B-glycated hemoglobin (HbA 1c): those with HbA1c levels of 6.5% or higher have diabetes [17]. The reference ranges were good control less than 7%; moderate control, 7–9%; and poor control, more than 9% [18].

Cognitive testing

Montreal Cognitive Assessment scale (MoCA) [19]. All subjects underwent cognitive assessment using the Arabic translated form of Montreal Cognitive Assessment to confirm the presence of mild cognitive impairment [19]. The MoCA's original validation analysis proposed a cut-off value of ≥ 26 out of 30 points to distinguish healthy subjects from mild cognitive impairment (MCI) [20].

MR imaging protocol

To get higher signal-to-noise ratio (SNR) and motion-free DTI, we used parallel imaging methods and single-shot spin-echo echo-planar imaging (EPI). Depending on the section numbers the total time for imaging of DTI was 7–9 min, in addition to the standard MR imaging exam time [21].

Acquisition of MR images

A 1.5-T MR unit has been used (Achieva; Philips Medical Systems, The Netherlands). T1-weighted sequences before and after paramagnetic contrast material given intravenously, T2-weighted sequences, and fluid-attenuated inversion recovery (FLAIR) sequences were acquired. Using a single-shot echo-planar image sequence with sensitivity encoding, or SENSE, parallel image scheme (reduction factor, 2), DT image data were obtained. The frame matrix was 128 × 128, with a 220 × 220 mm field of view. Parallel to the anterior commissure —posterior commissure line— were acquired transverse sections of 2.75 mm thickness. A total of 50 sections, without gaps, filled the entire hemisphere and brainstem. Thirty-two separate orientations represented diffusion weighting and the *b* value was 800 mm^2/s. Other parameters for the imaging were echo time = 70 ms, repetition period = 6599–8280 ms, number of acquisitions = two [21].

Data processing

We moved the image data for the diffusion-tensor to an offline workstation (extended MR "EWS" workspace, Philips Medical Systems) which is based on the Continuous Tracking Fiber Assignment (FACT) process. Anisotropy was determined using orientation-independent fractional anisotropy (FA) and diffusion-tensor MR color maps based on the values of FA and the three vector elements were developed. Through linking voxel to voxel with the FACT algorithm, three-dimensional FA was then acquired. The fiber tracking termination threshold values for FA were less than 0.15 and for the trajectory angles between the ellipsoids greater than 27° [21].

Three-dimensional tract reconstruction

We used a multi-region-of-interest (ROI) approach to recreate tracts of interest, which utilize established anatomical knowledge of tract trajectories. Tracking was carried out

from all pixels within the brain ("brute force" approach), and tests penetrating the manually identified ROIs were allocated to the different tracts associated with the ROIs. By using multiple ROIs for a tract of interest, we used three types of operations, AND, OR, and NOT, whose preference depended on the trajectory characteristic of each tract. Both FA and MD have been calculated on the following tracts on both sides: Superior longitudinal fasciculus, inferior longitudinal fasciculus, uncinate fasciculus, corpus callosum (splenium), and corpus callosum (Genu) [21].

The study was accepted by the Ethical Committee of Suez Canal Faculty of Medicine. Prior to inclusion in the study, written, informed consent was obtained from all the participants.

Statistical analysis

Using IBM SPSS software package version 20.0, data was fed to the computer and analyzed. (Armonk, NY: Published 2016 by IBM Corp). Using number and percent, qualitative data were represented. The Kolmogorov-Smirnov test had been used to check distribution normality. Quantitative data were represented using the range (minimum and maximum), mean, standard deviation and median. Data were tabulated and statistically analyzed to determine the difference between the groups under study with respect to the different parameters.

Descriptive statistics

For representing both quantitative and qualitative variables, frequencies were used. Mean and standard deviation (± SD) were only used for quantitative variables.

Analytical statistics

Student's t tests were used to compare two means. ANOVA was used for comparing between more than two groups and followed by post hoc test (Tukey) for pair wise comparison. The chi-square test (Fisher or Monte Carlo) was used to analyze the difference between various proportions at the level of 95%. Mann-Whitney test was used to compare between two groups for not normally distributed quantitative variables p value indicates level of significance [22].

Results

This study included 60 subjects, 30 diabetic patients, and 30 nondiabetic subjects as a control. The age of the diabetic group ranged between 60 and 69 years with a mean (63.57 ± 2.8) and for the control group ranged between 60 and 67 years with a mean (62.77 ± 2.21). Seventeen subjects (56.7%) are males and 13 (43.3%) are females in diabetic group, while in control group, 19 subjects (63.3%) are males and 11 subjects (36.7%) are females. There is no statistically significant difference between both groups regarding age and sex (Table 1).

Table 1 Demographic data of diabetics and controls

	Controls (n = 30)	Diabetics (n = 30)	Test of Sig.	p
Age (years)				
Range	60–67	60–69	t = 1.229	0.224
Mean ± SD	62.77 ± 2.21	63.57 ± 2.80		
Sex				
Male	19 (63.3)	17(56.7)		
Female	11 (36.7)	13(43.3)	χ^2 = 0.278	0.598

t Student's t test, χ^2 chi-square test, p p value for comparing between the studied groups

Mild Cognitive Impairment (MoCA score: 22–25) is highly significantly more frequent in the diabetics (56.7%) ($p < 0.01$). The mean value of total MoCA score is highly significantly lower in diabetics (24.87 ± 2.01) than in the non-diabetics (27.90 ± 0.76) ($p < 0.01$). Cognitive domains in MoCA scale that are mainly affected in the diabetic group are: orientation, short-term memory/delayed recall, executive functions/visuospatial, language, and attention. Abstraction and animal naming show no statistical difference between both groups (Table 2).

The mean duration of treatment among diabetic subjects is (3.17 ± 1.27) years. Ten patients (33.3%) are treated for less than 2 years and 20 patients (66.7%) are treated for more than 2 years. Mean values of the duration of treatment in diabetics with MCI (2.77 ± 1.1) years show no significant statistical difference than duration of treatment in diabetics without MCI (3.47 ± 1.33) years ($p > 0.05$). Moderate and poor glycemic control are significantly more frequent in diabetics with MCI ($p < 0.01$) (Table 3).

Table 2 Montreal Cognitive Assessment scale in diabetics and controls

	Controls (n = 30)	Diabetics (n = 30)	Test of sig.	p
MoCA				
MCI (22-25)	0 (0%)	17 (56.7%)	χ^2 = 23.721*	< 0.001*
Normal (≥ 26)	30 (100%)	13 (43.3%)		
MoCA total score	27.9 ± 0.8	24.9 ± 2	t = 7.724*	< 0.001*
Orientation	5.5 ± 0.6	4.7 ± 0.6	t = 5.086*	< 0.001*
Short-term memory	4.6 ± 0.5	3.7 ± 0.6	t = 6.188*	< 0.001*
Executive	4.5 ± 0.5	4 ± 0.6	t = 3.893*	< 0.001*
Language	3	2.6 ± 0.5	t = 4.097*	< 0.001*
Abstraction	2	2 ± 0	–	–
Animal naming	3	3 ± 0	–	–
Attention	5.3 ± 0.5	4.8 ± 0.7	t = 2.904*	0.005*

Data was expressed by using (mean ± SD), χ^2 chi-square test, t Student's t test, p p value for comparing between the studied groups
*Statistically significant at $p \leq 0.05$
MoCA Montreal Cognitive Assessment scale, *MCI* mild cognitive impairment.

Table 3 Relation between Montreal Cognitive Assessment scale and duration of treatment in diabetic subjects

	MOCA		Test of sig.	p
	Diabetics without MCI (*n* = 13)	Diabetics with MCI (*n* = 17)		
Duration of treatment(year)				
≤ 2 years	5 (38.5%)	5 (29.4%)	$\chi^2 = 0.271$	$^{FE}p = 0.705$
> 2 years	8 (61.5%)	12 (70.6%)		
Min.–Max.	1.5–6	1–5	$U = 74.0$	0.133
Mean ± SD	2.8 ± 1.1	3.5 ± 1.3		
HbA1c				
Good control	0 (0%)	8 (61.5%)	$\chi^2 = 16.467^*$	$^{MC}p = < 0.001^*$
Moderate control	4 (30.8%)	7 (41.2%)		
Poor control	1 (7.7%)	10 (58.8%)		

χ^2 chi-square test, *MC* Monte Carlo, *FE* Fisher's exact, *U* Mann-Whitney test, *p p* value for comparing between the studied groups
*Statistically significant at $p \leq 0.05$
MoCA Montreal Cognitive Assessment scale, *MCI* mild cognitive impairment, *HbA1c* glycosylated hemoglobin.

Fractional anisotropy in diabetic patients with MCI is highly significantly reduced at all selected tracts than diabetic patients without MCI and controls. Mean diffusivity in diabetic patients with MCI is highly significantly elevated at all selected tracts than diabetic patients without MCI and controls (Table 4).

Figure 1 shows the detailed tractography of the right uncinated fasciculus (UNC) in a normal subject. Figure 2 shows the detailed tractography of the right

Table 4 Fractional anisotropy and mean diffusivity of controls, diabetics without mild cognitive impairment, and diabetics with mild cognitive impairment

		Control *n* = 30)	Diabetics		*F*	*p*	p_1	p_2	p_3
			Without MCI (*n* = 13)	With MCI (*n* = 17)					
SLF FA	Right	0.48 ± 0.04	0.46 ± .047	0.40 ± .073	12.394*	< 0.001*	0.673	< 0.001*	0.005*
	Left	0.47 ± 0.03	0.44 ± 0.04	0.38 ± 0.07	20.329*	< 0.001*	0.147	< 0.001*	0.002*
ILF FA	Right	0.39 ± 0.05	0.48 ± 0.10	0.37 ± 0.04	12.293*	< 0.001*	< 0.001*	0.442	< 0.001*
	Left	0.4 ± ±0.03	0.48 ± 0.10	0.33 ± 0.04	28.890*	< 0.001*	< 0.001*	< 0.001*	< 0.001*
UNC FA	Right	0.43 ± 0.04	0.48 ± 0.12	0.39 ± 0.05	7.837*	0.001*	0.034*	0.121	0.001*
	Left	0.42 ± 0.04	0.47 ± 0.10	0.34 ± 0.04	19.967*	< 0.001*	0.091	< 0.001*	< 0.001*
CCS FA	Right	0.44 ± 0.08	0.50 ± 0.08	0.38 ± 0.04	11.778*	< 0.001*	0.018*	0.019*	< 0.001*
	Left	0.41 ± 0.02	0.47 ± 0.11	0.33 ± 0.03	25.579*	< 0.001*	0.004*	< 0.001*	< 0.001*
CCG FA	Right	0.40 ± 0	0.48 ± 0.10	0.38 ± 0.04	15.194*	< 0.001*	< 0.001*	0.563	< 0.001*
	Left	0.44 ± 0.02	0.47 ± 0.11	0.34 ± 0.04	27.118*	< 0.001*	0.186	< 0.001*	< 0.001*
SLF MD	Right	0.70 ± 0.07	0.72 ± 0.10	0.79 ± 0.07	6.440*	0.003*	0.947	0.003*	0.033*
	Left	0.7 ± ±0.08	0.73 ± 0.03	0.83 ± 0.08	15.162*	0.001*	0.582	0.001*	0.002*
ILF MD	Right	0.74 ± 0.03	0.71 ± 0.07	0.80 ± 0.04	16.340*	< 0.001*	0.205	< 0.001*	< 0.001*
	Left	0.75 ± 0.03	0.73 ± 0.09	0.84 ± 0.05	20.460*	< 0.001*	0.294	< 0.001*	< 0.001*
UNC MD	Right	0.75 ± 0.03	0.70 ± 0.07	0.79 ± 0.06	15.219*	< 0.001*	0.005*	0.008*	< 0.001*
	Left	0.75 ± 0.03	0.72 ± 0.08	0.83 ± 0.05	19.609*	< 0.001*	0.161	< 0.001*	< 0.001*
CCS MD	Right	0.76 ± 0.03	0.71 ± 0.06	0.79 ± 0.05	13.308*	< 0.001*	0.003*	0.042*	< 0.001*
	Left	0.77 ± 0.03	0.72 ± 0.06	0.82 ± 0.05	22.582*	< 0.001*	0.001*	< 0.001*	< 0.001*
CCG MD	Right	0.76 ± 0.03	0.73 ± 0.04	0.79 ± 0.06	7.537*	0.001*	0.065	0.080	0.001*
	Left	0.74 ± 0.03	0.74 ± 0.05	0.82 ± 0.06	24.996*	< 0.001*	0.848	< 0.001*	< 0.001*

Data was expressed by using (mean ± SD), *MCI* mild cognitive impairment, *F F* for ANOVA test, pair wise comparison between each 2 groups was done using post hoc test (Tukey)
p_1 *p* value for comparing between control and diabetics without MCI
p_2 *p* value for comparing between control and diabetics with MCI
p_3 *p* value for comparing between diabetics without MCI and diabetics with MCI
*Statistically significant at $p \leq 0.05$
UNC Uncinate, *SLF* superior longitudinal fasciculus, *ILF* inferior longitudinal fasciculus, *CCS* corpus callosum splenium, *CCG* corpus callosum genu, *FA* fractional anisotropy, *MD* mean diffusivity

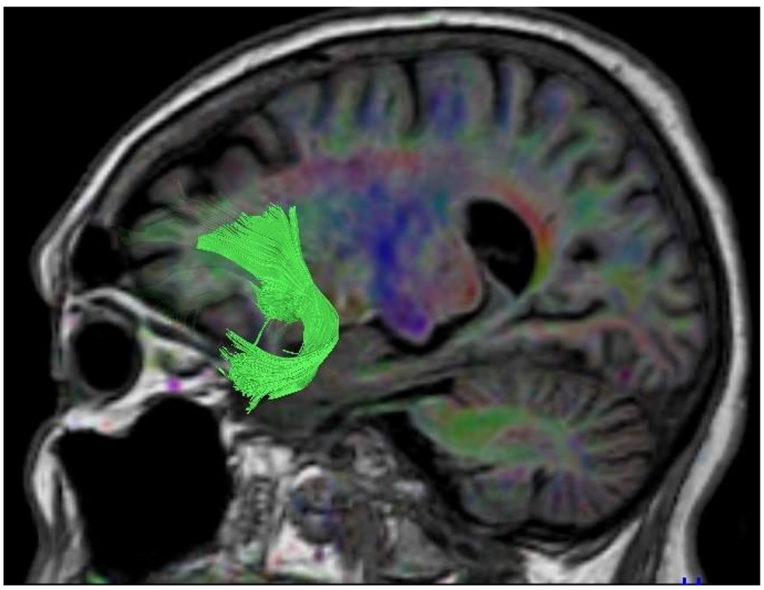

Fig. 1 Sagittal view of the detailed tractography of the right uncinated fasciculus (UNC) in a normal subject. Color coding is included to assist with identification of the fibers in the images. Fractional anisotropy (FA) and mean diffusivity (MD) are (0.50 ± 0.140) and (0.61 ± 0.198) respectively

superior longitudinal fasciculus (SLF) in a diabetic subject with mild cognitive impairment.

Fractional anisotropy in diabetic patients with MCI is highly significantly reduced at all selected tracts (except SLF) at left hemisphere than that at right hemisphere. Mean diffusivity in diabetic patients with MCI is highly significantly elevated at all selected tracts at left hemisphere than at right hemisphere (Table 5).

There was no significant statistical difference between fractional anisotropy and mean diffusivity and duration of treatment in diabetics at all selected tracts at left and right hemispheres (Table 6).

There was significant statistical difference between fractional anisotropy and mean diffusivity and glycemic control in diabetics at all selected tracts at left and right hemispheres except SLF (Table 7).

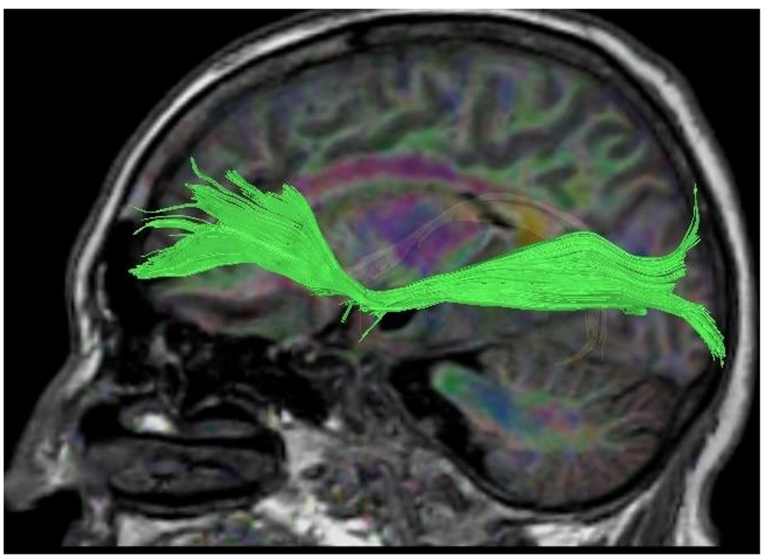

Fig. 2 Sagittal view of the detailed tractography of the right superior longitudinal fasciculus (SLF) in a diabetic subject with mild cognitive impairment. Color coding is included to assist with identification of the fibers in the images. Fractional anisotropy (FA) is reduced (0.239 ± 0.106) and mean diffusivity is elevated (MD) (0.986 ± 0.236)

Table 5 Fractional anisotropy and mean diffusivity at both right and left hemispheres in diabetics with mild cognitive impairment (n = 17)

	Right	Left	t	p
FA of selected tracts				
SLF FA	0.40 ± 0.073	0.38 ± 0.07	2.033	0.059
ILF FA	0.37 ± 0.04	0.33 ± 0.04	7.500*	< 0.001*
UNC FA	0.39 ± 0.05	0.34 ± 0.04	4.761*	< 0.001*
CCS FA	0.38 ± 0.04	0.33 ± 0.03	11.662*	< 0.001*
CCG FA	0.38 ± 0.04	0.34 ± 0.04	11.192*	< 0.001*
MD of selected tracts				
SLF MD	0.79 ± 0.07	0.83 ± 0.08	6.601*	< 0.006*
ILF MD	0.80 ± 0.04	0.84 ± 0.05	7.572*	< 0.001*
UNC MD	0.79 ± 0.06	0.83 ± 0.05	5.334*	< 0.001*
CCS MD	0.79 ± 0.05	0.82 ± 0.05	2.545*	0.022*
CCG MD	0.79 ± 0.06	0.82 ± 0.06	5.508*	< 0.001*

Data was expressed by using (mean ± SD), t Student's t test, p p value for comparing between right and left
*Statistically significant at $p \leq 0.05$
UNC uncinate, *SLF* superior longitudinal fasciculus, *ILF* inferior longitudinal fasciculus, *CCS* corpus callosum splenium, *CCG* corpus callosum genu, *FA* fractional anisotropy, *MD* mean diffusivity

Discussion

Many studies have built growing questions about mild cognitive impairment (MCI) in T2DM [3, 23–26]. In our study, 56.7% of the selected diabetic patients (17 patients) has mild cognitive impairment through assessment by MoCA scale and all control group show normal score. This comes in accordance with Naga Swetha and his colleagues (2017) when their results revealed that 57.3% of their selected diabetic patients had MCI [27]. In contrast, in many other studies, MCI prevalence was reported in patients with diabetes mellitus to be between 28 and 38% [28–31]. This difference may be due to different neuropsychological batteries used and most of those studies was done with young adults and exclude those of age more than 60 years. While the mean of our patients age was (63.57 ± 2.8) years.

In our study, specific cognitive domains of MoCA scale are affected in diabetics with MCI. Orientation, short-term memory, visuospatial/executive functions, language, and attention show significant statistical difference in diabetics with MCI. These findings are in line with those documented by Yue Wang and his colleagues 2015 [32] and Alagiakrishnan and his colleagues (2013) [33]. The cognitive impairment in T2DM is unclear, but

Table 6 Relation between mean values of fractional anisotropy, mean diffusivity and duration of treatment in diabetics (n = 30)

		Duration of treatment (years)			
		≤ 2 (n = 10)	> 2 (n = 20)	t	p
		Mean ± SD	Mean ± SD		
SLF FA	Right	0.42 ± 0.07	0.43 ± 0.06	0.271	0.788
	Left	0.39 ± 0.06	0.41 ± 0.07	1.05	0.300
ILF FA	Right	0.42 ± 0.08	0.42 ± 0.10	0.071	0.944
	Left	0.40 ± 0.11	0.39 ± 0.10	0.121	0.905
UNC FA	Right	0.43 ± 0.07	0.43 ± v0.11	0.126	0.901
	Left	0.40 ± 0.08	0.39 ± 0.11	0.353	0.749
CCSFA	Right	0.43 ± 0.08	0.44 ± 0.09	0	1.000
	Left	0.40 ± 0.09	0.39 ± 0.11	0.446	0.659
CCGFA	Right	0.42 ± 0.08	0.43 ± 0.09	0.226	0.823
	Left	0.40 ± 0.09	0.40 ± 0.11	0.109	0.914
SLF MD	Right	0.77 ± 0.07	0.76 ± 0.06	0.460	0.649
	Left	0.75 ± 0.08	0.80 ± 0.09	1.352	0.18
ILF MD	Right	0.76 ± 0.04	0.76 ± 0.08	0.109	0.914
	Left	0.79 ± 0.07	0.80 ± 0.10	0.201	0.842
UNC MD	Right	0.74 ± 0.06	0.76 ± 0.09	0.387	0.702
	Left	0.77 ± 0.06	0.79 ± 0.09	0.522	0.605
CCS MD	Right	0.75 ± 0.05	0.76 ± 0.07	0.352	0.748
	Left	0.77 ± 0.06	0.78 ± 0.08	0.488	0.629
CCG MD	Right	0.75 ± 0.05	0.77 ± 0.06	0.661	0.514
	Left	0.78 ± 0.07	0.79 ± 0.07	0.491	0.627

t Student's t test, p p value for associated between the three categories, *SLF* superior longitudinal fasciculus, *ILF* inferior longitudinal fasciculus, *UNC* uncinate, *CCS* corpus callosum splenium, *CCG* corpus callosum genu, *FA* fractional anisotropy, *MD* mean diffusivity

Table 7 Mean values of fractional anisotropy, mean diffusivity in diabetics according to glycemic control (n = 30)

		HbA1c			F	p
		Good control (n = 8) Mean ± SD	Moderate control (n = 11) Mean ± SD	Poor control (n = 11) Mean ± SD		
SLF FA	Right	0.45 ± 0.05	0.40 ± 0.09	0.43 ± 0.55	1.360	0.274
	Left	0.42 ± 0.04	0.39 ± 0.08	0.40 ± 0.06	0.445	0.645
ILF FA	Right	0.50 ± 0.09	0.43 ± 0.08	0.35 ± 0.02	12.761	< 0.001**
	Left	0.50 ± 0.10	0.40 ± 0.08	0.30 ± 0.02	17.329	< 0.001**
UNC FA	Right	0.50 ± 0.12	0.43 ± 0.10	0.37 ± 0.05	4.655	0.018**
	Left	0.49 ± 0.09	0.38 ± 0.08	0.33 ± 0.04	11.676	< 0.001**
CCS FA	Right	0.51 ± 0.07	0.44 ± 0.08	0.38 ± 0.03	9.859	0.001**
	Left	0.50 ± 0.10	0.38 ± 0.08	0.33 ± 0.03	13.326	< 0.001**
CCG FA	Right	0.50 ± 0.09	0.42 ± 0.08	0.38 ± 0.05	6.132	0.006**
	Left	0.51 ± 0.10	0.38 ± 0.08	0.33 ± 0.05	12.322	< 0.001**
SLF MD	Right	0.72 ± 0.01	0.80 ± 0.08	0.76 ± 0.09	4.627	0.01*
	Left	0.69 ± 0.05	0.79 ± 0.07	0.84 ± 0.08	9.98	0.001*
ILF MD	Right	0.70 ± 0.08	0.76 ± 0.05	0.81 ± 0.02	11.095	< 0.001**
	Left	0.70 ± 0.08	0.79 ± 0.06	0.87 ± 0.03	20.673	< 0.001**
UNC MD	Right	0.68 ± 0.08	0.73 ± 0.05	0.82 ± 0.03	16.769	< 0.001**
	Left	0.70 ± 0.08	0.77 ± 0.06	0.85 ± 0.01	16.986	< 0.001**
CCS MD	Right	0.69 ± 0.06	0.73 ± 0.04	0.82 ± 0.02	23.197	< 0.001**
	Left	0.70 ± 0.04	0.78 ± 0.06	0.83 ± 0.05	15.354	< 0.001**
CCG MD	Right	0.71 ± 0.02	0.74 ± 0.04	0.82 ± 0.03	27.863	< 0.001**
	Left	0.72 ± 0.02	0.77 ± 0.05	0.86 ± 0.03	35.023	< 0.001**

F *F* for ANOVA test, *p* *p* value for comparing between the different categories
**Highly statistically significant at $p \leq 0.01$
*Statistically significant at $p \leq 0.05$
UNC uncinate, *SLF* superior longitudinal fasciculus, *ILF* inferior longitudinal fasciculus, *CCS* corpus callosum splenium, *CCG* corpus callosum genu, *FA* fractional aniostropy, *MD* mean diffusivity

hyperglycemia, vascular disease, hypoglycemia, insulin resistance, amyloidosis, concomitant hypertension, and depression could play significant roles [34, 35].

In our study, we picked four tracts of white matter to be tested: superior longitudinal fasciculus, inferior longitudinal fasciculus, uncinate fasciculus, and corpus callosum "both genu and splenium." Consistent group differences in mean diffusivity values in the majority of tracts in both hemispheres, indicating that individuals with type 2 diabetes have abnormalities in the microstructure of the white matter.

In our study, fractional anisotropy in diabetic patients with MCI is highly significantly reduced at all selected tracts at "both right and left sides" than diabetic patients without MCI and controls. Mean diffusivity in diabetic patients with MCI is highly significantly elevated at all selected tracts at "both right and left sides" than diabetic patients without MCI and controls, FA changes had been less prominent. This can be inerpreted by the fact that the diffusion of white matter fibers is increased parallel (axial) and perpendicular (radial), which has a greater effect on the overall MD than on the axial and radial diffusion (FA) ratio.

Most researches showed a widespread decrease in FA or an rise in MD that could not be interpreted by vascular lesion or total brain volume differences [9, 36–38]. The least FA in this study is detected at the splenium of corpus callosum "mainly the left" with mean value 0.33 ± 0.03. This is similar to what is found by many studies confirming that corpus callosum may significantly contribute to the rate of cognitive decline [39–42]. In contrast, Zhang and his colleagues (2014) reported increase in MD in whole corpus callosum and superior longitudinal fasciculus related to MCI in their selected patients with T2DM [43].

In the majority of tracts in both hemisphere, we found significant group variations in MD values suggesting microstructural abnormalities in the white matter in type 2 diabetes patients. Such findings are consistent with previous reports from a type 2 diabetes study by DTI [9, 37].

We found that there is significant relation between cognitive decline assessed by MoCA scale and FA measured mainly at left SLF (p = 0.01). This matched with Menge and his colleagues who suggested that the FA

values of the SLF may be used as a clinical marker of cognitive function [44]. Also, Medina and his colleagues (2006) reported that white matter fibers which are deep in the posterior white matter especially the superior longitudinal fasciculus are influenced in patients with MCI relative to controls [45]. On the other hand, other studies founded no alterations in the corpus callosum of MCI patient [46–48].

We also found that there were more reduced FA and increased MD in the tested white matter tracts in left hemisphere than in the right with statsitical significance found between both hemispheres. This is the same as found by Zhang and his colleagues (2014) in their study [43]. This can be demonstrated by the HAROLD model (Hemispheric Asymmetry Reduction in Older Adults) [49] which claimed that decreases in age-related hemispheric asymmetry compensate the lower prefrontal activity lateralization during cognitive performance in older adults compared to younger ones.

In our study, duration of diabetes is not of statistical relation with the cognitive impairment found among diabetics with MCI. Same results was reported by Reijmer and his colleagues (2013) [9]. In contrast, Rosebud Roberts and his colleagues (2008) [50], Chen and his colleagues (2012) [51], and LIU and his colleagues (2017) [52] founded a statistical relation between MCI and duration of diabetes. The discrepancy in the results may be due to variations in the nature of the study, sources of research subjects, and variations in length or intensity of DM between subjects of research.

In our study, there is a statistical significance between the cognitive impairment and the degree of glycemic. We found that 41.2% of the diabetics with MCI were of moderate glycemic control with HbA1c = 7–9% and 58.8% had poor glycemic control with HbA1c > 9%. Several studies have shown that HbA1clevel and cognitive function have a very close relationship [3, 23–26, 53–61]. In the contrary, other studies founded that there is no significant relation between glycemic control and mild cognitive impairment [62, 63]. This discrepancy in confirming the relation between the glycemic control and cognitive decline rises from the point that studies which confirmed that point, were conducted mostly in patients above the mean age of 60 years, as our study.

Conclusion

Mild cognitive impairment is related to T2DM (56.7%). The integrity of the white matter measured using DTI vary in MCI diabetics compared with non-MCI diabetics. Such changes have major implications on the cognitive function. In left hemisphere, the FA values are statistically more reduced and MD values are statistically more elevated.

Abbreviations

CCG: Corpus callosum genu; CCS: Corpus callosum splenium; DM: Diabetes mellitus; DTI: Diffusion tensor imaging; FA: Fractional anisotropy; MCI: Mild cognitive impairment; MD: Mean diffusivity; MoCA: Montreal Cognitive Assessment scale; ILF: Inferior longitudinal fasciculus; SLF: Superior longitudinal fasciculus; UNC: Uncinate

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Authors' contributions

OA carried out the study conception and design, participated in its design and coordination, and drafted the manuscript. HT carried out the design of the study, the analysis, and interpretation of data and helped to draft the manuscript. NM participated in the sequence alignment, interpretation of data, and drafting of manuscript. AR carried out the study conception and design, and participated in its design. AH participated by acquisition of data and performed the statistical analysis. All authors read and approved the final manuscript.

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Availability of data and materials

The data can be publicly available at the Faculty of Medicine, Suez Canal University.

Ethics approval and consent to participate

The study was approved by the Ethics committee of Suez Canal Faculty of Medicine in 20 January 2016. Committee Number: 2612. An informed written consent was taken from all the participants in the study.

Consent for publication

Participants signed an informed consent for publication.

Competing interests

The authors declare that they have no competing interests (financial or non-financial).

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