White Matter Abnormalities in Type-2 Diabetes Patients with Mild Cognitive Impairment: A Diffusion Tensor Imaging Study

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Target Audience: Radiologists, MR technologists and clinicians who are interested in cognitive impairment in diabetes.

Introduction/Purpose: Patients with type 2 diabetes mellitus (T2DM) have considerably higher risk of developing cognitive impairment and dementia. A recent study has reported white matter (WM) integrity changes in T2DM patients with cognitive impairment in comparison with controls [1]. However, not all T2DM patients develop cognitive impairment. This raises an interesting and important question: whether the observed WM changes are contributable to diabetes, cognitive decline, or both. This study aims at addressing this question by studying WM alterations using diffusion tensor imaging (DTI) in three populations: T2DM patients with and without impaired cognition, and age-, gender- and education-matched healthy controls. In addition, the study also aims at correlating DTI changes with scores from neuropsychological assessments.

Methods: ***Patients***: With approval of the Institutional Review Board, 42 T2DM patients (based on diagnostic criteria of American Diabetes Association;52-72years) were recruited and divided into mild cognitive impairment (DM-MCI, n=20) and normal cognition (DM-NC, n=22) groups based on clinic symptoms and a battery of neuropsychological tests (Montreal Cognitive Assessment, Mini-Mental State Examination, Trail Making Tests, Auditory Verbal Learning Test, Hachinski test, and Activity of Daily Living test). 18 healthy controls (50-73years) were also enrolled in the study. Plasma fasting/postprandial glucose and Glycated hemoglobin A1c (HbA1c) were recorded. ***Imaging***: On a 3 Tesla MRI scanner (Discovery MR750, GE Health Care, Waukesha, Wisconsin, USA) with a 32-channel head coil, axial DTI images were obtained using a single-shot diffusion-weighted echo planar imaging sequence (TR/TE = 8500/66.3ms, FOV = 25.6×25.6cm^2, 70 slices, 64 diffusion-weighted directions with a b-value of 1000 s/mm^2). ***Data processing***: The FMRIB Software Library (FSL) with tract-based spatial statistics (TBSS) [2-3] was utilized to analyze the whole-brain DTI data and compare group differences using a standard atlas. Additionally, based on the skeleton created by FSL, regional fractional anisotropy (FA), mean diffusivity (MD), and the three diffusion eigenvalues were also evaluated on selected fibers or regions and compared among the three groups. Statistical analyses for group comparison were carried out using SPSS software (SPSS Inc., Chicago, IL).

Results: The DM-MCI group had higher level (p=0.008) of HbA1c (8.22±1.60%) than the DM-NC group (6.97±1.26%). Overall decreased FA and increased mean diffusivity (MD) (P<0.05) were observed between the DM-MCI and DM-NC groups in the whole-brain TBSS analysis (Fig. 1, left). In contrast, FA, MD and axial diffusivity (λ_1) exhibited no difference between the DM-NC and the control groups while radial diffusivity showed subtle changes only in specific regions (Fig. 1, right). The reduced FA and increased MD observed in the DM-MCI group were caused primarily by an elevated radial diffusivity (represented by λ_2). Atlas-based FA analyses on individual fiber tracts showed that the most pronounced FA reduction occurred in the internal capsule, corona radiate, and cingulum (hippocampus) (Tab. 1). Decrease in FA in specific fibers has been well correlated with the decreased neuropsychological scores in DM patients (see an example in Fig. 2).

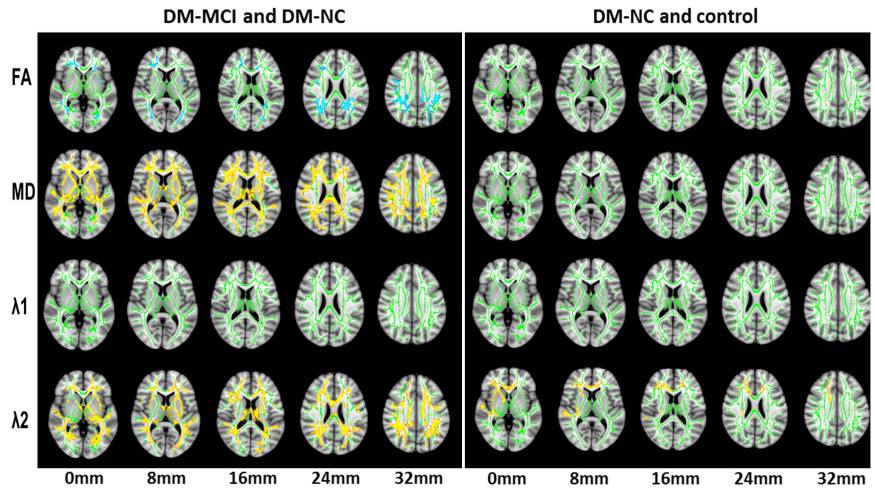

Fig. 1 FSL-TBSS analysis results showing the changes in FA, MD, λ_1 and λ_2 between subject groups. Green: mean FA skeleton (threshold = 0.2) without change. Light-blue: regions with decreased FA. red-yellow: regions with increased DTI metrics.

JHU WM Atlas	DM-MCI	DM-NC	t	p-val
ALIC.L	0.595±0.025	0.610±0.021	-2.083	0.04
ACR.R	0.472±0.024	0.487±0.019	-2.181	0.03
ACR.L	0.471±0.029	0.488±0.018	-2.391	0.02
CH.R	0.585±0.040	0.616±0.024	-3.101	0.00
CH.L	0.579±0.027	0.599±0.026	-2.439	0.01

Tab. 1 Difference (p<0.05) in mean FA values in selected fiber tracts between the DM-MCI and DM-NC groups. ALIC: Anterior limb of internal capsule. ACR: Anterior corona radiate.CH: Cingulum (hippocampus). R/L: right/left.

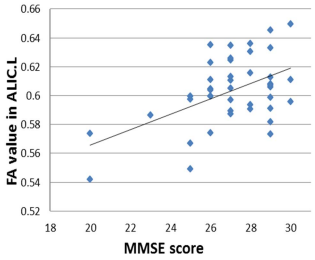

Fig. 2 Correlation between FA value and MMSE scores in the two DM groups in ALIC.L (r=0.51, p=0.001).

Discussion and conclusion: Our results suggested that the WM changes revealed by DTI are linked closely only to the sub-group of T2DM patients who exhibited mild cognitive impairment. Compromised myelin sheath, as indicated by the elevated radial diffusivity in the DM-MCI group, may explain the decreased FA and increased MD in T2DM patients whose poorer glucose control suggested by HbA1c may contribute to cognitive impairment and WM structural changes. Furthermore, the observed radial diffusivity change between the DM-NC and control groups (Fig 1, right) may indicate a very early phase of cognitive decline, which may be associated with T2DM, before the patients become symptomatic. Taking these together, this study provides new evidence to understand the cause for the WM structural changes in diabetes patients, and suggest DTI-based markers be used to assess the compromised cognition in T2DM.

References: [1] Zhang J, et al. Diabetes, 2014; 63(11):3596-605. [2] Jenkinson M, et al. FSL. Neuroimage. 2012; 15; 62(2):782-90. [3] http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS/UserGuide.[4] Smith SM, et al. Nat Protoc. 2007; 2(3):499-503