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Glymphatic System Impairment in Type 2 Diabetes Mellitus Associated with Cognitive Function

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Abstract: Objective: This study aims to investigate human glymphatic function in type 2 diabetes mellitus (T2DM) using the index for diffusion tensor image analysis along the perivascular space (DTI-ALPS) and to explore the relationship between this proposed measure of glymphatic clearance and cognitive functions. Methods: A total of 17 patients with T2DM and 20 age- and sex-matched health controls (HCs) were included in this study. All participants underwent neurological MRI and cognitive assessments. Both the average and bilateral DTI-ALPS indices, clinical and cognitive measurements were compared between the two groups. The correlations between DTI-ALPS indices and cognitive measurements were analyzed. Results: The average and right DTI-ALPS indices were significantly lower in the T2DM group than them in HC group (P = 0.011, P = 0.005). In HC group, the right DTI-ALPS index was higher than the left (P = 0.039), whereas no hemispheric difference was observed in T2DM. In correlation analyses, a lower DTI-ALPS index was associated with poorer TMT-B performance in T2DM (β = -0.502, P = 0.001), while no other significant correlations were found between DTI-ALPS index and cognitive measures in either group. Conclusion: This study demonstrated impaired glymphatic system function in T2DM patients and it is associated with worse performance in executive functions. The impaired glymphatic function in patients with T2DM may provide a new perspective for understanding the pathophysiology of T2DM-associated cognitive impairment.

Keywords: Diffusion tensor imaging; Glymphatic system; MRI; Type 2 diabetes mellitus.

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1. Introduction

Type 2 diabetes (T2DM) is the most common metabolic disease with a high incidence worldwide [1]. Brain damage caused by persistent hyperglycemia, which includes changes in neurophysiology and brain structures as well as the resultant

cognitive impairment involving memory, attention and executive functions, has emerged as an important risk factor for mild cognitive impairment (MCI), Alzheimer's disease (AD) and dementia [2,3]. With the increasing prevalence of diabetes and an aging population, the incidence of cognitive impairment is expected to increase gradually, posing great challenges for future health effects. Thus, identifying T2DM patients with high-risk for cognitive impairment and providing a preventive treatment is needed. However, understandings of potential therapeutic targets and mechanisms underlying the cognitive impairment associated with T2DM remains incomplete.

Since 2012, the brain glymphatic system has been discovered and identified the important role for clearing abnormal proteins and metabolites and maintaining brain homeostasis [4]. The glymphatic system transships metabolic waste and toxic substances from the brain through the perivascular space (PVS) to the dural lymphatic vessels, and finally to the extracranial deep cervical lymph nodes [5]. Accumulating evidences have indicated that impaired glymphatic system function is one of the pathophysiological mechanisms mediating neurodegenerative diseases and accelerating their progression, which is also closely related to advanced cognitive functions [6]. It has been hypothesized that failure to clear soluble amyloid-beta from perivascular space contributes to the accumulation of amyloid plaques and the progression of AD. Therefore, glymphatic disruption is considered the final common pathway for dementia and the function of brain glymphatic system might be used as a potential biomarker of cognitive decline.

At present, dynamic contrast enhanced MRI (DCE-MRI) is mainly used to evaluate the function of the human brain glymphatic system. After injecting contrast agent into the sheath of the subjects, the glymphatic system function of different brain regions was evaluated by measuring the change of T1-weighted signals over time to calculate the time required to produce tracer clearance [7]. Similarly, positron emission tomography (PET) also can be used to study the removal and drainage of perivascular space fluids [8]. The above two methods can obtain dynamic visualized fluid images of the whole brain glymphatic system. However, the injection of imaging agents or radionuclides are invasive, and multiple imaging must be performed within a few hours to a few weeks after DCE-MRI injection of contrast agents, making it difficult to carry out widespread application. Furthermore, PET has limited anatomical resolution and can only describe cerebrospinal fluid movement at the macroscale.

Recently, Taoka et al. proposed a new non-invasive alternative called diffusion tensor image analysis along the perivascular space (DTI-ALPS) to evaluate the human glymphatic function on diffusion tensor imaging (DTI) and susceptibility weighted imaging (SWI) [9]. This method measured the diffusivity perpendicular to the ventricular wall at the lateral ventricle body level to represent the interstitial fluid flow along the PVS. The ALPS index was calculated to quantificationally evaluate the glymphatic function. So far, DTI-ALPS has been used to assess the function of the glymphatic system in a variety of neurological disorders, including AD, dementia, Parkinson's disease (PD), cerebral small vessel disease (CSVD), ischemic stroke, attention deficit/hyperactivity disorder and idiopathic normal pressure hydrocephalus [10–15].

So far, cumulative evidences have confirmed the presence of a mass of toxic substances in diabetic brain tissues, including amyloid-β, hyperphosphorylated Tau, and advanced glycation end products [16–20]. Yang et al. also demonstrated ALPS-index was associated with the severity of T2DM, which suggested that disruption of the glymphatic system was also existed in T2DM. However, there is still lack of evidence about mechanisms underlying the associations between glymphatic functions and cognitive decline within T2DM. Thus, this study aims to investigate glymphatic function in T2DM using the DTI-ALPS index and to explore the relationship between DTI-ALPS index and cognitive functions.

2. Materials and methods

2.1. Participants

The study was conducted in accordance with the Helsinki declaration. The Human Ethics Committee of Shaanxi Provincial Peoples Hospital approved all experimental procedures after receiving informed consent.

Patients with T2DM were recruited from the Department of Endocrinology of Shaanxi Provincial People's Hospital, and healthy controls (HCs) matched for age, sex, and education level were obtained from our health examination center.

All the participants were between 40 and 70 years of age, right-handed, and educated for at least six years. The T2DM patients met the standard criteria proposed by the American Diabetes Association and without a history of hypoglycemia or hyperglycemia [21]. The other inclusion criteria in the HC group were as follows:

(1) No symptoms or a family history of diabetes;

(2) Fasting glucose < 7.0 mmol/L;

(3) Glycosylated hemoglobin A1c (HbA1c) level < 6.0%.

The exclusion criteria for both groups were as follows:

(1) History of neurological disorders, such as cerebral infarctions, brain tumors, vascular malformations, or traumatic brain injury;

(2) Illicit substance abuse, alcohol abuse, or psychiatric disorders;

(3) Any other systemic disease irrelevant to diabetes and affecting cognition;

(4) Inability to complete MRI examinations or unsatisfactory MRI images.

2.2. Clinical data and cognitive assessments

All participants' clinical data, including information regarding their age, sex, educational level, blood pressure, height, weight, and body mass index (BMI), were obtained from medical records and questionnaires. Laboratory tests, including blood biochemical analysis and evaluation of fasting plasma glucose (FPG) and HbA1c levels were performed and their results were recorded.

All participants underwent the following series of neuropsychological assessments: Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) were used to assess general cognitive function; Trail-Making Test A (TMT-A) reflected cognitive processing skills (psychomotor speed, processing speed, and visuospatial skills) and attention; Trail-Making Test B (TMT-B) provided information regarding executive function; Auditory Verbal Learning Test (AVLT) was used to evaluate episodic memory; and Clock Drawing Test (CDT) was performed to evaluate visuospatial skills. Neuropsychological tests were performed by a psychiatrist trained in systematic testing.

2.3. Image acquisition

Conventional MRI and DTI data were obtained using a 3.0 T MR scanner (Ingenia, Philips Healthcare, the Netherlands) equipped with a 32-channel phase-array head coil. Conventional MRI, including sagittal three-dimensional T1-weighted imaging (repetition time [TR]/excitation time [TE] = 7.5/3.5 ms, field of view [FOV] = 250 × 250 mm^2, matrix = 256 × 256, slice thickness = 1 mm) and T2 FLAIR (TR/TE = 6000/150 ms, FOV = 230 × 230 mm^2, matrix = 320 × 320, slice thickness = 6 mm) were used to identify visible brain lesions. DTI was performed using the following parameters: 32 directions, b value = 0, 1000 s/mm^2, TR/TE=5000/150 ms, slice thickness= 2 mm, field of view = 256 mm × 256 mm, matrix = 128 × 128, spatial resolution = 2 × 2 × 2 mm^3.

2.4. Data processing

Data pre-processing included the following steps:

(1) The image format was converted from DICOM to NIFTI;

(2) Non-brain tissues, such as the scalp and skull, were removed using the Brain Extraction Tool (BET), which was performed in FMRIB's Software Library (FSL);

(3) The diffusion-weighted images were realigned to the non-weighted b0 images to correct head motion and eddy current-induced distortions (also a tool of FSL).

Evaluation of DTI-ALPS index was accordant with previous studies [22]. Diffusivities maps were co-registered to the FA map template (https://neurovault.org/images/1406/) by spm12 package in MATLAB (R2014a). Four 5-mm-diameter ROIs were placed on bilateral projection fibers and association fibers on FA map template. Manual correction was adapted to confirm the accuracy of registration and the location of ROIs for each patient. Then we recorded the diffusivities of

ROIs and calculated the average DTI-ALPS index of bilateral sides. DTI-ALPS was computed as the ratio between the mean of x-axis diffusivity on the projection fibers (Dxproj) and association fibers (Dxassoc) and the mean of y-axis diffusivity on the projection fibers (Dyproj) and z-axis diffusivity on association fibers (Dzassoc).

2.5. Statistical analysis

Data were analyzed by using SPSS (SPSS version 20.0, IBM, USA). Intergroup comparisons of DTI-ALPS indices, clinical and cognitive measurements were performed using Student's *t* tests or χ^2 tests as appropriate. The correlations between the DTI-ALPS index and cognitive measurements were analyzed by using multiple linear regression analyses, with age, sex, and years of education as the covariates. The Bonferroni correction was applied to correct for multiple comparisons. All tests were taken to be significant at $P < 0.05$ (two-tailed).

3. Results

3.1. Clinical and neuropsychological data

A total of 17 patients with T2DM and 20 HCs were enrolled in this study. **Table 1** showed the demographic and clinical characteristics of the enrolled participants. There were no significant differences in age, sex, years of education, blood pressure, total cholesterol, triglycerides, low-density lipoprotein levels, MMSE, MoCA, TMT-A, AVLT and CDT between HCs and patients with T2DM. Compared with HCs, patients with T2DM showed a significantly worse cognitive domain in TMT-B ($P = 0.004$).

Table 1. The demographic and clinical characteristics of the enrolled participants

Clinic information	T2DM (n = 17)	HC (n = 20)	*T*/*Z*/χ^2 value	*P* value
Gender (male/female)	14/3	13/7	1.403	0.288
Age (years)	49.41 ± 8.97	51.95 ± 7.57	0.934	0.357
Formal education (years)	13.35 ± 3.12	13.90 ± 2.59	0.582	0.564
BMI (kg/m^2)	24.87 ± 3.42	22.55 ± 3.17	-2.006	0.055
Total cholesterol (mmol/L)	4.92 ± 1.03	5.00 ± 0.97	0.23	0.819
Triglycerides (mmol/L)	1.82 ± 0.94	1.33 ± 0.77	-1.432	0.109
HDL (mmol/L)	1.14 ± 0.29	1.50 ± 0.51	2.476	0.020
LDL (mmol/L)	2.86 ± 0.76	2.94 ± 0.73	0.308	0.760
Fasting glucose (mmol/L)	7.26 ± 2.38	4.94 ± 0.56	-3.819	0.001
HbA1c (%)	7.51 ± 1.73	5.48 ± 0.46	-4.410	< 0.001
MMSE	27.88 ± 1.50	28.20 ± 1.64	0.611	0.545
MoCA	25.71 ± 2.54	26.25 ± 1.45	0.815	0.420
TMT-A(s)	105.29 ± 25.27	87.05 ± 25.54	-1.175	0.248
TMT-B(s)	189.71 ± 83.71	118.85 ± 36.28	-3.241	0.004
CDT	21.35 ± 7.11	24.88 ± 3.86	1.911	0.064
AVLT-total	46.50 ± 10.35	42.40 ± 13.36	-1.008	0.321
AVLT-delay	9.50 ± 3.60	7.90 ± 4.13	-1.222	0.230

Note: AVLT: Auditory verbal learning test; BMI, Body mass index; CDT, Clock drawing test; HDL, High density lipoprotein; LDL, Low density lipoprotein; HbA1c, Glycated hemoglobin; MMSE, Mini-mental state examination; MoCA: Montreal cognitive assessment; TMT-A, Trail making test A; TMT-B, Trail making test B.

3.2. Comparison of DTI-ALPS index between two groups

Compared with HCs, patients with T2DM showed a significantly lower average DTI-ALPS index (1.68 ± 0.15 vs. 1.54 ± 0.17, $P = 0.011$) and right DTI-ALPS index (1.73 ± 0.19 vs. 1.53 ± 0.20, $P = 0.005$), as shown in **Figure 1**. In HCs, the right DTI-ALPS index was significantly higher than the left DTI-ALPS index (1.73 ± 0.19 vs. 1.64 ± 0.16, $P = 0.039$, shown in **Figure 2**). However, this difference was not found in T2DM group (1.53 ± 0.20 vs. 1.55 ± 0.16, $P = 0.517$).

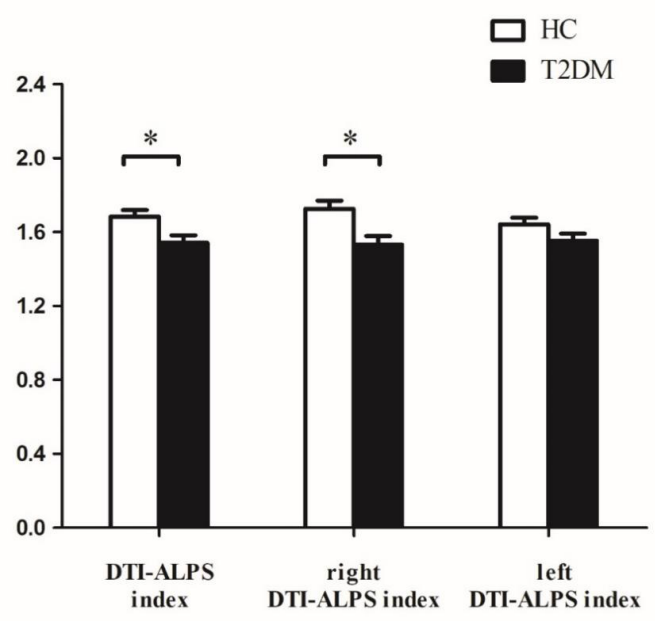

Figure 1. Group comparison of DTI-ALPS indices between patients with T2DM and healthy controls.

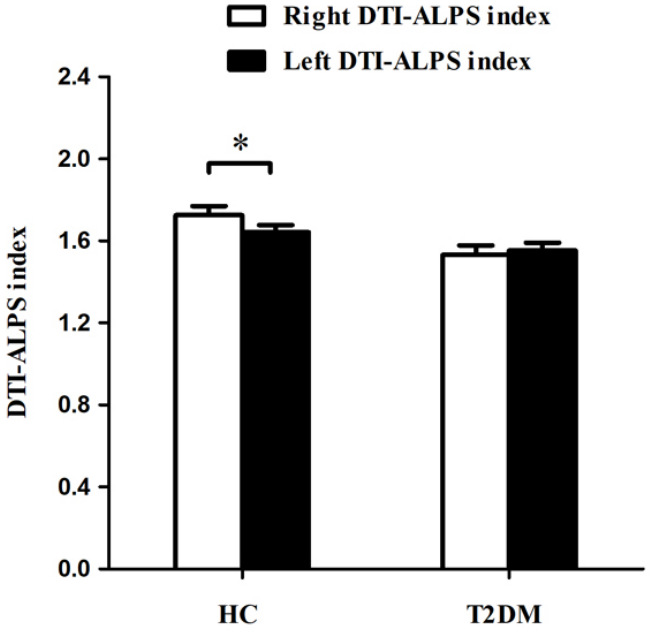

Figure 2. Interhemispheric differences in DTI-ALPS indices in healthy controls and patients with T2DM.

3.3. Relationship between DTI-ALPS index and cognitive impairment

The DTI-ALPS index showed significantly negative correlation with TMT-B (β = -0.502, $P = 0.001$), as shown in **Figure 3**, while DTI-ALPS index showed no significant correlation with any of other cognitive measures.

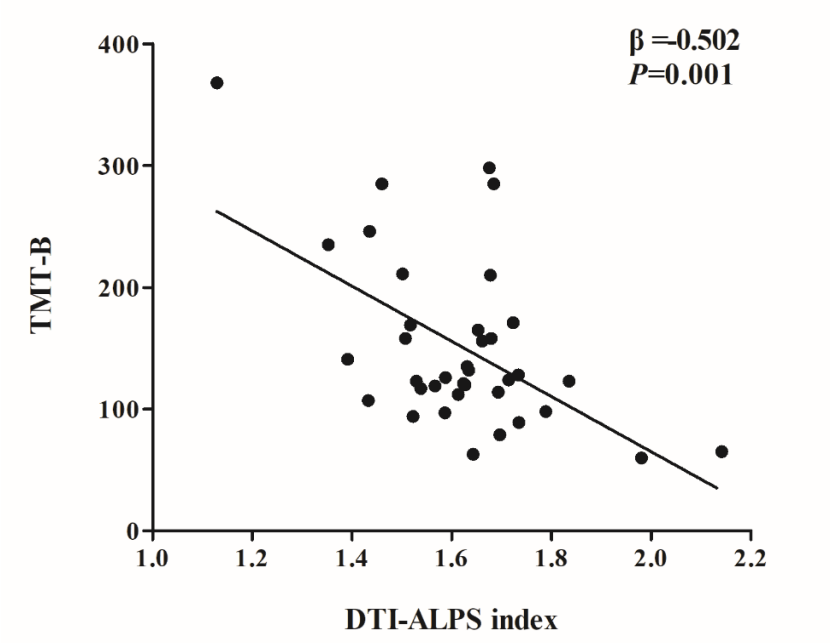

Figure 3. Negative correlation between DTI-ALPS index and TMT-B performance.

4. Discussion

In this study, we investigated *in vivo* glymphatic system function in T2DM patients using the DTI-ALPS index, a non-invasive diffusion-derived MRI index of diffusivity along the perivascular space. Our findings revealed that patients with T2DM exhibited significantly lower bilateral and right DTI-ALPS indices compared with HCs, indicating impaired glymphatic function associated with diabetes. Moreover, a right-greater-than-left hemispheric asymmetry of ALPS indices was observed in HCs but was absent in the T2DM group, suggesting that diabetes may disrupt the normal lateralization of glymphatic activity. Within the T2DM cohort, lower DTI-ALPS indices were significantly correlated with poorer TMT-B performance, implying that compromised interstitial fluid clearance may contribute to cognitive deficits, particularly executive dysfunction in this population.

Our observation of reduced DTI-ALPS indices in T2DM is consistent with recent studies reporting impaired perivascular or interstitial fluid transport in metabolic conditions [23,24]. Previous research in diabetic cohorts has similarly demonstrated lower ALPS values compared with healthy controls and linked these alterations to poorer cognitive performance, supporting the notion that glymphatic dysfunction constitutes an important mechanism underlying diabetes-related brain vulnerability. However, our findings not only corroborate but also extend previous evidence in several important respects.

For instance, we identified a hemispheric pattern in glymphatic function: healthy controls exhibited a right-greater-than-left ALPS asymmetry that disappeared in the T2DM group. This loss of lateralization suggests that diabetes may not only reduce global perivascular diffusivity but also disrupt the normal interhemispheric organization of glymphatic pathways, an aspect rarely examined in earlier studies. Given that prior reports seldom quantified hemispheric asymmetry, our results highlight lateralization metrics as potentially more sensitive markers of disease-related glymphatic disruption.

Furthermore, while earlier studies primarily emphasized global cognitive impairment, our results highlighted a domain-specific relationship between reduced ALPS index and cognitive performance in T2DM. This finding indicates that glymphatic dysfunction may not uniformly affect cognition but instead shows selective associations with certain domains. The observed pattern underscores the potential of ALPS as a sensitive imaging biomarker for subtle cognitive alterations in diabetes, warranting further investigation in larger and longitudinal cohorts.

On top of that, our associations remained significant after adjusting for age, sex, and years of education and survived multiple-comparison correction, further reinforcing the robustness and reproducibility of the ALPS-cognition relationship. Moreover, by explicitly separating average, right, and left ALPS indices, our side-resolved analysis revealed additional variance not captured by mean ALPS measures alone. This methodological refinement provides greater biological specificity and may help future studies achieve more consistent and physiologically meaningful results.

The present study further demonstrated that lower ALPS index was specifically associated with poorer TMT-B performance in patients with T2DM, which suggests that glymphatic dysfunction might preferentially affect cognitive domains related to information processing and executive control. Similar domain-specific associations have been observed in AD, where reductions in ALPS reductions were most strongly linked to processing speed and executive functions rather than global cognition [25,26].

Executive and processing-speed deficits are typically mediated by fronto-subcortical circuits that rely on intact white-matter integrity, which are known to be particularly vulnerable in diabetes [27]. Impaired glymphatic clearance may therefore contribute to cognitive dysfunction through disruption of these white-matter-based networks. Additionally, a recent study in stroke populations has shown that ALPS indices measured during the subacute phase were predictive of MoCA outcomes at 90 days, highlighting their potential as a prognostic biomarker for cognitive recovery [28].

This convergent evidence supports our interpretation that altered perivascular clearance, reflected by a reduced ALPS index, might serve as an early neuroimaging indicator of cognitive vulnerability in T2DM. The absence of significant correlations between ALPS and global cognitive scales in our study may reflect limited statistical power, mild cognitive heterogeneity, and the multifactorial nature of cognitive impairment in diabetes, which involves vascular, metabolic, and inflammatory mechanisms acting in concert. Future longitudinal studies combining ALPS metrics with multimodal imaging and detailed cognitive profiling may clarify the temporal dynamics and mechanistic pathways linking glymphatic dysfunction to cognitive decline in this population.

The glymphatic system is a well-organized cerebrospinal-fluid-interstitial transport system that is responsible for clearing abnormal proteins and metabolites such as amyloid-β, phosphorylated tau, and advanced glycation end products (AGEs), which are known to accumulate in diabetic brains. Its function is impaired with aging and in pathological conditions [29,30]. Failure of this clearance pathway may accelerate neurotoxic deposition, oxidative injury, and synaptic dysfunction, ultimately impairing cognition.

Several AD studies have shown that lower ALPS indices are associated with greater amyloid and tau burden on PET imaging [25,31]. These findings raise the possibility that similar mechanisms operate in T2DM, linking impaired glymphatic drainage to the early development of diabetes-related cognitive decline. Chronic hyperglycemia, insulin resistance, and oxidative stress are hallmarks of T2DM and can directly impair microvascular integrity, endothelial function, and blood brain barrier (BBB) permeability [32]. The pulsatile motion of cerebral arteries is a key driving force of perivascular cerebrospinal fluid (CSF) flow [4,33].

Diminished vascular compliance in diabetes may therefore attenuate this driving pressure, slowing glymphatic transport and leading to decreased ALPS indices. Experimental studies provide convergent evidence, whereby diabetic rodent models show delayed CSF tracer clearance on DCE-MRI, consistent with reduced glymphatic efficiency [34]. Endothelial dysfunction and basement membrane thickening in diabetes further narrow perivascular channels, exacerbating glymphatic stagnation. These mechanisms may underlie the observed glymphatic impairment in our cohort.

This study had several limitations:

(1) This was a single-center study based on a Chinese population and only recruited inpatients with T2DM. The sample size was modest, which may have limited statistical power to detect weaker associations. Our results require validation in a larger and more diverse population;

(2) The cross-sectional design precludes causal inference; whether reduced ALPS precedes or follows cognitive decline remains uncertain. Longitudinal data will be required to establish predictive validity;

(3) The ALPS index reflects diffusivity perpendicular to projection and association fibers at a specific periventricular

level and may not represent global glymphatic efficiency. Its value can be affected by local white-matter microstructure, age, and disease-related demyelination, which is worth further study in the future;

(4) Cognitive assessment in this study focused on conventional neuropsychological tests; incorporating task-based fMRI or network-connectivity analyses could provide a more comprehensive understanding of functional correlates.

5. Conclusion

This study demonstrated that patients with T2DM exhibit reduced DTI-ALPS indices, reflecting impaired glymphatic system function and an altered pattern of hemispheric asymmetry. The lower ALPS values were associated with poorer executive performance, suggesting that glymphatic dysfunction may be linked to specific aspects of cognitive control in T2DM. By applying a non-invasive diffusion-based imaging method, our findings provide supportive evidence that DTI-ALPS can serve as a potential imaging biomarker for assessing glymphatic function in metabolic disorders. Although further longitudinal and mechanistic studies are warranted, these results highlight a possible pathway through which vascular and metabolic disturbances may contribute to cognitive decline. Understanding glymphatic alterations in diabetes may aid in early identification of individuals at higher risk for cognitive impairment and promote the development of targeted prevention and intervention strategies.

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Disclosure statement

The authors declare no conflict of interest.

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