Dear Dr./Prof. World Journal of Diabetes,

Thank you very much for your decision letter and advice on our manuscript (Manuscript #93382) entitled “Exploring the glymphatic function and its influencing factors in different glucose metabolism states: a DTI-ALPS analysis”. We also thank the reviewers for their constructive comments and suggestions. We have revised the manuscript accordingly, and all amendments in the revised manuscript are highlighted in yellow. In addition, our point-by-point responses to the comments are listed below this letter.

Peer-review #1:

1. The background effectively sets the stage by underscoring the prevalence and impact of diabetes and prediabetes on global health, linking these conditions to potential cognitive impairments and glymphatic dysfunction. The aim is clearly defined, though it could be strengthened by explicitly stating the expected contribution of the study to existing knowledge or potential clinical applications.

Response: Modifications have been made to the last paragraph of the Introduction section (highlighted in yellow).

2. However, the study might benefit from a more detailed description of the DTI-ALPS technique, particularly how it differentiates from other MRI techniques in studying the glymphatic system.

Response: In paragraph 4 (beginning with "recent advances") and paragraph 5 (beginning with "the DTI-ALPS index"), we have described in detail the principles and methods of the DTI-ALPS index. Currently, the DTI-ALPS index is calculated using only DTI imaging, or imaging that can be transformed into DTI, such as DSI. No other magnetic resonance imaging techniques can be used to calculate the DTI-ALPS index for the time being. Therefore, studies on DTI-ALPS do not need to detail the differences with other magnetic resonance imaging techniques in the study of DTI-ALPS.

3. The statistical methods are appropriate for the data analysis presented, but the manuscript could include information on the power analysis to ensure adequacy of the
sample size for detecting a significant effect.

Response: We have added power analysis in the subsection 'Participants and clinical data collection'.

4. The results are detailed and provide a comprehensive view of the DTI-ALPS indices across different groups. It would be beneficial to include more detailed statistical data, such as confidence intervals and effect sizes, to enhance the interpretability of the findings.

Response: In the revised manuscript, we have added confidence intervals in the statistics analysis section. We have set the effect size in the power analysis.

5. The connection between DTI-ALPS indices and clinical features is intriguing; however, the manuscript would benefit from a discussion on the biological plausibility or mechanisms that might explain these associations.

Response: The biologic plausibility or mechanism of the association between the DTI-ALPS index and clinical features are discussed in the Discussion section.

6. Discussion: The discussion comprehensively addresses the implications of the findings, linking them back to the literature and hypothesizing on potential physiological explanations. However, it tends to reiterate results rather than fully exploring their implications. It could be improved by discussing potential limitations of the DTI-ALPS index itself and how it might interact with other biomarkers of disease. The section could also benefit from a more critical examination of the limitations, such as the potential confounding effects of medications or comorbid conditions not controlled for in the study.

Response: The rationale for the relationship between DTI-ALPS and clinical features is comprehensively discussed in Sections 4.1 and 4.3 of the Discussion section. For instance, in Section 4.1, we present two arguments: firstly, chronic hyperglycemia can potentially modify water diffusion characteristics in brain tissue; secondly, the deposition and elimination of Aβ and tau proteins can potentially impact tissue water diffusion properties. In Section 4.3, we provide evidence for the correlation between DTI-ALPS and other clinical features while extensively discussing the underlying reasons behind this outcome.
7. Conclusion: The conclusion succinctly summarizes the key findings and their implications, but it could be enhanced by explicitly stating future research directions or how these findings could influence clinical practice or policy.

Response: Necessary revisions have been made in the conclusion section and highlighted in yellow.

We hope that our revised manuscript is now acceptable for publication in your journal and look forward to hearing from you soon.

With best wishes,
Yours sincerely,

BIN TIAN
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Review by Editorial Board

The Authors have made the suggested changes to the Manuscript according to the reviewer’s advice which improved the text. I would just like to suggest to Authors to include the data on patients’ therapy in case of present T2DM, while some newer agents (GLP-1RA) are under investigation for neuroprotection, and in case of their use of patients, to comment the results.

Thank you for your comments. This is an excellent idea that warrants further exploration: the impact of drugs on DTI-ALPS. Although we emphasize in the methods section that the volunteers recruited in the T2DM group were ‘the first diagnosis of T2DM’ (page 8), the study did not include some new hypoglycemic agents, such as GLP-1 RA, on the DTI-ALPS for several reasons. 1. In clinical treatment, GLP-1 RA is often administered in combination with other drugs, and it is crucial to distinguish the protective effects of GLP-1 RA on the nervous system from those of other medications. 2. If there are changes in DTI-ALPS following administration of GLP-1 RA, it is essential to determine whether these changes are attributed to a decrease in blood glucose levels or the neuroprotective properties inherent to GLP-1 RA itself. 3. There are various classifications for GLP-1RA based on their molecular structure characteristics, including those derived from human GLP-1 and aggrecan 4 structures. Each category included multiple drugs. Further investigations are required to ascertain whether these different types of drugs exhibit consistent effects on the DTI-ALPS. Your proposal is highly commendable as a potential research direction, and we have duly acknowledged this potential avenue for investigation in the limitations section of our manuscript. However, studying the influence of GLP-RAs on DTI-LAPS requires a more intricate process, which we will discuss later when designing a specific topic targeting drug effects on DTI-LAPS. Thank you again for your valuable comments.