Point-by-point reply

Reviewer 3

This manuscript demonstrated the relationship between mtDNA and various inflammatory markers with cerebrovascular hemodynamics and vascular remodeling in patients with T2D. While the data presented in the manuscript are extensive, there is a lack of novelty. My concerns are as follows:

1. The primary concern of this article is the lack of novelty. The manuscript appears overly similar to another paper published by the same laboratory in IJMS in 2023, both discussing the relationship between mtDNA and multiple inflammatory markers in T2D. Although this manuscript adds result about the connection between these markers and cerebrovascular remodeling and reactivity modification in T2D, changes in cerebral vasculature in T2D have been reported by several laboratories [10.7863/jum.2006.25.5.599] [10.2337/diabetes.54.9.2638] [10.1371/journal.pone.0056264]. Studies investigating the relationship between T2D and mitochondria and mtDNA are also not uncommon [10.1152/ajpendo.00314.2018]. Similarly, research on the relationship between mtDNA in the cardiovascular system and cardiovascular diseases such as atherosclerosis exists [10.1001/jamacardio.2017.3683]. Therefore, this manuscript merely extends the laboratory's existing work on known research. Additionally, the article fails to emphasize the potential clinical applications of the findings.

   Thank you for your valuable comments. The recommended references and the appropriate changes have been added in the Introduction section [ref 4,8,11,16,28].

   Also, the potential clinical applications of the findings have been introduced in the Conclusion section [ref 16]

2. The English language of the manuscript still needs polish. Long sentences decrease logical flow and hinder reader comprehension. Additionally, the emphasis on p-values in Result 3.2 makes the text confusing.

   Thank you for your pertinent comment. The Results section 3.2 has been reorganized. In univariable regression analysis, only significant p-values have been introduced.

3. Patient inclusion criteria and grouping could be showed by a simple flowchart to make it clearer.

Thank you for your suggestions. The flowchart with regard to the selection of the patients, inclusion/exclusion criteria and grouping has been added (Fig 1).

4. Section 3.1 of the main text seems to lack subtitle.

Thank you for your observation. The subtitle for Section 3.1 has been added.

5. In table 2, when the parameter is uICAM-1, the result of umtDNA as variables is not shown. Similarly, only in sICAM-1 part the result of PT dysfunction is shown.

Thank you for your valuable comment.
In Table 2, in the model for uICAM-1, umtDNA did not result as significant and therefore was not included in the table.
In the same model, the results of PT dysfunction are included (see NAG, KIM-1).