Dear Editors,

Re: Manuscript NO: 65746

Title: Advanced Glycation End Productions (AGEs) and Tendon Stem/Progenitor Cells in the Pathogenesis of Diabetic Tendinopathy

We would like to thank you and the reviewers for the very useful comments and your time for critical and careful review of our manuscript.

We have responded on a point by point basis to Reviewers' comments as required and indicated how the suggestions have been incorporated in the revised manuscript when it is appropriate. A major revision of the manuscript has been carried out accordingly. We believe that the manuscript is greatly improved and, and to be further considered for publication in World Journal of Stem Cells.

We look forward to hearing from you.

Yours Sincerely,

Professor Yunfeng Rui

(On Behalf of All Co-authors)

Reviewer comments:

Reviewer 1 Comments for the Author:

In this manuscript, the authors reviewed and discussed the effects of AGEs and the roles of TSPC in the development of diabetic tendinopathy. The topic is of interest and importance to the field. Manuscript is generally well written and English presentation is readable and clear.

1. As the title of manuscript is "Advanced Glycation End Productions (AGEs) and Tendon Stem/Progenitor Cells in the Pathogenesis of Diabetic Tendinopathy", but the description of the relationship between AGEs and their effect in TSPC biology is quite week. The authors need to emphasize the reported mechanisms how AGEs alter or affect the physiological roles of TSPC since in the present manuscript, it is separately discussed and difficult to find their associations.

Answer: Thank you for your comments and suggestions. In this mini review, we also tried to summarize the relationship between AGEs and TSPCs. However, there's only few original articles reported the effects of AGEs on TSPCs. According to your suggestions, we also added one paragraph to discuss how AGEs affect TSPCs.

"Up to date, there's only a few studies focused on the influence of AGEs on TSPCs. Xu L et al reported that AGEs could reduce the cell viability and increase apoptosis and autophagy of TSPCs in vitro [72]. In this study, they also found AGEs also inducing senescence and enhancing the ossification of TSPCs in vitro. However, the researchers did not further investigate the underlying mechanisms of AGEs

induced ossification of TSPCs. In MSCs, AGE-2 and AGE-3 showed the ability of enhance the ALP activity and intracellular calcium content via activating RAGE in vitro [29]. Therefore, we speculate the activation of RAGE in TSPCs could also lead to the apoptosis, senescence, erroneous differentiation through activating several signal pathways, such as Wnt/β-catenin, P38/MAPK and Notch signaling pathways, ROS, Akt/eNOS, etc."

2. In the section of "AGEs induce cellular events in tendon cells", the authors should emphasize and give information in details when refer to TSPC or other tendon cells. The reported or suspected molecular mechanisms should be provided. Since in this version, there were some details of molecular mechanisms underlying other AGEs induced diabetic complications, but a little on tendinopathy were explained. If there is no report, a clear statement should also be given.

Answer: Thank you for your comments and suggestions. Because there's only a few studies investigate the AGEs on TSPCs, and the underlying mechanism did not detailly illustrate. Thus, in this version, we discussed the effects of AGEs on various kinds of musculoskeletal cells from the aspects of proliferation, differentiation and apoptosis instead of the cell types. We separately discussed the effects of AGEs on tendon cells and the possible signal pathways in each paragraph. And at the end of this section, we separately discussed the effects of AGEs on TSPCS from the current study and raised our speculations.

3. Please briefly explain how different between AGE2 and AGE3 is in the manuscript. The mechanisms of AGEs generation under diabetic conditions may be useful for the reader to follow the story.

Answer: Thank you for your comments and suggestions. In manuscript, we added the description of AGE-2 and AGE-3 when they were firstly used. "Among the subtypes of AGEs, AGE-2 (glyceraldehyde-derived AGEs) and AGE-3 (glycolaldehyde-derived AGEs) are the main subtypes that can be detected in the sera of diabetic patients and exhibit toxic bioactivities in various cells"

4. In the section "AGEs alter the biomechanical properties of tendon", in addition to the studies in animal, are there any studies on human tissue? This information should be described.

Answer: Thank you for your comments and suggestions. Currently, there's no studies reported biomechanical effects of AGEs on human tendon tissues. According to your suggestion, we described this in manuscript.

5. Please make sure the full spelling of BG and MSC is given when they are first used.

Answer: Thank you for your comments and suggestions. We have changed the "BG" into "blood glucose" and "MSC" into "bone mesenchymal stem cells (MSCs)" while it was firstly used in the manuscript.

Reviewer 21 Comments for the Author:

Dear Authors, the manuscript is well organized and summarizes current knowledge on diabetic tendinopathy. Moreover, based on own findings and other authors' investigations you give the insight on molecular-level events within the diabetic tendons, and argue the role of AGEs and TSPCs in

development and progression, as well as future therapeutic target. I find your review of interest for readership.

Answer: Thank you for your comments and suggestions.