

## **Detailed response to the reviewers**

Dear editors and reviewers,

We deeply appreciate your thoughtful review and comments on our manuscript (Manuscript NO: 65113 entitled "Mesenchymal Stem Cells for Enhancing Biological Healing after Meniscal Injuries").

We have reviewed the comments carefully and revised our manuscript accordingly.

The reviewer's comments or questions have been addressed in a point-by-point manner.

Thank you for your consideration.

Sincerely yours

**Peer Reviewer: 1.**

Comments to the Author:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This is a review article examining the therapeutic effect of MSCs on meniscus injury, which is of high importance in musculoskeletal disorders. Authors refer to many past reports including the latest ones and two tables are useful for understanding this field. On the other hand, the text is somewhat descriptive, and I think it lacks several themes to be discussed for the readers of the *World Journal of Stem Cells*. I propose that it is necessary to improve the sentence structure and add content before publishing.

**Author response)** Thank you for thoughtful review and comments. We will revise our manuscript according to the reviewer's comments to be suitable for publication in the *World Journal of Stem Cells*.

ROLE OF THE MENISCUS: WHY SHOULD WE PRESERVE THE MENISCUS?

BASIC ANATOMY OF THE MENISCUS

THE LIMITED HEALING POTENTIAL OF A TORN MENISCUS

These parts are useful in the sense that they help non-specialized readers understand this

manuscript concerning knee meniscus. However, considering the theme of this paper, I think that there should be enough discussion about how to evaluate the meniscus healing. An overview of typical animal disease models and their evaluation methods, as well as of subjective and objective evaluation methods used in clinical research, will improve the quality of the paper and help the reader's understanding.

**Author response)** Thank you for thoughtful review and comments. We agree with the reviewer's opinion. We will add a paragraph regarding "how to evaluate the meniscus healing" to improve the quality of our paper and help reader's understanding according to the reviewer's comments.

**Author action)** We added a paragraph about "how to evaluate the meniscus healing" according to the reviewer's comments (Please see the "HOW TO EVALUATE THE MENISCUS HEALING" section in revised manuscript).

#### **"HOW TO EVALUATE THE MENISCUS HEALING"**

**As the importance of meniscal preservation is strongly emphasized, various meniscus repair techniques have evolved and improved. To evaluate healing effects of these new techniques, they are generally first assessed in animal models. In a recent systematic review regarding animal model studies of meniscus repair and regeneration, Bansal et al. analyzed a total of 128 full-length peer-reviewed manuscripts[30]. Authors demonstrated that most studies conducted histologic (90%), macroscopic (85%), and healing/integration (83%) analyses in terms of meniscal healing outcome parameters. In addition to these outcome measures, biochemical analysis, magnetic resonance imaging (MRI), assessment of vascularization, gene expression, immunohistochemistry, and arthroscopy were also performed to assess the meniscus healing. In clinical studies, there have been various subjective and objective evaluation methods for assessing the**

meniscus healing. In terms of subjective evaluation methods, some patients reported outcome measures (PROMs) are currently available to assess the function, symptoms and quality of life of patients with meniscal injuries[31, 32]. These include the Hughston Clinic Questionnaire[33], International Knee Documentation Committee (IKDC) subjective knee form[34], Knee injury and Outcome Osteoarthritis Score (KOOS)[35], Lysholm Knee Scale[36], Western Ontario McMaster Osteoarthritis Index (WOMAC)[37], EuroQoL-5 dimension (EQ-5D)[38], Twenty-six-item Knee Quality of Life (KQoL-26)[39], Short Form-6 dimensions (SF-6D)[40], Western Ontario Meniscal Evaluation Tool (WOMET)[41], Tegner Activity Scale[42], Cincinnati Knee Score[43], Tapper and Hoover Meniscal Grading Score[44], Knee Outcome Survey - Activities of Daily Living Scale (KOS-ADLS)[45], Short Form - 12 Item Health Survey (SF-12)[46]. Although there are many PROMs to assess meniscal injuries and healing, evidences for the validity of these PROMs are still insufficient[31]. In terms of objective evaluation methods, there are several methods to assess the meniscus healing. Although the most reliable examination tool is arthroscopy[47, 48], it is an invasive method and still depends largely on the surgeons' skills[49]. As a non-invasive method, conventional MRI sequences have been widely used to assess meniscal injuries and healing. However, using conventional MRI, assessing meniscal tissue composition changes ahead of surface breakdown is challenging[50]. Recently, quantitative MRI techniques, such as T2 mapping, are used to assess the meniscus healing more effectively[50, 51]. Some authors recommended magnetic resonance arthrography (MRA) or computed tomography (CT) arthrography as an alternative objective evaluation method[52-55].”

## A CELL BASED APPROACH FOR ENHANCED MENISCUS HEALING

### APPLICATION OF MSCS IN BIOLOGICAL MENISCUS HEALING

The concept of MSC has changed considerably from its original proposal. In particular, there are increasing reports that the efficacy as a source of secretory factors is more important than that as a cell source. Since it is also an essential issue of this paper, authors would better to mention its definition and the mechanism of therapeutic effect.

**Author response)** Thank you for thoughtful review and comments. We agree with the reviewer's opinion. Recently, the secretory effect (paracrine effect) is more emphasized in MSCs. We will add some sentences according to the reviewer's comments.

**Author action)** According to the reviewer's comments, we added some sentences with recent references (Please see 2<sup>nd</sup> to 8<sup>th</sup> line of the "APPLICATION OF MSCS IN BIOLOGICAL MENISCUS HEALING" section in revised manuscript).

**"The precise roles and mechanisms of MSCs for enhanced meniscus healing are still unknown. Although there are some controversies, it is recently accepted that the therapeutic effects derived from MSCs in various musculoskeletal therapies are mainly due to their paracrine effects[88, 89]. Various growth factors can be secreted by the paracrine functions of MSCs, which might lead to enhanced angiogenesis, cell differentiation and migration, and various additional regenerative effects[88, 90, 91]."**

Intra-articular injection of MSCs for meniscus healing Animal Studies/Human Studies

Tissue engineering using MSCs for meniscus healing Animal Studies/Human Studies

These parts were a bit descriptive and felt hard to read. Adding sub-headlines seems to make it easier to read. For example, how about to classify animal experiments by model and clinical researches by MSC origin. Please consider.

**Author response)** Thank you for thoughtful review and comments. We agree with the reviewer's opinion. We will reframe "Intra-articular injection of MSCs for meniscus healing Animal Studies/Human Studies" and "Tissue engineering using MSCs for meniscus healing Animal Studies/Human Studies" sections with adding sub-headlines according to the reviewer's comments.

**Author action)** According to the reviewer's comments, we reframed the sections. We added sub-headlines with classifying animal studies by models and human studies by MSC origins (Please see the "INTRA-ARTICULAR INJECTION OF MSCS FOR MENISCUS HEALING" and "TISSUE ENGINEERING USING MSCS FOR MENISCUS HEALING" sections in revised manuscript)

## **Editorial Office's Comments.**

### **Issues raised:**

(1) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s).

**Author response)** Thank you for the comments. We will upload the approved grant application form.

(2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

**Author response)** We provided our own pictures in our initial submission. Therefore, we don't have to obtain permissions. We will prepare and arrange the figures using PowerPoint according to the editorial office's comments.

(3) Please obtain permission for the use of picture(s). If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34):

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**Author response)** We provided our own pictures in our initial submission. That is, we did not use figures published elsewhere. Therefore, we don't have to obtain permissions.

**Company editor-in-chief.**

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Stem Cells, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

**Author response)** Thank you for thoughtful review and decision for conditionally accept. We will revise our manuscript according to the comments of the reviewer and editorial office.

Thank you again for giving us an opportunity to revise our manuscript.