Reviewer #1:
Scientific Quality: Grade A (Excellent)
Language Quality: Grade A (Priority publishing)
Conclusion: Minor revision
Specific Comments to Authors: It is a well-written review that summarizes the current knowledge of bone marrow mononuclear cells for OA therapy. A few minor comments are listed below for further consideration.
Reply: Thank you. We appreciate the positive comments and have made every effort to address the issues raised by your thoughtful observations and critiques in our responses below.

1. Full gene nomenclatures should be provided at the first appearance instead of later.
Reply: The nomenclature was revised and written in extended fashion at first, both in the abstract and the main body of the manuscript.

2. It is better to detail the percentage of synovial macrophages and synovial fibroblasts if possible.
Reply: Although there is variation in the precise numbers presented in the literature, we detailed the requested information based on the scientific literature we find most accurate.

3. Some citations have formatting issues. A bibliography managing software, such as Endnote, is highly recommended.
Reply: Apologies for that. We did use Endnote and the formatting style "Vancouver" as suggested in the guide for the authors.

For this version of the manuscript, we carefully addressed all references. We downloaded and used the "World Journal of Stem Cells" Endnote formatting style. Although most PMIDs and DOIs became then included in the references, some had to be inserted manually. The journals' abbreviations for the entire list of references were also corrected manually. Of note, for some references, such as #25, 26, 32, etc… no PMID or DOI was available, and such references are essential in this manuscript

4. Since the authors commented that '…it only makes sense to capitalize on the macrophage-mediated effects of BMNC to re-establish mechanisms of joint homeostasis to develop a targeted OA therapy,' it will be beneficial to briefly comment on the reason(s) why the current/future investigation on focusing on the BMNC instead of purified macrophages and macrophage progenitors from the bone marrow, especially when considering the accumulating evidence that suggests mesenchymal stem cells post a (pro)tumorigenic risk.
Reply: We included additional information highlighting the important role of hematopoietic and progenitor cells in BMNC as a reservoir of macrophages. Since macrophages are demanded in high counts during effective inflammation and its resolution, the alternative use of purified adult macrophages may represent a finite source of therapeutic macrophages. We also quoted studies identifying that a large portion of the regulatory effects of MSC are associated to activation of a macrophage-derived homeostatic response, and thus BMNC represents a more direct, targeted approach.

Although the data about stem cell tumorigenicity in the literature is diverging, to the knowledge of these authors mesenchymal stem cells preparations (autologous and allogeneic) currently in use for joint

therapy have not been associated to tumor development. Most reports of tumorigenicity in the literature relate to the use of induced pluripotent stem cells (IPSc)[1-4]. Studies from our lab using fetal cartilage progenitor cells xenografts in the joints of immunosuppressed rats did identify tumorigenesis. However, these authors believe that discussing stem cell-derived tumorigenesis would require more context and therefore would drift from the main focus of this manuscript. Should the reviewers deem it mandatory, we would certainly include it.

Reviewer #2:
Scientific Quality: Grade C (Good)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: The authors investigated bone marrow mononuclear cells for joint therapy. This manuscript is valuable because the role of macrophages benefit patients.
Reply: Thank you.

5 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

> ***Science editor:*** 1 Scientific quality: The manuscript describes a review of the bone marrow mononuclear cells for joint therapy. The topic is within the scope of the WJSC. (1) Classification: Grade A and Grade C; (2) Summary of the Peer-Review Report: It is a well-written review that summarizes the current knowledge of bone marrow mononuclear cells for OA therapy. The questions raised by the reviewers should be answered; (3) Format: There is 1 table and 3 figures; (4) References: A total of 124 references are cited, including 34 references published in the last 3 years; (5) **Self-cited references: There are 4 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations (i.e. those that are most closely related to the topic of the manuscript) and remove all other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated.**
> Reply: To our understanding no action is required in this regard since the self-citation (n=4) is less than 10% (n=12). All self-citations directly relate to the subject and content of this manuscript. Please let us know if further action is expected in this matter.
>
> (6) References recommendations: The authors have the right to refuse to cite improper references recommended by the peer reviewer(s), especially references published by the peer reviewer(s) him/herself (themselves). If the authors find the peer reviewer(s) request for the authors to cite improper references published by him/herself (themselves), please send the peer reviewer's ID number to editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately. 2 Language evaluation: Classification: Two Grades A. 3 Academic norms and rules: No academic misconduct was found

in the Bing search. 4 Supplementary comments: This is an invited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJSC.

(1) Issues raised:

a. The "Author Contributions" section is missing. Please provide the author contributions.
Reply: Apologies. The "Author Contributions" section has been inserted.

b. 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.
Reply: A PowerPoint document with the original images has been uploaded.

c. (3) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout.
Reply: The references section has been formatted as requested.

d. (4) 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): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable.
Reply: All figures composed of images that have been previously published, either as part of a digital thesis or as a peer reviewed manuscript, had their legends/title formatted as described above.

The content of **Figure 1** was originally prepared for this manuscript. Images on **Figure 3** are published on a manuscript in which Dr. Menarim and Dr. Dahlgren are first and corresponding authors, respectively. The content from **Table 1** is published in an electronic version of a Master Thesis chaired by Dr. Menarim. Permission for reproduction of images on **Figure 2** was granted by Dr. Valdis Goncars on 4/29/21 via email (attached).

References

1 Takei Y, Morioka M, Yamashita A, Kobayashi T, Shima N, Tsumaki N. Quality assessment tests for tumorigenicity of human ips cell-derived cartilage. Scientific reports 2020; 10: 12794 [PMID: PMC7393378 chondrocyte induction method" (PCT/JP2014/079117). This patent is licensed to Asahi KASEI corporation. All other authors declare no conflict of interest. DOI: 10.1038/s41598-020-69641-4

2 Sato Y, Bando H, Di Piazza M, Gowing G, Herberts C, Jackman S, Leoni G, Libertini S, MacLachlan T, McBlane JW, Pereira Mouriès L, Sharpe M, Shingleton W, Surmacz-Cordle B, Yamamoto K, van der Laan JW. Tumorigenicity assessment of cell therapy products: The need for global consensus and points to consider. Cytotherapy 2019; 21: 1095-1111 [PMID: DOI: https://doi.org/10.1016/j.jcyt.2019.10.001

3 Kanemura H, Go MJ, Shikamura M, Nishishita N, Sakai N, Kamao H, Mandai M, Morinaga C, Takahashi M, Kawamata S. Tumorigenicity studies of induced pluripotent stem cell (ipsc)-derived retinal pigment epithelium (rpe) for the treatment of age-related macular degeneration. PLOS ONE 2014; 9: e85336 [PMID: DOI: 10.1371/journal.pone.0085336

4 Yasuda S, Kusakawa S, Kuroda T, Miura T, Tano K, Takada N, Matsuyama S, Matsuyama A, Nasu M, Umezawa A, Hayakawa T, Tsutsumi H, Sato Y. Tumorigenicity-associated characteristics of human ips cell lines. PLOS ONE 2018; 13: e0205022 [PMID: DOI: 10.1371/journal.pone.0205022