

Dear reviewers:

Thank you very much for your comments and advice to our manuscript entitled "**Therapeutic Applications of Adipose-derived Stromal Vascular Fractions in Osteoarthritis**" (Manuscript NO.: 76905, Review). We completely accept your recommendation and fully agree that these recommendations can further strength the quality of the manuscript. We have revised the manuscript very carefully and according to the suggestions. To clearly present the response, the comments are shown in *italics* and our responses are shown in **blue font**. A thorough, point-by-point response to each point was raised and all changes, a word file of the revised manuscript with all changes labelled in **red font** has been uploaded. If you have any further questions about the revision, please do not hesitate to contact us.

Best regards,

Liang Jin

## Comments:

### Reviewer #1 (Remarks to the Author)

*Scientific Quality: Grade B (Very good)*

*Language Quality: Grade B (Minor language polishing)*

*Conclusion: Accept (General priority)*

*Specific Comments to Authors: This paper reviews with pathogenesis, diagnosis, and current clinical treatments for OA. The paper is well written. The paper contains minor typos that should be fixed. As the content of the paper relates more to existing studies and techniques for OA treatment, the title is not appropriate. A title such as the following or another would be more appropriate: - A Short Review of Therapeutic Applications of Adipose-derived Stromal Vascular Fractions in Osteoarthritis - Therapeutic Applications of Adipose-derived Stromal Vascular Fractions in Osteoarthritis: A Short Review In Section Discussion, the following sentence is incomplete: "As a result, it is critical for the early diagnosis and treatment of OA".*

**Response:** Thanks for your valuable and constructive comments, we have read through the manuscript and corrected several minor typos. Considering the Reviewer's suggestion, we have chosen 'Short Review of Therapeutic Applications of Adipose-derived Stromal Vascular Fractions in Osteoarthritis' as the manuscript title.

Moreover, thanks for your suggestion, we have modified the discussion.

Text change:

### Discussion

Unfortunately, no complete cure exists for OA, and once a cartilage lesion occurs, it will gradually degenerate. As a result, the early diagnosis and treatment of OA is critical. **Considering that osteoarthritis is a whole joint disease, OA should be treated with combined therapy. Through intraarticular injection therapy, treatment agents can directly reach the damaged site, which can not only allow drugs and especially stem cells to avoid being cleared by the body but also reduce the potential systemic effects of drugs<sup>[70]</sup>. Especially for traumatic arthritis, cartilage adipose stem cells provide a new avenue for the treatment of this type of arthritis through their powerful differentiation ability and paracrine and anti-inflammatory effects. Therefore, intraarticular injection therapy should be added to the combined treatment of OA.** Increasing evidence shows that intraarticular injection of SVF is an effective treatment option for repairing articular cartilage damage, but there is a lack of clinical outcome data for long-term follow-up. Furthermore, the use of SVF to treat OA has certain individual differences, such as differences in extraction methods and equipment, which result in a variation in the number and quality of extracted cells. Simultaneously, the amount of fat acquired and the final cell yield of different patients are difficult to reconcile. The number of SVF cells used in the final treatment of OA varies by up to 10-fold in different studies. As a result, more detailed and comprehensive extraction standards and treatment guidelines for the use of SVF for OA treatment are needed.....

**Reviewer #2 (Remarks to the Author):**

*Scientific Quality: Grade D (Fair)*

*Language Quality: Grade B (Minor language polishing)*

*Conclusion: Major revision*

*Specific Comments to Authors: Dear authors, you performed a review about the available treatment for osteoarthritis, focusing on Adipose-derived Stromal Vascular Fractions. The review is of interest for physician who manage patients with OA. However, the information reported are sometimes vague and not supported by appropriate references.*

*Please address the issue reported below:*

- *“The primary method of diagnosing OA is imaging examination, which mainly includes X-rays, computed tomography (CT), MRI, ultrasonography, and arthroscopy. X-ray examination is one of the preferred methods for the clinical diagnosis of OA”, please support these information with references such as guidelines or consensus*

**Response:** Thanks for your constructive comments. We have added the relevant references in the manuscript.

**Text change:**

**Diagnosis and therapy of OA**

The primary method of diagnosing OA is imaging examination, which mainly includes X-rays, computed tomography (CT), MRI, ultrasonography, and arthroscopy. X-ray examination is one of the preferred methods for the clinical diagnosis of OA<sup>[19,20]</sup>.

[19] Roemer FW, Demehri S, Omoumi P, Link TM, Kijowski R, Saarakkala S, Crema MD, Guermazi A. State of the Art: Imaging of Osteoarthritis-Revisited 2020. *Radiology*. 2020 Jul;296(1):5-21. doi: 10.1148/radiol.2020192498. Epub 2020 May 19. PMID: 32427556.

[20] Khatri C, Dickenson E, Ahmed I, Bretherton C, Ranaboldo T, Shaw C, Quarcoopome J, Plastow R, Downham C, Rasidovic D, Plant C, Barlow T. ARthroscopy in Knee OsteoArthritis (ARK-OA): a multicentre study assessing compliance to national guidelines. *Eur J Orthop Surg Traumatol*. 2021 Oct;31(7):1443-1449. doi: 10.1007/s00590-021-02905-5. Epub 2021 Feb 21. PMID: 33611640.

- *Please, discriminate about the different therapeutic approaches considering the stage of the disease*

**Response:** Thanks for your constructive comments. Considering the Reviewer’s suggestion, we have supplemented the following sentences to discriminate about the different therapeutic approaches considering the stage of the disease.

**Text change:**

..... Treatment for OA primarily consists of lifestyle changes, physical therapy, drug therapy, intra-articular therapy, and surgery. However, there is no complete cure for OA. The goal of treatment in the early stage of OA is to reduce pain and stiffness. Therapeutic approaches normally involve moderate exercise, diet, and oral medication. The goal of treatment in the intermediate and late stages of OA is to maintain physical function. The therapeutic approaches normally include intraarticular injection therapy and surgery. According to the Osteoarthritis Research Society International (OARSI), suitable structured land-based exercise is one of the most effective ways to treat OA, as it can reduce joint pain and stiffness.....

In addition, we have added the following description for surgical treatment:

..... For example, for frontal malalignment and varus or valgus malalignment, high tibial osteotomy (HTO) could be used to correct the proximal tibial angle, thereby reducing pain and delaying the progression of arthritis.....

• “According to the International Cartilage Regeneration & Joint Preservation Society (ICRS), exercise is the most effective way to treat OA, as it can reduce joint pain and stiffness. Furthermore, losing weight is also one of the important ways to improve OA.”, please report appropriate reference.

**Response:** Thanks for your constructive comments. We have added the relevant references as following:

...Furthermore, losing weight is also one of the important ways for obese patients to improve OA<sup>[28]</sup>...

[28] Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA, Kraus VB, Lohmander LS, Abbott JH, Bhandari M, Blanco FJ, Espinosa R, Haugen IK, Lin J, Mandl LA, Moilanen E, Nakamura N, Snyder-Mackler L, Trojian T, Underwood M, McAlindon TE. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage*. 2019 Nov;27(11):1578-1589. doi: 10.1016/j.joca.2019.06.011. Epub 2019 Jul 3. PMID: 31278997.

Besides, we have corrected this sentence to " According to the Osteoarthritis Research Society International (OARSI), suitable structured land-based exercise is one of the most effective ways to treat OA ", which would be more appropriate.

• “The injected drugs include glucocorticoids, sodium hyaluronate, platelet-rich plasma (PRP), bone morphogenetic protein 7 (BMP-7), and stem cells”, please argue better the treatment proposed. Read and cite Migliore A, Paoletta M, Moretti A, Liguori S, Iolascon G. The perspectives of intra-articular therapy in the management of osteoarthritis. *Expert Opin Drug Deliv*. 2020 Sep;17(9):1213-1226. doi: 10.1080/17425247.2020.1783234. Epub 2020 Jun 22. PMID: 32543240.

**Response:** Thanks for your constructive comments. We have read and cited the article you recommend, and supplemented the following sentences to argue better the treatment proposed.

#### **Text change**

It should be noted that ultrasound can be used to guide the use of intraarticular injections in patients with advanced osteoarthritis and obesity. A novel intraarticular injectable drug-loaded delivery system using nanoscale materials, including micelles, liposomes, and dendrimers, has been proposed. This method can slow drug release and prolong drug retention time in the joint cavity<sup>[29]</sup>. Besides, we added the sentences in the “**discussion**” part to further supplement the importance of this treatment. The sentences are as following:

Considering that osteoarthritis is a whole joint disease, OA should be treated with combined therapy. Through intraarticular injection therapy, treatment agents can directly reach the damaged site, which can not only allow drugs and especially stem cells to avoid being cleared by the body but also reduce the potential systemic effects of drugs<sup>[70]</sup>. Especially for traumatic arthritis, cartilage adipose stem cells provide a new avenue for the treatment of this type of arthritis through their powerful differentiation ability and paracrine and anti-inflammatory effects. Therefore, intraarticular injection therapy should be added to the combined treatment of OA.

[29] Migliore A, Paoletta M, Moretti A, Liguori S, Iolascon G. The perspectives of intra-articular

therapy in the management of osteoarthritis. Expert opinion on drug delivery. 2020;17(9):1213-26.  
[70] Georgiev T. Multimodal approach to intraarticular drug delivery in knee osteoarthritis. Rheumatology international. 2020;40(11):1763-9.

• *Recently, a new intrarticular agent is proposed for the treatment of OA. Please, read and cite Moretti A, Paoletta M, Liguori S, Ilardi W, Snichelotto F, Toro G, Gimigliano F, Iolascon G. The Rationale for the Intra-Articular Administration of Clodronate in Osteoarthritis. Int J Mol Sci. 2021 Mar 7;22(5):2693. doi: 10.3390/ijms22052693. PMID: 33799992; PMCID: PMC7962069.*

**Response:** Thanks for your constructive comments. We have read and cited the article you recommend, and supplemented the following sentences at the end of the discussion:

...Recently, it has been concluded that clodronate can reduce pain and improve joint mobility by intraarticular injection for OA treatment. Combined with HA, clodronate can also relieve pain and reduce bone marrow lesions (BMLs) in early OA. In the future, it may be used in conjunction with SVF for better results <sup>[71]</sup>.

[71] Moretti A, Paoletta M, Liguori S, Ilardi W, Snichelotto F, Toro G, et al. The Rationale for the Intra-Articular Administration of Clodronate in Osteoarthritis. International journal of molecular sciences. 2021;22(5).

**Reviewer #3(Remarks to the Author):**

*Scientific Quality: Grade B (Very good)*

*Language Quality: Grade B (Minor language polishing)*

*Conclusion: Major revision*

*Specific Comments to Authors: Overall: The present manuscript is a well written and detailed review focusing on therapeutic applications of adipose-derived stromal vascular fractions. This is a very timely review of a "hot" topic.*

*Abstract: Please fix the definition of osteoarthritis in the abstract. The contemporary concept of osteoarthritis now assumes the disease as a highly heterogeneous disorder characterized by progressive cartilage loss, remodeling of adjacent bones and concomitant low-grade inflammation (PMID: 30911813).*

**Response:** Thanks for your constructive comments. Considering the Reviewer's suggestion, we have fixed the definition of osteoarthritis in the abstract as follows:

**Osteoarthritis (OA) is considered to be a highly heterogeneous disease with progressive cartilage loss, subchondral bone remodeling, and low-grade inflammation.**

And we have read cited the article (PMID: 30911813) in the Introduction part, the reference number is [2].

*Keywords should be preferably selected from the MeSH browser.*

**Response:** Thanks for your constructive comments. We have selected appropriate keywords from MeSH browser, the modified keywords are as follows:

**Arthritis, Articular cartilage, Stromal vascular fraction, Mesenchymal stem cells, Cell therapy**

*Minor comments: Introduction: Please, fix those expressions: 1. "OA is a complete joint disease" – OA is considered a whole joint disease. 2. "This disease not only causes" – This disease does not only cause... 3. Economic burden is usually brought to society and not only to the patients. 4. "It is worth noting that, for different genders, the prevalence of OA in females is higher than in males" – "for different genders" is abundant. The introduction should ideally end with the aim of the present manuscript. If it is a review please describe the purpose of this review in addition to its justification.*

**Response:** Thanks for your constructive comments. Considering the Reviewer's suggestion, we have fixed the expressions in the "introduction" part. And at end of the introduction, we added sentences as following:

**.... Since OA can cause great personal and economic losses, we must pay attention to it. The purpose of this paper is to introduce the pathogenesis, diagnosis and current clinical treatment methods of OA and briefly summarize the clinical research and mechanism of SVF in the treatment of osteoarthritis....**

*Please discuss further intraarticular injections as a part of a multimodal approach to the osteoarthritic joint. Since you agree that OA is a whole-joint disease, an urge has arisen for the implementation of intraarticular injections in a whole joint approach for the management of KOA (PMID: 32803403)*

*Minor English check may be beneficial.*

**Response:** Thanks for your constructive comments. Considering the Reviewer's suggestion, we added the sentences in the "discussion" part and cited the literature(PMID: 32803403). The

sentences are as following:

..... Considering that osteoarthritis is a whole joint disease, OA should be treated with combined therapy. Through intraarticular injection therapy, treatment agents can directly reach the damaged site, which can not only allow drugs and especially stem cells to avoid being cleared by the body but also reduce the potential systemic effects of drugs <sup>[70]</sup>. Especially for traumatic arthritis, cartilage adipose stem cells provide a new avenue for the treatment of this type of arthritis through their powerful differentiation ability and paracrine and anti-inflammatory effects. Therefore, intraarticular injection therapy should be added to the combined treatment of OA.....

[70] Georgiev T. Multimodal approach to intraarticular drug delivery in knee osteoarthritis. *Rheumatology international*. 2020;40(11):1763-9.

Moreover, we have asked native English speakers to rewrite the manuscript that the reviewers thought we lacked details or clarity. Editorial certificate was listed below.

**SPRINGER NATURE**

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## Editing Certificate

This document certifies that the manuscript

**A Short Review of Therapeutic Applications of Adipose-derived Stromal Vascular Fractions in Osteoarthritis**

prepared by the authors

**Qi Tang, Xiansheng Zhao, Ao Guo, Ruotong Cui, Huaile Song, Ziyang Qi, yi Pan, Yue Yang, Fangfang Zhang, Liang Jin**

was edited for proper English language, grammar, punctuation, spelling, and overall style by one or more of the highly qualified native English speaking editors at SNAS.

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**Reviewer #4 (Remarks to the Author):**

*Scientific Quality: Grade C (Good)*

*Language Quality: Grade B (Minor language polishing)*

*Conclusion: Major revision*

*Specific Comments to Authors: Dear authors, thanks for submitting your manuscript. It describes the background and stem cell therapy potential of osteoarthritis. Some parts of the manuscript need some major revision to make the manuscript ready for publication. Title: ok Abstract: ok Keywords: words used in the title should not be part of the keywords (e.g. osteoarthritis)*

**Response:** Thanks for your constructive comments. Considering the Reviewer's suggestion, we have selected appropriate keywords from the MeSH browser, the modified keywords are as follows: Arthritis, Articular cartilage, Stromal vascular fraction, Mesenchymal stem cells, Cell therapy

*The "Pathogenesis" part should mention prearthritic deformities. Severe valgus or varus malalignment leads to lateral or medial gonarthrosis. It should further be discussed that frontal malalignment needs to be appreciated and addressed by correction osteotomy when developing a concise treatment plan.*

**Response:** Thanks for your constructive comments. We agree with you and have added the following statements in corresponding positions according to your opinions:

**Pathogenesis of OA**

...It should be noted that prearthritic deformities of the limbs could also lead to osteoarthritis. For example, severe valgus or varus malalignment leads to lateral or medial gonarthrosis. This can produce a change in the distribution of high stresses within the joint, resulting in a force imbalance, which in turn accelerates arthritic pathology...

**Diagnosis and therapy of OA**

..... For example, for frontal malalignment and varus or valgus malalignment, high tibial osteotomy (HTO) could be used to correct the proximal tibial angle, thereby reducing pain and delaying the progression of arthritis....

*The best stem cells alone cannot prevent arthritis in severe malalignment. Also, in the manuscript the role of stem cells in post traumatic arthritis should be discussed.*

**Response:** Thanks for your constructive comments. We agree with you and have added this sentence to the discussion section as you suggested:

.... Especially for traumatic arthritis, cartilage adipose stem cells provide a new avenue for the treatment of this type of arthritis through their powerful differentiation ability and paracrine and anti-inflammatory effects....

*At the end of the discussion, please give a conclusion of your work. The conclusion paragraph should be identified by a common wording like: "In conclusion..." e.g.*

**Response:** Thanks for your constructive comments. We agree with you and have added the conclusion sentences at the end of the discussion according to your suggestion:

In conclusion, SVF is an effective treatment for repairing articular cartilage damage, especially for relieving pain and other symptoms and improving joint function in OA patients. At the same time, clinical treatment with SVF is very safe. Relevant mechanistic studies reveal the beneficial role of

SVF and its paracrine molecules in the treatment of osteoarthritis, which can mediate intercellular communication and interact with the cellular microenvironment and a variety of cell types, thus triggering appropriate cellular responses, inhibiting inflammation, promoting cartilage repair and regeneration and restoring joint homeostasis to reduce pain. However, various factors can change the characteristics of SVF and its secretion, such as individual differences in donors and different preparation standards, which may limit its therapeutic effect. Therefore, further in-depth research is still needed to make stem cells a routine clinical treatment for diseases such as osteoarthritis.

*References: Some references about secondary arthritis should be added and discussed*

**Response:** Thanks for your constructive comments. We took your advice and checked the references carefully. Relevant references have been added.

**Reviewer #5 (Remarks to the Author):**

*Scientific Quality: Grade D (Fair)*

*Language Quality: Grade B (Minor language polishing)*

*Conclusion: Major revision*

*Specific Comments to Authors: Dear authors I commend you for your work on exploring the utility of SVF in the treatment of OA I have some serious queries which prevent me from considering the work for publication When we look into the available literature on the use of SVF for OA we have abundant literature on the same subject and i do not find any distinct discussion or different perspective that is being communicated to the community through this article. Moreover i find this article to be of review nature but authors claim it to be original research which I could not accept.*

**Response:** Thanks for your valuable and constructive comments. Firstly, osteoarthritis is one of the world's leading causes of disability. Clinically, palliative drugs cannot fundamentally cure this disease. The stromal vascular fraction (SVF) from adipose tissues is a heterogeneous cell population. According to studies, it contains a large number of mesenchymal stem cells (MSCs), which have been used to treat OA with good therapeutic effects. At present, although there are abundant literature and relevant reports. However, in this review, we present an updated status of the comprehensive and systematic review of pathogenesis, diagnosis, and current clinical treatments for OA, especially focusing on therapeutic applications of adipose-derived stromal vascular fractions. Moreover, we systematically summarized the mechanism of SVF in the treatment of OA. Although this hotspot review may lack forward-looking or groundbreaking thinking, we have done a great deal of investigation, collation, and analysis. In the review, a comprehensive and logically thought-out innovative narrative is presented. We thought this might help others a little. Thus, this is a very timely review of a “hot” topic. And this review is of interest to both physicians who manage patients with OA and science researchers who focuses on the biological mechanisms of OA.

The other four reviewers also confirmed this review and point to constructive suggestions. We completely accept reviewers' recommendations and fully agree that these recommendations can further strengthen the quality of the manuscript. We have revised the manuscript very carefully and according to the suggestions. We firmly believe that revision is more perfect for the summary of the background and stem cell therapy potential of osteoarthritis.

Moreover, we checked our manuscript, we have not claimed it to be original research. Maybe because of our writing mistakes, the reviewers misapprehended it. We have asked native English speakers to rewrite the manuscript that the reviewers thought we lacked details or clarity. The editorial certificate was listed below. We hope the explanations and changes above would make you

and other readers much easier to understand our manuscript.

SPRINGER NATURE

Author Services

Editing Certificate

This document certifies that the manuscript

A Short Review of Therapeutic Applications of Adipose-derived Stromal Vascular  
Fractions in Osteoarthritis

prepared by the authors

Qi Tang, Xiansheng Zhao, Ao Guo, Ruotong Cui, Huaile Song, Ziyang Qi, Yi Pan, Yue Yang,  
Fangfang Zhang, Liang Jin

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should be English-ready for publication; however, the author has the ability to accept or reject our suggestions and changes. To verify the final  
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## RE-REVIEW REPORT OF REVISED MANUSCRIPT

Dear editor:

Thank you very much for your comments and advice to our manuscript entitled "**Therapeutic Applications of Adipose-derived Stromal Vascular Fractions in Osteoarthritis**" (Manuscript NO.: 76905, Review). We completely accept your recommendation and fully agree that these recommendations can further strength the quality of the manuscript. We have revised the manuscript very carefully and according to the suggestions. A thorough, point-by-point response to each point was raised and all changes, a word file of the revised manuscript with all changes labelled in **red font** has been uploaded. If you have any further questions about the revision, please do not hesitate to contact us.

Best regards,  
Liang Jin

### SPECIFIC COMMENTS TO AUTHORS

1. Expand NCT in the Table 1 footer

**Response:** Thanks for your valuable and constructive comments. We have expand NCT in the Table 1 footer.

2. Consequences to be changed in table 2 heading to results

In the discussion also comment on the benefit of using AD-based SVF compared to BM-MSCs as AD-MSCs are found to be superior as shown in <https://doi.org/10.1177%2F1947603520951623>

Comment and ease of its extraction and its regulations in processing which limit their earlier clinical translation

**Response:** Thanks for your constructive comments. We have added the relevant content in the discussion according to your advice.

3. Please check this reference, wrong DOI? (47 Tantuway V, Sharma AK, Mehta MH, Sharma R, Mantry P, Mehto P, et al Use of Autologous Adipose-derived Stromal Vascular Fraction Grafting in Treatment of Knee Osteoarthritis: A Safety and Efficacy Study. J Med Res Prac 2017; 6: 119-127 [DOI: 10.18203/issn.2455-4510.intjresorthop20164834])

**Response:** We have carefully checked the information of this reference, we found that but we did not find the PMID and DOI of this article. We have provided the full pdf of this article.

4. Please provide an "Audio core tip" file. You can record an audio about the content of "Core Tip", and the file format can be mp3 or wav.

**Response:** Thanks, we have provided the audio core tip in the mp3 format.

5. Please provide the grant application form(s) or certificate of funding agency for every grant, or we will delete the part of "Supported by...".

**Response:** Thanks, all the certificate of funding agency for every grant have been provided.