

## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Stem Cells*

**Manuscript NO:** 88551

**Title:** Human mesenchymal stem cells exhibit altered mitochondrial dynamics and poor survival in high glucose microenvironment

**Provenance and peer review:** Invited manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 05198253

**Position:** Peer Reviewer

**Academic degree:** MD, PhD

**Professional title:** Academic Research, Chief Doctor, Doctor, Research Scientist

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** Jordan

**Manuscript submission date:** 2023-09-28

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2023-09-28 08:53

**Reviewer performed review:** 2023-10-04 07:43

**Review time:** 5 Days and 22 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation

<b>Scientific significance of the conclusion in this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

## SPECIFIC COMMENTS TO AUTHORS

Overall, the study presents intriguing findings on the impact of high glucose on the mitochondrial dynamics of mesenchymal stem cells (MSCs), providing a potential mechanism for the reduced efficacy of MSC-based therapies in diabetes mellitus (DM) environments. However, several areas need clarity, elaboration, and refinement. Major problems: This article has too little experimental validation, and the pathway selection builds on the literature. It is recommended that the authors perform RNA sequencing of the treated cells and combine it with bioinformatics analysis for more in-depth mechanistic exploration. Abstract: The phrasing "reputable type of stem cells that has enchanted regenerative abilities" seems colloquial and lacks scientific precision. Suggest revising for clarity and accuracy. Provide specific data in the results section of the abstract to provide quantifiable evidence of the findings. Introduction: The introduction provides a comprehensive overview of the current knowledge on the topic. However, it would benefit from being more concise and directly relevant to the study's objectives. In the last sentence of the introduction, specify what "these changes" refer to, for clarity. References [2,3] discuss the positive outcomes of MSCs but then state there

were short-lived therapeutic results. Please clarify this discrepancy. **Materials and Methods:** For the glucose conditions (low and high), it would be beneficial to provide a rationale for the specific concentrations chosen. Clarify the source and characteristics of the hAD-MSCs, such as their passage number at the beginning of the experiment. For the cytotoxicity assays, provide more details on the LDH Assay methodology, including the number of cells seeded and any controls used. The procedure for the apoptosis assay should be elaborated upon. It's essential to understand the exact steps taken to ensure reproducibility. **Results:** In section 3.1, it would be beneficial to provide actual percentages or quantitative data regarding cell viability and cytotoxicity, instead of qualitative terms like "remarkably low" or "significantly greater." In the mitochondrial dynamics section (3.2), provide specific values for the changes in TMRE fluorescence intensity and NAD<sup>+</sup>/NADH ratios. For the western blot results (3.4), include the actual fold-changes or percentages to understand the magnitude of the observed effects. Additionally, consider presenting representative blots for clarity. The results section is missing statistical information. State the statistical significance for each data point and consider adding p-values to the figures. **Discussion:** The discussion provides a broad overview of the findings and their implications. However, it would benefit from a more focused discussion, directly related to the study's results. The paragraph discussing the discrepancies in mTOR regulation in different cell types is quite lengthy. Consider streamlining it or presenting it in a more structured manner to enhance readability. The sentence "The findings of our study deserve consideration in broader context..." seems slightly biased. Reframe to a more neutral tone. **Conclusion:** The conclusion adequately summarizes the main findings. However, it largely mirrors the abstract. Consider adding future implications or research directions. **General/Miscellaneous:** Throughout the manuscript, there are instances of repeated information (e.g., the properties of MSCs, the characteristics of DM). Streamlining these will enhance readability. There are



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7041 Koll Center Parkway, Suite  
160, Pleasanton, CA 94566, USA  
**Telephone:** +1-925-399-1568  
**E-mail:** [bpgooffice@wjgnet.com](mailto:bpgooffice@wjgnet.com)  
**https://**[www.wjgnet.com](http://www.wjgnet.com)

occasional grammatical errors. Consider a thorough proofreading or editing pass. It would be beneficial to have a figure showing the impact of high glucose on MSCs in a schematic diagram, detailing all the changes observed in the study. Ensure all figures mentioned in the text (e.g., Figure 1a, Figure 2 a &b) are provided for review. Confirm the consistency in the use of abbreviations throughout the manuscript (e.g., "hMSCs" vs. "hAD-MSCs"). In conclusion, the manuscript provides valuable insights into the impact of high glucose on MSCs, which has significant implications for MSC-based therapies in DM environments. Addressing the above comments will further strengthen the manuscript, making it a robust addition to the existing literature.

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**Peer-review model:** Single blind

**Reviewer's code:** 06215468

**Position:** Peer Reviewer

**Academic degree:** N/A

**Professional title:** N/A

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** Jordan

**Manuscript submission date:** 2023-09-28

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2023-10-02 20:31

**Reviewer performed review:** 2023-10-05 10:47

**Review time:** 2 Days and 14 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation

<b>Scientific significance of the conclusion in this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input checked="" type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

## SPECIFIC COMMENTS TO AUTHORS

1. According to the citation of the article, it is known that mesenchymal stem cells used to treat diabetes mainly include bone marrow mesenchymal stem cells, Wharton's jelly mesenchymal stem cells, umbilical cord mesenchymal stem cells and amniotic mesenchymal stem cells and induced pluripotent stem cells. Choosing adipose-derived stem cells as the research object to realize the investigation of high diabetes or hyperglycemia on the cellular and molecular characteristics of MSCS needs to be clear. 2. As far as I know, the study of the biological behavior changes of adipose-derived stem cells under high glucose conditions, there have been studies (high glucose-induced reactive oxygen species generation promotion stemness in human adipose-derived stem cells <https://pubmed.ncbi.nlm.nih.gov/26780864/>) , so the author uses the phrase "Little is known about the impact of diabetic microenvironment, granular hyperglycemia" is inaccurate, and this part has not been discussed in the article. 3. LDH is used to detect cytotoxicity, but there is only one normal glucose culture in the control vs. high sugar culture conditions of different days? 4. According to the official instructions



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160, Pleasanton, CA 94566, USA  
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**https://**www.wjgnet.com

(<https://www.abcam.com/products/assay-kits/tmre-mitochondrial-membrane-potential-assay-kit-ab113852.html>), TMRE fluorescence intensity is only qualitative test, and I personally think that other experiments are needed to verify the results again. 5. The balance of NAD<sup>+</sup>/NADH pool is very important to the balance of mitochondrial membrane potential, but whether there are other factors, such as high glucose leading to high osmotic pressure environment, has not been elaborated in this research. 6. "It has been reported that mTOR is important to preserve mitochondrial dynamics and generate the required mitochondrial potential to produce ATP. PI3K is required to remove the inhibitory effect of tuberous sclerosis tumor suppressor (TSC1) which binds mTOR and in activations it." This key part lacks citation. Moreover, it is different from the mTOR signal path (<https://www.genome.jp/pathway/map04150>) related to the KEGG website. Generally speaking, I think this article should be rejected.

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**Title:** Human mesenchymal stem cells exhibit altered mitochondrial dynamics and poor survival in high glucose microenvironment

**Provenance and peer review:** Invited manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 03478635

**Position:** Editorial Board

**Academic degree:** PhD

**Professional title:** Senior Research Fellow

**Reviewer's Country/Territory:** Japan

**Author's Country/Territory:** Jordan

**Manuscript submission date:** 2023-09-28

**Reviewer chosen by:** Yu-Lu Chen

**Reviewer accepted review:** 2023-10-16 00:55

**Reviewer performed review:** 2023-10-17 01:06

**Review time:** 1 Day

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
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	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

## SPECIFIC COMMENTS TO AUTHORS

Figure 6 and the description of the Figure 6 in text may be revised to represent summary of the research and introduce the diabetic microenvironment more clearly.

## RE-REVIEW REPORT OF REVISED MANUSCRIPT

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**Peer-review model:** Single blind

**Reviewer's code:** 06215468

**Position:** Peer Reviewer

**Academic degree:** N/A

**Professional title:** N/A

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** Jordan

**Manuscript submission date:** 2023-09-28

**Reviewer chosen by:** Jing-Jie Wang

**Reviewer accepted review:** 2023-11-13 06:05

**Reviewer performed review:** 2023-11-13 06:14

**Review time:** 1 Hour

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input checked="" type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Peer-reviewer</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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**Telephone:** +1-925-399-1568  
**E-mail:** bpgoffice@wjgnet.com  
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statements

Conflicts-of-Interest: [ ] Yes [Y] No

#### **SPECIFIC COMMENTS TO AUTHORS**

I think the author's answer based on the question is scientific. At present I agree to the publication of this article.