Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Thank you for asking my opinion about the manuscript entitled "HIF-2α increases bone mass by promoting BMSCs osteogenesis in bone marrow microenvironment via inhibiting mTOR signaling". I believe that this manuscript should be MAJOR revision: Q1. It is very important to change and modify the title. the title is not appropriate. Q2. Are the objectives and the rationale of the study clearly stated? Q3. In the abstract, the research gap was not clearly stated. In addition, the authors need to rewrite the study objectives to be more academic writing Q4. In the introduction, include the study's significance and novelty. What makes the study different from the rest and what does it add to the current knowledge?. Q5. In the introduction, the authors should have explained the purpose of this study and the existing gaps in this field and explained why this study was conducted. Q6. Are the methods clear and replicable? Do all the results presented to match the methods described? Q7. If relevant are the results novel? Does the study provide an advance in the field? Is the data plausible? Q8. References are relevant, correct, and not recent. The number of references should be increased. please add some references. since this is a scientific review, all the sentences need to be

supported with references. This study is very beautiful. I liked the sequence and enjoyed reading. Please add more references on similar studies. Q9. There are a lot of grammatical errors. This must be taken care of and addressed. Q10. What are the limitations of the study? A description of limitations is missing at the end of the discussion section. • If your manuscript is related to mine, you can cite it (ORCID: https://orcid.org/0000-0002-5107-5550).

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Although biological analyses are well done, analyses on bones are rather insufficient. In addition of simple mass, some features such as density, chemical compositions, and inside morphologies may be affected. Without such multi-angle analyses, true phenomena cannot be discussed. More detailed analyses on bones are necessary.

PEER-REVIEW REPORT

Name of journal: *World Journal of Stem Cells*

Manuscript NO: 89703

Title: Unveiling the role of hypoxia-inducible factor 2alpha in osteoporosis: Implications for bone health

Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03373045

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Professor

Reviewer's Country/Territory: Egypt

Author's Country/Territory: China

Manuscript submission date: 2023-11-09

Reviewer chosen by: Yu-Lu Chen

Reviewer accepted review: 2023-11-30 08:48

Reviewer performed review: 2023-12-08 08:19

Review time: 7 Days and 23 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The following points need to be addressed before considering this work to be published. Major Concerns 1. Rationale and Novelty: The introduction implies a lack of studies on the association between HIF-2α and osteoporosis, but this relationship is well-documented. The study's novelty requires clarification to highlight its unique contributions amidst existing research. 2. In Vitro Experiments and Mice Group Clarification: It remains unclear from which group of mice the MSCs were extracted for the in vitro experiments in Figure 6D-K and Fig. 7. Were these BMSCs from naïve mice? If so, the rationale for not exploring similar parameters in other mouse genotypes needs clarification instead of solely focusing on naïve mice in these particular experiments. 3. Supplementary Data for WB Experiments: The uncropped whole blots of the Western blot experiments should ideally be provided as supplementary figures, including replicates for comprehensive evaluation. Minor Concerns 1. Abstract Revision: The abstract requires substantial improvement, especially in the background and methodology sections. The claim that few studies exist on HIF-2α's role in osteogenesis needs removal, and the study's rationale must be articulated clearly. Detailed

methodology is also necessary. 2. Detailed Quantitative Assessments: The histology experiment's quantitative assessments need elaboration for better comprehension. 3. Language Editing: The manuscript requires language editing for improved clarity and readability.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Stem Cells*

Manuscript NO: 89703

Title: Unveiling the role of hypoxia-inducible factor 2alpha in osteoporosis: Implications for bone health

Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06139840

Position: Peer Reviewer

Academic degree: PhD

Professional title: Professor

Reviewer's Country/Territory: Iraq

Author's Country/Territory: China

Manuscript submission date: 2023-11-09

Reviewer chosen by: Jing-Jie Wang

Reviewer accepted review: 2024-01-19 07:45

Reviewer performed review: 2024-01-19 07:47

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Peer-reviewer	Peer-Review: [Y] Anonymous [ ] Onymous

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

SPECIFIC COMMENTS TO AUTHORS

Thank you for asking my opinion about the manuscript entitled "Unveiling the Role of HIF-2a in Osteoporosis: Implications for Bone Health". I believe that this manuscript should be major revision: Q1. It is very important to change and modify the title. The title is not appropriate. Q2. Are the objectives and the rationale of the study clearly stated? Q3. In the abstract, the research gap was not clearly stated. In addition, the authors need to rewrite the study objectives to be more academic writing Q4. In the introduction, include the study's significance and novelty. What makes the study different from the rest and what does it add to the current knowledge?. Q5. In the introduction, the authors should have explained the purpose of this study and the existing gaps in this field and explained why this study was conducted. Q6. Are the methods clear and replicable? Do all the results presented to match the methods described? Q7. If relevant are the results novel? Does the study provide an advance in the field? Is the data plausible? Q8. References are relevant, correct, and not recent. The number of references should be increased. please add some references. since this is a scientific review, all the sentences need to be supported with references. This study is very beautiful. I liked the sequence and enjoyed reading. Please add more references on similar studies. Q9. There are a lot of grammatical errors. This must be taken care of and addressed. Q10. What are the limitations of the study? A description of limitations is missing at the end of the discussion section.