



## PEER-REVIEW REPORT

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

**Manuscript NO:** 74043

**Title:** The important factor of sex hormone affecting differentiation and commitment of mesenchymal stem cells

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

**Peer-review model:** Single blind

**Reviewer's code:** 05935626

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor

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

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

**Manuscript submission date:** 2021-12-12

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2021-12-14 12:33

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**Review time:** 2 Hours

<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 Grade E: Do not publish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 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 checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



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

I would like to congratulate the authors for this article. It can bring new perspective on the development of the referred study. I have some comments: The referred study by Alessio et al. is interesting and I believe it has been reviewed by the reviewers accordingly. Since the referred study is already done, the suggested study which involve sex hormones (estrogen and androgens) on the differentiation and commitment of MSCs would be a great idea and interesting for another research or project development. Regarding the statistical method used and sample size, it would be more informative if the authors can give suggestion about the appropriate method and sample size to avoid bias, in detail.



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**Peer-review model:** Single blind

**Reviewer's code:** 03712811

**Position:** Editor-in-Chief

**Academic degree:** MD, PhD

**Professional title:** Director, Full Professor

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

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

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<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input checked="" type="checkbox"/> Grade E: Do not publish
<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 type="checkbox"/> Major revision <input checked="" type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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## SPECIFIC COMMENTS TO AUTHORS

The submitted Letter to the Editor, aims at providing a critical reading of an article published in 2019 in the World Journal of Stem Cells, entitled: "Circulating factors present in the sera of naturally skinny people may influence cell commitment and adipocyte differentiation of mesenchymal stromal cells", contributed by Alessio N, et al. In this article, the Authors start from the background assumption that "Research on physiopathology of obesity may receive new hints from studies on skinny people (SP)". The Authors are aware of the fact that "These are individuals who show a poor or null gaining of body weight, in spite of high-calorie intake, by far exceeding the body requirements". The declared aim of the study was "To evaluate how circulating factors present in the SP sera may affect adipogenesis of mesenchymal stromal cells (MSCs)". While a Letter to the Editor may undoubtedly contribute a debate on such a relevant issue, unfortunately the submitted Letter has been shaped in quite an aggressive tone, as it is clearly indicated by sentences like: "It is unbecoming to judge the effect of other cytokines in the SP sample on MSCs without excluding the influence of androgens". Indeed, to this end, Alessio et al. are well aware of the issue of sex hormones controlling MSC fate: "We selected only male since estrogen fluctuation may introduce further complexity to data analysis. Indeed, estrogen may influence MSC osteo-adipo commitment[24,25]". Thus, the Authors likely decided to avoid confounding bias associated with the well-known effect of sex hormones on MSC differentiating/paracrine potential. Overall, the main value of the study of Alessio et al. is the novel finding that SP priming of MSCs affected adipocyte cell commitment and reduced spontaneous adipogenesis, showing striking differences between differentiation



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in SP-primed samples, compared with the ones that had been primed with serum harvested from normal people (NP). The Authors are aware of the preliminary nature of their cytokine assay in NP and SP sera: “we performed a preliminary analysis of SP cytokine content to identify possible molecules that may play a role in the physio-pathology of adipogenesis and related phenomena”. Nevertheless, the performed assessment was a wide-ranging cytokine profiling: cytokine content of NP and SP sera was evaluated by array analysis. “The relative levels of 62 cytokines were analyzed in NP and SP groups by the Human Obesity Antibody Array C1 (RayBiotech, United States)”. In actual fact, the same Authors “focused on four factors (ACRP30, ANGPT1, IGFBP1, and RANTES) that could be related to the physiological status of SP: Eating an excess of calories without weight gain”. In other words, they decided to focus on a number of factors whose differential expression in SP sera may account for the observed MSC responses, as shown in Figure 6. Overall, the reported findings may have molecular underpinning in the pattern of observed differential cytokine expression. Of course, considering other additional factors potentially contributing to the observed phenomena is something deserving further investigation and it may well be a subject for a Letter to the Editor. Nevertheless, this Letter cannot be shaped with an excessive opinionated tone, largely neglecting the reliability of the study itself (“In such a small sample size, statistical analysis and conclusion inference are prone to bias, and too small sample size will significantly reduce the credibility of the conclusion”). Besides, the submitted Letter presents flaws in both grammar and sentence construction.



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**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Dcotor

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

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

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<b>Scientific quality</b>	<input checked="" type="checkbox"/> Grade A: Excellent <input 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 type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



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

The letter focus on conclusions taken by the work of Alessio et al (2019) in respect to MSCs differentiation in fat cells. Therefore, the title of the letter should point specifically differentiation in this cell type, instead of a general capacity. Authors refers to mesenchymal stem cells as pluripotent cells, however, MSCs are widely described as multipotent cells.



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**Peer-review model:** Single blind

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**Position:** Peer Reviewer

**Academic degree:** MD

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<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<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 checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



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### **SPECIFIC COMMENTS TO AUTHORS**

The manuscript arouses considerable interest for the topic it deals with. However, there are some observations to highlight from a technical point of view. In particular, it would be interesting to consider the age of each female and male sample in order to obtain more specific data. Furthermore, it would be clearer to describe the process of differentiation and commitment of the MSCs also through images with associated captions. From a point of view of materials and methods, the manuscript highlights few methods of analysis. In particular, as regards the statistical method, the manuscript lacks a descriptive part of this method and the meaning of the statistical parameters it takes into consideration, such as variance. Finally, as far as the reference bibliography is concerned, the manuscript has few references and of those that exist, some are much less recent and should be replaced with other more recent references that can best support the issue being addressed.



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**Reviewer's code:** 03812042

**Position:** Editorial Board

**Academic degree:** MSc, PhD

**Professional title:** Assistant Professor, Professor, Research Associate

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

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<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 checked="" type="checkbox"/> Minor revision <input 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
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### **SPECIFIC COMMENTS TO AUTHORS**

In this paper the authors wrote a letter to the Editor in which commented the article written by Alessio N, published on world journal of stem cell. Alessio et al in their paper studied why skinny people (SP) intake excess calories than the body needs while present normal body composition. They summarized these reasons as the existence of some factors in the human serum of SP that promote the differentiation of mesenchymal stromal cells (MSCs) towards brown adipocytes. The authors of the letter to the Editor point out several important weakness of the published paper and hypothesizes an important role of sexual hormones in the results found by Alessio N. et al. I think that authors are right. However, the abstract is confusing and should be rewritten describing the most important comments within the Letter to the editor. Moreover, they should describe better and more deeply the study design and the results of the published paper of Alessio N. et al.