

Dear Editors,

Thank you very much for the review of our manuscript entitled: "RAGE axis: A contributor to the risk of severe illness from COVID-19 in diabetes patients; Manuscript NO: 622787", submitted to the World Journal of Diabetes.

We sincerely appreciate all valuable comments and suggestions, which helped us to improve the quality of the article. Our responses to the Reviewers' comment are described below in a point-to-point explanation format. All comments and suggestions has been introduced to the manuscript (highlighted within the document).

The article has been prepared in accordance with World Journal of Diabetes – Guidelines and Requirements for Manuscript Revision: Minireviews.

I hereby confirm that this manuscript or a major portion thereof has not been published previously, accepted for publication elsewhere and it is not under consideration for publication elsewhere. The work has been conducted under internationally accepted ethical standards. All authors have contributed significantly to the work, and they have reviewed and approved the final version of the manuscript.

Moreover, we declare that there are no conflicts of interest. We hope that our manuscript will be acceptable for publication in World Journal of Diabetes.

Sincerely yours,

Armando Rojas, PhD, Biomedical Research Laboratories, Medicine Faculty, Catholic University of Maule, Talca, Chile. [arojasr@ucm.cl](mailto:arojasr@ucm.cl). Corresponding author.

### **Point by point explanations to reviewers' s comments.**

The authors would like to thank the editor and two anonymous referees who kindly reviewed the original version of this manuscript and provided valuable suggestions and comments. We present our response to the comments and suggestions.

#### **Reviewer # 1.**

- 1- Thanks to authors for this well designed review. Receptor for Advanced Glycation Endproducts (RAGE) as a transmembrane receptor of the immunoglobulins has been shown that related to ongoing low-level inflammation in chronic diseases especially diabetes mellitus. This review explores the literature to explain a mechanism why more severe consequences occur in diabetic patients with Covid-19.

**Answer:** All authors really appreciate the comment endorsing our work

- 2- RAGE should be expressed openly in it's first usage, as in keywords, not as an abbreviation.

**Answer:** As suggested, RAGE is now openly expressed in its first use.

- 3- Same abbrev. issue should be performed for ECM, AGEs, HMGB1 in their first usage.

**Answer:** As suggested, all terms denoted by abbreviations in the text, now appear openly expressed in their first use.

- 4- Title is appropriate to reflect the inclusion of the review.

**Answer:** We appreciate your comment about the title.

- 5- Correction for "diabtes,"

**Answer:** This and others grammars and typos have been corrected throughout the text.

- 6- Any projections may be mentioned on how this pathway coincides with possible side effects of metformin and sodium–glucose cotransporter 2 inhibitors in diabetic Covid-19 patients.

**Answer:** The authors greatly appreciate this excellent observation. This suggestion have been now covered in the text by the addition of 5 paragraphs and the corresponding references (See, page 13, paragraphs 1-5.

7- How does pathophysiologic pathway explain viral particles inside the cells in endotheliitis / endothelialitis?

**Answer:** The authors greatly appreciate again this excellent observation. This question has been answered and included in the text. See page 10, paragraph 4 and 5 and page 11, paragraphs 1, 2, 3.

8- Could RAGE explain all aspects of increased susceptibility to hyperinflammation in Covid-19. If not, “RAGE axis seems to be a key player “ should be “RAGE axis seems to be one of key players”

**Answer:** As suggested, the correct phrase is “RAGE axis seems to be one of key players” and as such appears now in the text.

**Reviewer #2:**

1- The abstract is poor and should be rewritten, stating firmly and comprehensively the content of the manuscript.

**Answer:** All authors thank this suggestion. The abstract was then written, and we now stating all contents that has been covered in the manuscript.

2- The meaning and the importance of RAGE should be explained in the abstract as well as in the Introduction.

**Answer:** We greatly appreciate this suggestion and the importance of the RAGE axis are now stated in the text of both the Abstract (see paragraph 1) and the Introduction sections (see page 4, paragraph 2)

3- Some minor typing errors should be corrected throughout the manuscript.

**Answer:** Authors appreciate your comment and we corrected all typos in the text.