



**CENTRO DE INVESTIGACIÓN Y DE ESTUDIOS AVANZADOS
DEL I. P. N.
Departamento de Genética y Biología Molecular**

Mexico City, Friday June 23rd, 2020.

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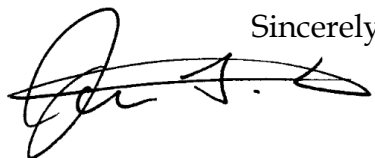
Dear Editors,

We have enclosed to this letter the revised text of our review entitled “The gut microbiota of a population highly affected of obesity and type 2 diabetes and the susceptibility to COVID-19” requesting to consider it for publication in the World Journal of Gastroenterology.

The text conforms to the style detailed in the Guidelines_for_Manuscript_Preparation_and_Submission-Topic_Highlight, and all authors have read and agreed with the content. The work has not been published previously in whole or in part, nor is it under consideration by another journal.

All corrections are highlighted in yellow color, and all authors have read and agreed with the content.

Please find attached to this letter a detailed response one-by-one, to all the queries raised by reviewers 1 and 2.

Sincerely,


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Type of manuscript: Review

Title: The gut microbiota of a population highly affected of obesity and type 2 diabetes and the susceptibility to COVID-19.

Authors: Jaime García-Mena, Karina Corona-Cervantes, Daniel Cuervo-Zanatta, Tizziani Benitez-Guerrero, Juan M Vélez-Ixta, Norma G Zavala-Torres, Loan E Villalobos-Flores, Fernando Hernández-Quiroz, Claudia Pérez-Cruz, Selvasankar Murugesan, Fernando G Bastida-González, Paola B Zárate-Segura.

Reviewer #1.

Scientific Quality: Grade B (Very good) Language Quality: Grade B (Minor language polishing) Conclusion: Accept (General priority).

Specific Comments to Authors:

It is an interesting manuscript. Authors succeed to present their data data about the association between dysbiosis of the gut microbiota and metabolic diseases, could suggest that the high levels of susceptibility to SARS-CoV-2 infection and COVID-19 morbidity in the Mexican population. This paper was written in a clear way adding information to the existing literature. Therefore, maybe interesting to the readers in "World Journal of Gastroenterology".

Answer: We thank the reviewer for the encouraging comments. The whole authorship has reviewed the text again to improve the use of English language in it.

Reviewer #2.

Scientific Quality: Grade B (Very good) Language Quality: Grade B (Minor language polishing) Conclusion: Minor revision.

Specific Comments to Authors:

1. In my opinion could be more elegant to change for all the text T2D with T2DM. Please correct it.

Answer: The reviewer is right, we involuntary oversighted this, and we have already updated the term T2D to T2DM in all the text, according to the suggestion.

2. Thus, T2DM is a relevant co-morbidity and negative prognostic factor for patients with COVID-19 infection as recently evidenced by authors in full length original study (Outcomes in Patients With Hyperglycemia Affected by COVID-19: Can We Do

More on Glycemic Control? Diabetes Care. 2020 Jul;43(7):1408-1415. doi: 10.2337/dc20-0723][←Sardu et al., 2020a] and meta-analysis of published data (Impact of diabetes mellitus on clinical outcomes in patients affected by Covid-19. Cardiovasc Diabetol. 2020 Jun 11;19(1):76. doi: 10.1186/s12933-020-01047-y)[←Sardu et al., 2020b] . Please discuss this point and these references, stressing the concept of T2DM and much more of altered glucose homeostasis and hyperglycemics vs. normoglycemics condition as negative prognostic factors for COVID-19 infection. What is your opinion? Please discuss it and report the results of these two studies on T2DM and COVID-19.

Answer: We thank the reviewer for the enlightening comment that give us the opportunity to improve the review. We have considered the suggestion, carefully revised the above-mentioned references, and expanded the topic in pages 6-7. We had previously introduced the topic, and therefore we expanded the information and added a reference as suggested by the reviewer (Sardu et al., 2020a). However, the second suggested reference was not included (Sardu et al., 2020b), as we rather included data from other reported original study, which we considered more suitable to sustain our statement (Huang et al., 2019).

The amended paragraph reads as follows, "...T2DM was also a co-morbidity associated with adverse outcomes in hospitalized patients with SARS-CoV-2 in both China and Italy (Huang et al., 2019, Sardu et al., 2020a). In the Italian cohort, hyperglycemic COVID-19 patients had a higher risk for mechanical ventilation, shock, and multiple organ failure requiring Intensive Care Unit (ICU) assistance and showing higher mortality rates than normoglycemic COVID-19 patients. Whereas hyperglycemic COVID-19 patients treated with insulin infusion had reduced inflammation and coagulation markers, and better prognosis (Sardu et al., 2020a)." page 7.

3. Regards the ACE2 receptors, their expression and clinical outcomes, do not forget to report that hypertension is more common than T2DM in patients with COVID-19 infection (Hypertension, Thrombosis, Kidney Failure, and Diabetes: Is COVID-19 an Endothelial Disease? A Comprehensive Evaluation of Clinical and Basic Evidence. Journal of Clinical Medicine 2020; doi: 10.3390/jcm9051417)[←Sardu et al., 2020c]. Indeed, a particular interest has been invested on the expression of ACE2 receptors and on clinical outcomes in hypertensive patients, and in hypertensive patients under ACEi/ARBs drugs. Indeed, hypertensive patients represent a class of high risk patients (Could anti-hypertensive drug therapy affect the clinical prognosis of hypertensive patients with COVID-19 infection? Data from centers of southern Italy. J Am Heart Assoc. 2020 Jul 7:e016948. doi: 10.1161/JAHA.120.016948)[←Sardu et al., 2020d]. Notably, there is not actual evidence to discontinue this chronic therapy in hypertensive patients with COVID-19 infection. Please discuss this point, to remark a brief description of hypertensive patients and antihypertensive drugs in COVID-19 disease.

Answer: We thank again the reviewer for sharing her/his insight on the topic. We acknowledge the comment and strength the association between hypertension and high risk for COVID-19 in page 8 and included new references as suggested. However, this review aims to discuss the current literature about the association between obesity/T2DM and COVID-19. We believe the above description on hypertension and ACE2 receptors (Sardu et al., 2020d) definitively off limits the topic of this review and cannot be included.

The amended texts read as follows:

“One of the first reports from Wuhan, China, indicated that most COVID-19 hospitalized patients presented underlying diseases, such as diabetes, hypertension, and cardiovascular disease. The occurrence of hypertension worsened the prognosis and associated with higher rate of death (Huang et al., 2019)” page 8.

“Moreover, OB, T2DM and HBP conditions are accompanied by an inflammatory status, and some molecular mechanisms induced by inflammation alter the microvasculature resulting in endothelial dysfunction (ED) and lung damage. Thus, COVID-19 patients with these comorbidities have higher rates of ICU treatment (Sardu et al., 2020c)” page 8.

4. Again, in your article there is not description about the possible link existing between these disorders and ABO group as a potential pro-thrombotic status and the endothelial dysfunction in patients with covid-19 disease? However, in covid-19 patients the ABO group could be a pro-thrombotic status (Implications of AB0 blood group in hypertensive patients with covid-19. BMC Cardiovasc Disord. 2020 Aug 14;20(1):373. doi: 10.1186/s12872-020-01658-z). Indeed, authors suggest that non-0 covid-19 hypertensive patients have significantly higher values of pro-thrombotic indexes, as well as higher rate of cardiac injury and deaths compared to 0 patients (Implications of AB0 blood group in hypertensive patients with covid-19. BMC Cardiovasc Disord. 2020 Aug 14;20(1):373. doi: 10.1186/s12872-020-01658-z). Moreover, AB0 blood type influences worse prognosis in hypertensive patients with covid-19 infection (Implications of AB0 blood group in hypertensive patients with covid-19. BMC Cardiovasc Disord. 2020 Aug 14;20(1):373. doi: 10.1186/s12872-020-01658-z). In my opinion this information has to be updated in the text and references.

Answer: We appreciate the interesting suggestion of an additional topic for the discussion. However, the scope of this review is to emphasize the high risk that obesity and T2DM imposes on patients affected by COVID-19, and the role played by the gut microbiota. The associations of blood types (i.e. AB0 groups) is noteworthy, but out of the scope of our review.

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