April 20, 2021

Responses to Comments

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: This review starts with the postulation of T2D cases upsurge in the coming 10-20 years. The authors further describe how probiotics, diet and anti-diabetic medication affect gut microbiome and the mechanisms behind as to how the changing gut microbiome affect body weight, inflammation, and glucose homeostasis in the diabetic patients. It is suggested gut microbiome is a therapeutic target for diabetes and an area worth further in-depth study. Overall, the review is comprehensive and well-organized.

Response: Thanks for your encouraging comments.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: This is an interesting review regarding the relationship between the gut microbiota and diabetes. The paper is worthy of publication but would require some minor adjustments. Suggestions for revision are listed below:1. I don't see the link between the part of the manuscript tackling the epidemiology of diabetes and the part of the manuscript that deals with the involvement of gut microbiota in diabetes. You need to make the transition less abrupt.

Response: We appreciated this comment. We add “Observational findings from recent epidemiological, physiological and metabolomics studies, complemented by cellular and animal experiments and clinical trials in human, it appears that the microbial communities may contribute to the pathogenesis of a variety of common metabolic disorders, including obesity, diabetes and their complications” in the manuscript to make transition from epidemiology of diabetes to gut microbiota smoothly.

2. Supplementation with probiotics and also synbiotics might be beneficial to patients diagnosed with diabetes also because these products lower oxidative stress levels. Oxidative stress is a key player in the development of diabetes and diabetes-related complications. See the following papers: Gaman MA et al. World J Diabetes (2020), Pourrajab et al. Crit Rev Food Sci Nutr (2020), Sohouli MH et al. Adv Nutr (2020).

Response: As suggested by the review, oxidative stress plays an important role in the treatment and development of diabetes and complications associated with diabetes. we have added “Oxidative stress is a key player in the development of diabetes and diabetes-related complications. Supplementation with probiotics and also synbiotics could be beneficial for patients diagnosed with diabetes also because these products lower oxidative stress levels” in the manuscript.

3. Berberine might be useful in the management of diabetes also because its administration is associated with a

decrease of the BMI and other indices of obesity (see Xiong P et al., Complement Ther Clin Pract (2020)).
Response: Thanks for your comments, we have added “Berberine is useful in diabetes management because its administration is associated with a decrease of obesity indices, such as body mass index (BMI) and waist circumference (WC)” in the manuscript.

4. Are other antidiabetic drugs associated with changes in the gut microbiota? Insulin? Gliclazide?
Response: We appreciate this comment. Here we mainly summarize the antidiabetic drugs associated with changes in the gut microbiota that are well reported. We also search other antidiabetic drugs such as dapagliflozin, gliclazide, and insulin with gut microbiota. In dapagliflozin and gliclazide, neither treatment significantly affected either gut microbiome alpha diversity or composition and, after treatment, no associations were found between microbiome composition and other clinical parameters in T2D patients treatment with dapagliflozin and gliclazide for 12 weeks (PMID: 31816432). Insulin is a peptide hormone and is widely used to manage blood sugar in the treatment of diabetes. But there is no research report on changes of gut microbiota in diabetic animals or patients treated with insulin.

5. Do the authors have any conflicts of interest to disclose (as the commercial name of metformin was mentioned)?
Response: We have no conflicts of interest to disclose. We delete the commercial name of metformin “Glucophage” in the manuscript.