
Dear Editor and Reviewers:

Thank you for your letter and the reviewers' comments on our manuscript entitled "Differences in metabolic improvement after metabolic surgery are linked to the gut microbiota in nonobese diabetic rats" (Manuscript NO.: 83463, Basic Study). Those comments are very helpful for revising and improving our paper, as well as the important guiding significance to other research. We have studied the comments carefully and made corrections that we hope will be met with approval. The main corrections are in the manuscript, and the responses to the reviewers' comments are as follows (the replies are highlighted in blue).

Replies to the reviewers' comments:

Reviewer #1:

1. English polishing is necessary.

Response: Thank you for your suggestion. We have repolished the English in the article. If there are any other issues, please let us know, and we will revise it again.

2. The procedure of STZ administration is omitting in Methodology section.

Response: We sincerely thank the reviewer for careful reading. We have already added information about the dosage and use of streptozotocin in the article. The following are the modifications in the methodology:

Diabetes was induced in rats by 60 mg/kg streptozotocin, and the rats were housed in individually ventilated cages.

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3. As STZ-SD rats are the animal models of T1DM, what is the purpose of OGTT and ITT performance at baseline and 6wks after surgery? What can you get with OGTT, what is the idea? To diagnose already presented diabetes, to assess the insulin response to glucose challenge in T1DM rat? The same comment if for ITT. The better solution is to perform 5-point daily glycemic profile or to calculate average glycemia, and to measure fructosamine and basal C peptide levels at baseline and 6 weeks after the surgery.

Response: Thank you for your careful comments. We agree with your opinion very much and added glycosylated hemoglobin (to assess average blood glucose levels for 8-12 weeks) and the average serum glucose of rats for six weeks in Figure 2. For STZ-induced type I diabetes, in some scholars and our previous studies^[1-4], long-term hyperglycemia could lead to insulin resistance, so we conducted ITT and OGTT tests to evaluate the improvement in blood glucose metabolism in rats after surgery.

Reviewer #2:

1. English language needs to be spruced up in order to enhance the quality of the presentation.

Response: Thank you for your suggestion. We have repolished the English in the article. If there are any other issues, please let us know, and we will revise it again.

2. Firmicutes/Bacteroidetes (F/B) ratio is an important entity that would provide an insight into the nature and magnitude of the metabolic improvement.

Response : Thank you for your suggestion. We have added the Firmicutes/Bacteroidetes (F/B) ratio in Figure 2, and if there are any other issues, please let us know, and we will revise it again.

3. What special care the authors have taken in order to document physical activity and heterogeneity of microbiota.

Response: Thank you for your comment. In the experiment, we collected fresh feces from rats that did not eat at 8 am by 1) fixing the mouse and lifting its tail; 2) gently pressing the mouse's lower abdomen with the fingers; 3) collecting fresh feces into several sterile EP tubes with corresponding numbers; 4) dividing each tube into 2-3 segments; and 5) storing at -80 °C and transporting it on dry ice.

We tried our best to improve the manuscript and made some changes marked in red in the revised paper that will not influence the content and framework of the paper. We earnestly appreciate the editors'/reviewers' work and hope that the corrections will be met with approval. Again, thank you very much for your comments and suggestions.

1 **Paudel YN**, Ali MR, Shah S, Adil M, Akhtar MS, Wadhwa R, Bawa S, Sharma M. 2-[(4-Chlorobenzyl) amino]-4-methyl-1,3-thiazole-5-carboxylic acid exhibits antidiabetic potential and raises insulin sensitivity via amelioration of oxidative enzymes and inflammatory cytokines in streptozotocin-induced diabetic rats. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie* 2017; **89**: 651-659 [PMID: 28262618 DOI: 10.1016/j.biopha.2017.02.043]

2 **Murali B**, Goyal RK. Improvement in insulin sensitivity by losartan in non-insulin-dependent diabetic (NIDDM) rats. *Pharmacological research* 2001; **44**(5): 385-389 [PMID: 11712869 DOI: 10.1006/phrs.2001.0858]

3 **Abdelmageed ME**, Shehatou GSG, Suddek GM, Salem HA. Protocatechuic acid improves hepatic insulin resistance and restores vascular oxidative status in type-2 diabetic rats. *Environmental toxicology and pharmacology* 2021; **83**: 103577 [PMID: 33383195 DOI: 10.1016/j.etap.2020.103577]

4 **Tan C**, Zheng Z, Wan X, Cao J, Wei R, Duan J. The role of gut microbiota and amino metabolism in the effects of improvement of islet β -cell function after modified jejunoileal bypass. *Scientific reports* 2021; **11**(1): 4809 [PMID: 33637880 PMCID: PMC7910448 DOI: 10.1038/s41598-021-84355-x]