

## RESPONSES TO REVIEWERS' CONCERNS

**Name of Journal:** *World Journal of Gastroenterology*

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**Manuscript NO:** 27821

**Effects of sleeve gastrectomy with jejuno-jejunal or jejuno-ileal loop on glycolipid metabolism in diabetic rats**

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Dear Editor Gong,

Thank you very much for your letter and for the reviewers' comments concerning our manuscript entitled "**Effects of sleeve gastrectomy with jejuno-jejunal or jejuno-ileal loop on glycolipid metabolism in diabetic rats**". The comments from reviewers are very valuable and helpful for revising and improving our paper. Based on the comments, careful modifications have been made to the original manuscript. A revised manuscript with the correction sections marked in highlight has been uploaded for easy checking/editing purpose. We hope the following point-by-point responses and the revised manuscript will meet the editor's and reviewers' requirements for considering this manuscript for publication in *World Journal of Gastroenterology*.

**Reviewer (1):**

1. **In the CONCLUSION section of the abstract, they described only their results. They should mention the significance of the results.**

We have modified the CONCLUSION as follows: SG combined with intestinal loop induces better glycolipid metabolism than simple SG, with the lipid metabolism better improved with SG-JI compared to SG-JJ.

2. **Figures or schema should be presented to show the surgical reconstruction.**

The schema describing SG, SG-JJ and SG-JI has been added to Figure

3. **Reference #1 should be referred at line 15 on p4.**

Reference #1 has been labelled at the required place.

#### **Reviewer (2):**

1. **The study design is straight forward. Outcomes show clear differences between groups over the 24 weeks after operation. However, it is not clear if the rats suffer any consequences the intestinal bypass and malabsorption induced by the bypass. Did rats have untoward effects from bypass? Were liver function tests normal?**

In this study, no rat died of complications of jejunio-jejunal or jejunio-ileal loop, and three rats died of residual stomach leakage. The results from clinical studies demonstrate that the intestinal bypass is safe relatively [1-4]. Therefore, the primary aim of this study is not the safety of SG, SG-JJ and SG-JI, but the effects of SG, SG-JJ and SG-JI on glycolipid metabolism. In our previous study, we have demonstrated that duodenal-jejunal bypass (DJB), a type of intestinal bypass surgery, could improve the liver function [5], and accordingly, the liver function was not measured in the present study.

2. **The statement on page 9, HOMA-IR section "At 24 wk after surgery,**

**HOMA-IR...and it was higher than in the SG group..." is confusing. The SG and SHAM groups value are the highest values. I think this is misstated.**

We are so sorry that this is a mistake, and it has been amended as follow: At 24 weeks after surgery, the HOMA-IR in the SG-JJ ( $3.72 \pm 0.54$ ) and SG-JI ( $3.73 \pm 0.79$ ) groups was comparable, and it was lower than that in the SG group ( $4.86 \pm 0.62$ ,  $P < 0.05$ ).

**3. Minor: do not abbreviate week to wk in the text.**

All of "wk" have been replace by "weeks".

**4. Also in the HOMA-IR figure, the values again rise by week 24. Does this trend increase and is the effect of SG and SG with bypass durable in the long term?**

Dietary control is very important for patients with SG [6]. In this present study, we used rats with postoperative HFD to simulate patients with an undesirable diet. Therefore, the values of HOMA-IR again rose by week 24. In clinics, dietary and life style control are suggested to patients undergoing SG. The long-term effect of SG on diabetes control is uncertain. In this study, we demonstrated that SG-JJ and SG-JI could provide better glycolipid metabolism than SG despite a maintained HFD chow by 24 weeks after surgery. We hope that further clinical studies could demonstrate whether SG-JJ or SG-JI could enhance antidiabetic effects in the long-term view (no less than 5 years).

**5. I am not sure I understand the term "accordant" in the first sentence on page 14 beginning "The contribution of ghrelin to diabetes..." Please explain.**

It is defective that we did not explain the meaning of "accordant" clearly. This part of "DISCUSSION" has been described as follows:

Researchers have verified that serum ghrelin levels reduced remarkably after SG in multiple clinical studies, and they believe that body weight loss and diabetes control after SG are associated with the reduced serum ghrelin levels. However, Chambers et al performed SG on both ghrelin-deficient and wild-type mice, and did not find any difference in diabetes control between the two types of mice.

**6. Much of the discussion is speculative and the outcomes in this study do not definitively define the mechanisms of action of the various treatment groups. The discussion can be written more succinctly and shortened.**

The discussion has been simplified and the indirect speculations have been deleted

**7. The authors point out that considerable clinical study is needed before this can be applied to humans. Can they suggest next steps required before considering using this clinically in humans? Are more animal studies required or do they believe that clinical trials are warranted now?**

To enhance the antidiabetic effect of SG, SG with different intestine bypass was performed by surgeons. But little animal experiment evidence of these surgeries has been reported. In our study, we demonstrated that SG-JJ and SG-JI enhanced diabetes control and lipid metabolism compared with SG alone. However, the results of animal experiment cannot be transferred into humans directly. We suggest that further clinical studies should be performed, to explore the optimal procedures (SG, SG-JJ, or SG-JI) for individual patients, after controlling for differences in BMI, age, duration and severity of T2DM, serum lipid, compliance of postoperative administration and so forth.

**Reviewer (3):**

**1. Please provide the figures or schemes of the operations!**

The schema describing SG, SG-JJ and SG-JI has been added to Figure 1.

**2. Authors mentioned about the additional procedure for SG like duodeno-jejunal bypass, loop gastroileostomy, jejunio-ileal bypass and duodeno-ileal bypass. However, it is not clear how the results of the study in animals correspond with the mentioned procedures?**

To improve the effect of SG on diabetes control, SG combined with single-anastomosis duodeno-jejunal bypass, gastroileostomy loop, jejunio-ileal bypass or duodeno-ileal bypass have been performed in multiple clinical trials. These studies demonstrated that SG with different intestine bypasses showed better antidiabetic effect. However, there has been few prospective randomized controlled trials. In this study, we performed a randomized controlled trial to compare the effect of SG, SG-JJ and SG-JI on diabetes control, and showed that all of the three surgeries have excellent antidiabetic effect shortly after surgeries. What's more, this study demonstrated that SG-JJ and SG-JI could provide better glycolipid metabolism than SG alone despite a continuous HFD chow by 24 weeks after surgery. We have added the above to the first section of DISCUSSION.

**3. Authors did not write about the limitations. This section should be included in the text.**

We are sorry that the limitations of this study have not been indicated peculiarly. We have expounded the limitations of this study in this article as follows: There are some limitations in this study. First, the calorie content in feces was not measured, so the calorie absorption from food could not be calculated. Second, we demonstrated that SG-JJ and SG-JI enhanced diabetes control and lipid metabolism compared with SG alone. However, the results of animal experiment cannot be transferred into humans directly. We suggest that further clinical studies should be performed, to explore the optimal

procedures (SG, SG-JJ, or SG-JI) for individual patients, after controlling for differences in BMI, age, duration and severity of T2DM, serum lipid, compliance of postoperative administration and so forth.

Finally, we appreciate the editors' and reviewers' work, and hope that the revision will meet with your requirements.

Sincerely,

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## REFERENCES

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