

World Journal of Gastroenterology

11 May 2022

Dear Professor Lian-Sheng Ma,

Re: "Duodenal-jejunal bypass reduces serum ceramides via inhibiting intestinal bile acid-FXR pathway"

Thank you for your email dated 10th May 2022 regarding our manuscript. We now submit a revised version which takes into account the comments of all reviewers, both as a clean copy and a version with changes marked. In response to the specific issues raised:

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The authors designed this study to investigate of luminal bile acids following duodenal-jejunal bypass. Overall, the study is very interesting. The manuscript is well written. I suggest the author to update the figures with black, white, and gray color. No other comments.

We appreciate the reviewer's comments. We have made revisions of the figures using black, white and gray colors, as suggested.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This is an interesting study of the duodenal-jejunal bypass and intestinal bile acid-FXR pathway. This study measured the changes of individual luminal bile acid and ceramide concentrations within the enterohepatic circulation after duodenal-jejunal bypass in a high-fat diet and streptozotocin-induced diabetic rat model. The research is well performed, and the results are very interesting. The animals and surgical procedures are reasonable, and RNA analysis results are excellent. **Minor comments:** 1. The manuscript requires a minor editing. Please take attention about some abbreviations. 2. The figures are too small, please update them with high resolution ratio images.

We appreciate the reviewer's comments. We have made revisions regarding abbreviations and updated the figures with high resolutions, as suggested.

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: Bile acids are traditionally known as lipid absorption-facilitating agents. It was not until recent years that the role of bile acids as signaling molecules in modulating metabolism has been unveiled. The intestinal lumina, where bile acid concentrations are high, is the main place for bile acid signaling. The interaction between bile acids and Farnesoid X receptor is more complicated, as different subtypes of bile acids have distinct effect on the downstream pathway of Farnesoid X receptor. Chenodeoxycholic acid represents the most potent Farnesoid X receptor stimulator while ursodeoxycholic acid and β -muricholic acid are Farnesoid X receptor inhibitors. Coincidentally, the changes in lipid metabolism after intestine-selective Farnesoid X receptor inhibition is similar to the changes following duodenal-jejunal bypass that hepatic fat accumulation is alleviated and the key transcriptional regulators and enzymes involved in

hepatic de novo lipogenesis are downregulated. In this study, the authors investigate of luminal bile acids following duodenal-jejunal bypass. This study is very well designed and the manuscript is very well written. Methods are described in detail, and the results are interesting. The results are discussed with updated references. The limit of the study is also discussed. The reviewer recommends to accept this interesting study after a minor editing.

We appreciate the reviewer's comments and have made revisions as per the suggestion.

We wish to thank all reviewers and editors for their constructive comments, and are grateful for the opportunity to improve the manuscript.

Yours sincerely,

Dr. Xiang Zhang

on behalf of the co-authors