

## ESPS PEER-REVIEW REPORT

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

**ESPS manuscript NO:** 27230

**Title:** Alterations in gut microbiota during remission and recurrence of diabetes after duodenal-jejunal bypass in rats

**Reviewer's code:** 03641052

**Reviewer's country:** United States

**Science editor:** Jin-Lei Wang

**Date sent for review:** 2016-05-19 09:21

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

### COMMENTS TO AUTHORS

In this preliminary study, the authors hypothesize that the relationship between gut microbiota and diabetes recurrence after bariatric surgery has not been investigated. The authors speculate that the recurrence of diabetes after bariatric surgery may also be accompanied by alterations in gut microbiota. The authors perform a range of surgical techniques and routine and sophisticated lab techniques. The authors conclude that postoperative high fat diet (HFD) can re-exacerbate insulin resistance and induce recurrence of diabetes after initial remission in duodeno-jejunal bypassed (DJB) rats. The authors also conclude that alterations in gut microbiota may contribute to the recurrence of diabetes after DJB, possibly by influencing serum lipopolysaccharide (LPS) and total bile acids (TBAs). The hypothesis pursued is a significant topic. However, many of the study conclusions are unsupported, thus making the study weak and dampened enthusiasm. Moreover, there are several technical deficits, and lack of presentation of representative raw datasets contributes to weakness of interpretation. These type of studies have been performed earlier as well, but given the controlled conditions, the present study may be a worthy contribution. These criticisms are presented below.

Major Comments 1. The authors should clearly indicate everywhere in the manuscript that the diabetes has been induced by a combination of high fat diet and low-dose streptozocin injection. It seems that the authors have not been enthusiastic to highlight the contribution of the streptozocin injection. This, in fact, creates confound in observations. Streptozocin damage beta cells. So, the HOMA-IR measurements and their interpretations should be inferred in the background of the streptozocin injections. The inference that high fat diet post-DJB is only due to insulin resistance is inaccurate. All these conclusions should be changed. 2. The different groups of animals are not clear. For example, after the surgeries, high fat diet is continually administered. It is not at all clear how some animals still remain in remittance (DJB-RM group) despite the HFD. This reviewer remained confused about this group while reading through the entire manuscript. Because the genetic background of the rat was homogenous, how did this happen? This needs to be explicitly explained. 3. How many days after induction of diabetes were the different abdominal surgeries performed? 4. Please perform appropriate statistical analyses. For comparing more than two groups, ANOVA should be used, rather than comparing only two groups at a time. This error occur multiple times. 5. The biggest drawback of the study is the lack of details related to the microbiome analyses. The reviewer appreciates that these are difficult surgeries, and it takes endeavor for post-surgical animal husbandry for 12 weeks. So, as a preliminary study, a small sample size like 5 or 6 animals in a group may still be accepted. However, a lot of controls needs to be presented. First, what does colonic contents mean? Was the colon dissected and lavaged? How were the samples for microbiome analyses obtained? What were the controls that eukaryotic tissues were not analyzed? How were alignments made to reference genomes? Details need to be presented. 6. The LPS assay was performed only at the 4th week. The values may have changed due to post-surgery low-grade inflammation. No direct evidence is provided with changes in the microbiome. Escherichia coli is a facultative anaerobe, and not necessarily indicative of inflammation. The LPS change may be a result of normal immune response. 7. The authors provide preliminary evidence that Bacteroidetes/Firmicutes ratio increases in the DJB-RC recurrence group. This higher ratio has earlier been reported to be associated with obesity, as this combination may be effective in extracting energy. However, the food consumption of the rats have not changed. All these ob

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<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
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		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

### COMMENTS TO AUTHORS

This is a very well designed, performed and written experimental study for investigation of the role of alterations in gut microbiota in the pathogenesis and remission of type 2 diabetes after bariatric surgery. For investigation of this aim the authors created and used a rat model of diabetes recurrence after duodenal-jejunal bypass (DJB) and compared the results obtained in diabetes rats induced by high-fat diet after bypass and in the group with sham operation. The study was performed in Wistar rats. The authors examined in details different parameters like oral glucose tolerance test, they measured insulin, glucagon-like peptide (GLP-1), fasting serum total bile acids (TBAs), LPS using ELISA method and for study of gut microbiota used 16s rDNA-based method. The authors found that after DJB surgery the rats with diabetes recurrence showed a reduced relative abundance of Firmicutes and an increased relative abundance of Bacteroidetes and E. coli. The author assumed that alterations in gut microbiota may contribute to the recurrence of diabetes after DJB, possibly by influencing serum LPS and TBAs. The study is set up correctly. The paper is written well. Introduction gives a good overview of the study background and the authors raised clearly the



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aim of the study. The aim of the study is fulfilled. The material studied is large enough and allows to drawn the conclusions. The Tables and Figure of high quality give a good overview about the results. This study makes a contribution to better understanding of the role of alterations in gut microbiota in modulation of host metabolism and in remission of diabetes after bariatric surgery. This experimental study may have also the practical application because authors suggest the administration of gut microbiota as a new therapeutic target to prevent diabetes recurrence after bariatric surgery. Some minor suggestions: 1. It should be necessary to explain some abbreviations, like GLP-1, TBAs and LPS in Material and Methods p. 7. 2. It would be useful to describe more detailed the principal of method of 16s rDNA-based study of gut microbiota, p. 8.



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<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" type="checkbox"/> Accept
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		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

### COMMENTS TO AUTHORS

This study is very interesting. In the study, the authors determined the alterations in gut microbiota during remission and recurrence of diabetes after duodenal-jejunal bypass in rats. The study is well desinged, and the results are interesting. Some language revision needed.