4th of April， 2017

Dear Editor Song,

Please find the revised manuscript enclosed in Word format, with changes highlighted (file name: **33838-Revised manuscript.doc**). Furthermore, we provide the following documents (**33838-Conflict-of-interest statement.pdf; 33838-Copyright assignment.pdf, 33838-Google Scholar.pdf, 33838-Grant application form(s).pdf and 33838-Audio core tip.mp3)** as requested. We provide point-by-point responses to the comments from editor and reviewers below.

Title: Diabetes-induced mechanophysiological changes in the small intestine and colon

Author: Mirabella Zhao, Donghua Liao, Jingbo Zhao

Invited review: Number ID: 02526196

Name of journal: *World Journal of Diabetes*
ESPS Manuscript NO: 33838
Columns: Review

Responses to the comments from Editor:

1, Please highlight the changes made to the manuscript according to the peer-reviewers' comments.
Reply: We have highlighted the changes made to the manuscript according to the peer-reviewers' comments.

2, Please provide the postcode.
Reply: The postcode has been added.

3, Please provide the approved grant application form(s). For manuscripts supported by various foundations (i.e., charitable, not-for-profit organizations), the authors should provide a copy of the full approved grant application form(s), consisting of the information section and body section in PDF format. The approved grant application form(s) will be released online together with the manuscript in order for readers to obtain more information about the study and to increase the likelihood of subsequent citation.
Reply: The approved grant application form has been provided.

4, A copy of signed statement should be provided to the BPG in PDF format.
Reply: A copy of signed conflict-of-interest statement has been provided.

5, In order to attract readers to read your full-text article, we request that the first author make an audio file describing your final core tip. This audio file will be published online, along with your article. Please submit audio files according to the following specifications:
Acceptable file formats: .mp3, .wav, or .aiff
Maximum file size: 10 MB
Reply: The audio file (mp3 format) describing the final core tip of the review has been made by first author and provided.

Point to point response to the comments from reviewers

Reviewer's code: 02441070:
This paper make a review on diabetes-induced mechanophysiological changes in the small intestine and colon. It could give a systemic review in such area. The references should be reduced.
Reply: We are appreciative of the positive comments for our manuscript. The reference number has been greatly reduced due to content removal of the section on celiac disease and diabetes, We have also deleted some old references when revising the manuscript

according to the suggestion. However, we have to add some new references in relation to the new section on gut microbiota changes and modification of the section on colon cancer and diabetes according to two other reviewers.

Reviewer's code: 02625944:

In this review, Zhao et al. summarized diabetes-induced mechanophysiological changes in the small intestine and colon. The topic is clinically important and the review was written well in-depth. There are some comments.

Reply: We appreciate the comments and suggestions. The point-by-point responses to different comments are provided below.

1. The mechanophysiological changes in small intestine and colon also result in changes in microbiota. The authors may add the section on microbiota.

Reply: This is a very good suggestion. In fact, we have read and collected literatures relating to gut microbiota and diabetes, however, we thought the review would be too long if we included too many topics, therefore we did not include this topic in our manuscript. We now re-evaluate the manuscript according to your comments, we think that it is important to add the section on gut microbiota modification in relation to diabetes-induced intestinal and colon changes as this topic is more relevant for the scope of this review than the topic of celiac disease. Thus, we remove the section of celiac disease according to your comment 2 as it is distant from the scope of the review.

2. Celiac disease is an autoimmune disease and it seems that mechanophysiological changes plays only a minor role. This section sounds a little strange in the scope of this review.

Reply: we appreciate this comment. We have re-evaluated our manuscript and decide to remove the section on celiac disease as it is of less relevance and distant from the scope of the review. Instead, we have included a section on gut microbiota modification in the review.

3. The section of colon cancer also seems a little different from the scope of this review since the risk of colon cancer is already increased with obesity and without diabetes. The link between the colon cancer and mechanophysiological changes should be more clearly described.

Reply: Thank you for the comment and suggestion. We have now modified and added contents in the second paragraph of this section to describe possible links between colon cancer and the mechanophysiological changes.

4. Gastric motility as well as small intestine and colon motility is also important. Why the authors did not mention gastric motility in this review?

Reply: This is also a very good comment. In fact, we have read and collected a lot of literatures in relation to gastric motility disorders in diabetes. However, we decide not to include the topic on gastric motility disorders due to two reasons. Firstly, the gastric motility disorders have been comprehensively reviewed just recently by authors such as (Marathe CS, Rayner CK, Jones KL, Horowitz M. Novel insights into the effects of diabetes on gastric motility. Expert Rev Gastroenterol Hepatol. 2016;10(5):581-93.). Secondly, in our review we would like to focus on the topic of disorders of the small intestine and colon in diabetes. However, for the convenience of readers to easily access the knowledge about esophageal and gastric motility disorders in diabetes when they read our review, we have added " *It is well known that, the esophageal and gastric motility disorders are also very common, however these have been reviewed in detail recently (See references [11, 12]). Furthermore, as we focus on the topic of diabetes-induced mechanophysiological changes in the small intestine and colon in this review, therefore the topic of esophageal and gastric disorders in the diabetes are not included in this review.* " at the end of the Introduction.

5. There are several anti-diabetic agents available which act through GI tract such as alpha-glucosidase inhibitors and GLP-1 receptor agonists. This review would become more clinically relevant if the authors mention these agents in the article.

Reply: This is a very good suggestion. In a recent review " Yang et al. Am J Physiol Gastrointest Liver Physiol. 2017, in press.", the link between GLP-1/GLP-1 receptor expression and gastrointestinal motility mediated by gut microbiota has been investigated. Moreover, there is also evidence on relations between the glucosidase inhibitors and GLP-1 receptor agonists to gut microbiota. Therefore, we have added a paragraph in the new section on gut microbiota modification where the effects of glucosidase inhibitors and GLP-1 receptor agonists on diabetes and the GI tract are discussed as following:

"GLP-1 regulates glucose homeostasis by stimulating the secretion of insulin from pancreatic β-cells[188] and plays important roles in metabolism as well as gastrointestinal motility[188-190]. In relation to diabetes, GLP-1 acts as a pharmacological agent with definite therapeutic potential in diabetes treatment, regulating blood glucose by stimulating insulin secretion from insulin-producing β-cells in a blood-glucose dependent manner and inhibiting glucagon secretion from the glucagon-producing a-cells[191, 192]. On other hand, it has been demonstrated that GLP-1 is progressively up-regulated in pancreatic islets during type 2 diabetes development[193]. More recently, the link between GLP-1/GLP-1 receptor (GLP-1R) expression and gastrointestinal motility mediated by GM has been investigated[194]. They found that the expression of GLP-1R in myenteric neural cells in the GI tract was suppressed and the GI transit time became shorter in Germ-free (GF) mice after transplantation of GM. Therefore, they suggest that the GM accelerates the GI motility while suppressing the expression of GLP-1R in myenteric neural cells throughout the GI tract. There are also other anti-diabetic agents which act in the GI tract such as alpha-glucosidase inhibitors[195] and GLP-1 receptor agonists[196, 197]. It is interesting to notice that alpha-glucosidase inhibitors and GLP-1 receptor agonists also affect the GM[198-200]. Alpha-glucosidase inhibitors such as acarbose treatment has been demonstrated to increase the content of gut Bifidobacterium longum and partially restore the imbalance of GM in patients with type 2 DM[198], and the changes in GM are strongly associated with the levels of various metabolic indicators[200]. In contrast, GLP-1 receptor agonists such as liraglutide seem to modulate the composition of the GM[199]. Other therapeutic agents targeting DM such as metformin[201] and antibiotics[202] also affect the GM. Thus, there is an interplay between drugs used for DM and the GM, however, the exact mechanism of the interaction is complex and needs to be investigated more thoroughly."

Reviewer's code: 03648962:

No specific comments

Reply: : We are appreciating positive comments for our manuscript.

Reviewer's code: 03469232:

The review entitled "Diabetes-induced mechanophysiological changes in the small intestine and colon" shows that exploring DM-induced intestinal and colonic changes is important for the management of diabetes complicated with gut disorders such as diarrhea, constipation, colon cancer, and celiac disease. The manuscript addresses an

interesting issue and is well written; however, I would suggest a few revisions to improve the manuscript.

Reply: We are appreciative of the comments and suggestions. The point-by-point responses to different comments are provided below.

1) Recently, accumulating evidence suggests that gut microbiota exerts a role in the pathogenesis of diabetes and obesity [Rev Endocr Metab Disord. 2015;16:55-65.] as well as metabolic syndrome [World J Gastroenterol. 2014;20:16079-94.]. Moreover, the link between GLP-1/GLP-1 receptor expression and gastrointestinal motility mediated by gut microbiota has been investigated [Yang et al. Am J Physiol Gastrointest Liver Physiol. 2017, in press.]. Gut microbiota may modulate immune function, neuroendocrine system, and autonomic nervous system, which is one of the topical theme. I would suggest to add a paragraph describing the association between diabetes and gut microbiota related to functions of small intestine and colon to this review.

Reply: This is a very good suggestion. In fact we have read and collected some literatures relating to the link between gut microbiota and diabetes, however, we thought that the review would be too long if we included so many topics, therefore, we did not include this topic in our manuscript. We now re-evaluate the manuscript according to your comment, and we think that it is important to include a section describing the association between diabetes and gut microbiota modification related to the functions of small intestine and colon to this review. Now, we have added a section on this topic in which we also discuss the link between GLP-1/GLP-1 receptor expression and gastrointestinal motility mediated by gut microbiota. Furthermore, as reviewer (reviewer's code: 02625944) suggested, we decide to remove the section on celiac disease as it is distant and of less relevance for the scope of this review.

2) Abbreviations should be correctly used. For example, the authors need not to abbreviate "magnetic resonance imaging" as "MRI" in page 12, line 6, because the term, "MRI" is appeared only once in the manuscript. In addition, complete expression of "AGE" and "RAGE" in page 13, "GLP-2" in page 15, "CNS" in page 18, "IDDM" in page 19, "IGF-

1" in page 21, "DRG" in page 24, and "DPP" in page 29 should be described because these abbreviations are first appeared in the text.

Reply: Thank you for the comment. We have corrected all errors mentioned above accordingly to your suggestion.

3) I would suggest to delete "(Forrest et al, 2008)" and "(2001)" in page 23, line 3-4. Thank you for the opportunity to review your manuscript.

Reply: "(Forrest et al, 2008)" and "(2001)" have now been deleted.

Thank you again for publishing our manuscript in the *World Journal of Diabetes*.

Sincerely yours,

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