

September 23, 2014



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 11732-review.doc).

Title: Intestinal microbiota and type 2 diabetes: from mechanism insights to therapeutic perspective

Author: Jun-Ling Han, Hui-ling Lin

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 11732

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) Reviewer 227589:

The submitted manuscript addresses an area of great interest and importance within the field of diabetes as well as in regards to the role the gut microbiome plays in health and disease. Overall the manuscript is well written and the authors incorporate many of the clinical studies that have been conducted in recent years. A few suggestions:

The authors should carefully look for grammar and diction issues. There are a few odd sentences that should be clarified.

Re: The mistakes in grammar and sentences were corrected.

In several places are the abbreviations mentioned before the entire word - please make appropriate changes when first mentioning a phrase that is later abbreviated -

Re: The abbreviations mentioned before the entire word were revised.

The authors mention the endocannabinoid system and CB1 receptors in the gut. CB2 receptors are present on immune cells - is there any information on their potential involvement?

Re: The potential role of CB2 receptors in glucose homeostasis has been discussed.

The manuscript would benefit from a figure that illustrates the various effects that the gut microbiota may have on the development and maintenance of diabetes. It would be helpful to the reader to include a figure illustrating the discussed variables.

Re: Two figures that illustrated underlying mechanism of intestinal microbiota in the pathogenesis of type 2 diabetes have been added.

(2) Reviewer 2731212:

This is an adequate review of the role of the microbiome in diabetes, insulin resistance, and obesity. It

provides a useful summary of the more important studies in this area.

The authors provide little in the way of synthesis or interpretation and the review would be more compelling and valuable if the authors strove to resolve discrepancies in the data and to provide specific mechanistic hypotheses that could be tested by further studies. (For example, why do ob/ob mice have reduced Bacteroidetes whereas diabetic humans have increased Bacteroidetes? What does this say about the potential role of Bacteroidetes in maintaining the ecology of the microbiome?)

Re: The studies that have aimed to evaluate the association between gut microbiota and diabetes have produced conflicting results and discrepancies in the data. There may be many factors influencing the results, such as race, eating habits, geographical location, and research methods. Figures that interpreted underlying mechanism of intestinal microbiota in the pathogenesis of type 2 diabetes have been added.

The language could be improved and there are numerous errors of spelling and grammar. In the abstract alone: "some obvious evidence," "feacel microbiota," "it is needed to take more studies."

Re: The errors of spelling and grammar were corrected. In the abstract, the phrase "some obvious evidence" was replaced with "a lot of clear evidence"; "feacel microbiota" was corrected into "fecal microbiota"; "it is needed to take more studies" was replaced with "Further studies are required".

(3) Reviewer 2822134:

This is an interesting review addressing the role of the microbiota in obesity and type 2 diabetes. Major comments:

1. Although hepatic inflammation is mentioned, a brief alinea about steatosis /steatohepatitis is missing.

Re: The content about non-alcoholic fatty liver disease (NAFLD) has been enriched according to the reviewer's comments.

2. The beneficial effects of antibiotics are questionable. Already in 1955 it was shown that antibiotics induce weight gain (J Nutr 1955; 56: 151).

Re: Weight gain induced by antibiotics was discussed in our revised paper.

3. beneficial effects of probiotics are not proven, and this paragraph should be written with much more caution. For example, first sentence could be changed in: "A modulating effect of the gut microbiota on type 2 DM was suggested by recent observations". second sentence:, may confer health benefits to the host. minor comments:

Re: The sentence "The protective effect of gut microbiota modulation against diabetes had been confirmed in" has been changed to "A modulating effect of the gut microbiota on type 2 DM was suggested by recent observations". The sentence "Probiotics are nonpathogenic live microorganisms that, when ingested, confer health benefits to the host" was replaced with "Probiotics are nonpathogenic live microorganisms that may confer health benefits on the host".

4. What are the physiological effects of GLP-2?

Re: The physiological effects of GLP-2 have been added in our revised manuscript.

5. page 4: "Intestinal microbiota and energy homeostasis" could be changed in "Intestinal microbiota

and body weight" which probably better reflects the content of this paragraph.

Re: As suggested by the reviewer, the subtitle "Intestinal microbiota and energy homeostasis" has been changed to "Intestinal microbiota and body weight".

(4) Reviewer 2907177:

IT'S A NARRATIVE REVIEW, AND SHOULD BE A SYSTEMATIC REVIEW MANY KEYWORDS ARE NOT MESHES

Re: We have made a systematic review according to the suggestions of reviewers and added 2 figures to help illustrate the contents of this manuscript.

THERE ARE AT LEAST TWO PUBLICATIONS RECENTS AND SIMILAR TO YOUR: 1. Gomes AC, Bueno AA, de Souza RG, Mota JF. Gut microbiota, probiotics and diabetes. *Nutr J* 2014;13:60. [Epub ahead of print] PMID: 24939063. 2. Tilg H, Moschen AR. Microbiota and diabetes: an evolving relationship. *Gut* 2014 May 15. [Epub ahead of print] PubMed PMID: 24833634.

Re: This review focused on some different emphases compared with the two publications mentioned above.

(5) Reviewer 1241484:

The paper by Han and Lin, provide a revision of the bibliographic records regarding the link between intestinal microflora and type 2 diabetes. Although the topic is interesting, in respect to the identification of the potential role of the gut microbiota in human health, I have a number of major concerns.

First, authors focused mainly in describing the reported differences between lean and obese and in many cases (page 4, first long paragraphs) just described what has been described in obese independently of whether the subjects developed diabetes type 2.

Re: Evidences of changes in intestinal microbial composition in T2DM have been replenished.

Second, in other cases (page 5, lines 14-17) general concepts such as the implication of bile acids are described without any experimental direct linking with diabetes type 2.

Re: We added the data about bile acids linking with T2DM. For example, fasting serum taurine-conjugated bile acid concentrations were higher in T2DM and intermediate in impaired glucose tolerance (IGT) persons compared with normoglycemic controls. Furthermore, effects of bile acid sequestrants on T2DM also implicate that bile-acid metabolism is associated with the glucose homeostasis.

Third, the review looks more focus in obesity than in the disease. Note that not only obesity but other diseases or disorders may influence gut microbiota and in turns potential acquisition of diabetes type 2 and therefore focusing a review about diabetes mainly in obesity might not be appropriate.

Re: The revised manuscript laid more emphasis on T2DM than obesity.

Important reference that has been published recently linking obesity and diabetes type 2 is missing: *Gut Microbes*. 2013 Jul-Aug;4(4):306-15.

Re: Reference of the study by Hernández E has been added (ref 81).

3 References and typesetting were corrected

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

Sincerely yours,

A handwritten signature in cursive script that reads "Junling Han".

Jun-Ling Han, MD

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