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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 62969

Title: Gut Microbiota Dysbiosis in Chinese Children with Type 1 Diabetes Mellitus: A Case-control Study

Reviewer's code: 03674832
Position: Editorial Board
Academic degree: MD, PhD
Professional title: Professor
Reviewer's Country/Territory: Greece
Author's Country/Territory: China

Manuscript submission date: 2021-01-23
Reviewer chosen by: Jin-Lei Wang
Reviewer accepted review: 2021-01-25 06:14
Reviewer performed review: 2021-01-25 08:50
Review time: 2 Hours

Scientific quality	[Y] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[Y] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

Evaluation of the ORIGINAL ARTICLE paper Manuscript NO: 62969 entitled "Fecal Microbiota Dysbiosis in Chinese Children with Type 1 Diabetes Mellitus: A Case-control Study". The aim of this study was to investigate if alterations in the gut microbiota correlate with fasting blood glucose (FBG) in Chinese children with T1DM. The authors suggest that the study showed that the investigation of T1DM-and association of fecal microbiota provide novel insights into the pathogenesis of the disease, which would shed light on the diagnosis and treatment of T1DM. Comments for the authors

1. This is well written paper on an interestingness issue with findings: Alterations of gut microbiota plays vital role in the development of autoimmune diseases such as type 1 diabetes mellitus (T1DM). 2. The text, the table and the large number of figures are appropriate and highly informative. 3. The number of references is huge and they are up to date. 4. There are substantial practical implications of the results of the paper in T1DM patients. 5. Adding the following paper will strengthen the results of the paper: Vatanen T, Franzosa EA, Schwager R, et al. The human gut microbiome in early-onset type 1 diabetes from the TEDDY study. Nature. 2018 Oct;562(7728):589-594

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 62969

Title: Gut Microbiota Dysbiosis in Chinese Children with Type 1 Diabetes Mellitus: A Case-control Study

Reviewer's code: 02508010

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Taiwan

Author's Country/Territory: China

Manuscript submission date: 2021-01-23

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-01-23 16:07

Reviewer performed review: 2021-01-27 06:32

Review time: 3 Days and 14 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

The manuscript reported an original paper in title "Fecal Microbiota Dysbiosis in Chinese Children with Type 1 Diabetes Mellitus: A Case-control Study". The authors aimed to investigate the alterations of gut microbiota in Chinese children with T1DM and its associations with the fasting blood glucose (FBG). They concluded that the fecal microbiota of T1DM patients altered with positively and negatively correlated to the FBG. In addition, they proposed that T1DM-associated fecal microbiota can provide novel insights into the diagnosis and treatment of T1DM. This article is a well-designed, and clear writing paper. However, some criticisms are listed below. The major comments 1. This paper compare the microbiota difference of T1DM and controls at bacterial composition and functional level. It is a comprehensive and detail study but the entire manuscript is too complicated to read. It need to be concise. 2. It is interesting to analyze the T1DM-associated microbial functional alteration between the microbiota of T1DM and controls. The results find that several metabolic pathways differ between two groups, especial in glycan metabolism are associated with the pathogenesis and development of T1DM. Do you find the significantly different bacteria (Bacteroides vulgatus ATCC8482, Bacteroides ovatus, the Eubacterium hallii group, and Anaerostipes hadrus) contribute to the functional metabolism? 3. Because this study is a cross-sectional study, the main limitation of this study is that does the alteration of gut microbiota in T1DM patients cause or trigger the T1DM develop? Therefore, I think this association is a preliminary result, further causal-development study desires further investigation. The minor comments 1. In Page 4, AIM, line 59. "Our present study aims to investigated the alterations of…." The investigated change to investigate. 2.

In Page 7, lines 132-137. "Leiva-Gea et al. demonstrated…. the production of mucin [15]." This information in background seems not related to the study design and results,

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do you mean that lactate- and butyrate-producers bacteria may associated with T1DM? However, in the results (functional assay), there are no data presenting this correlation. 3. In Page 8, lines 141-142. "Furthermore, maintaining the eubiosis of early-life gut microbiota in children can reduce the risk of developing T1DM." I do not see any evidence to support this conclusion. 4. In Page 9, Participants selection, line 154. "A total of 51 confirmed T1DM children…." Are the enrolled children newly diagnosed or in treatment? It needs to clearly present. 5. In Page 9, Participants selection, lines 162-63. "The levels of fasting blood glucose (FBG) of these participants were detected in the morning." Were they asked to fasting? 6. In Page 9, Participants selection, lines 166-168. "The protocols for the present study were approved by the Ethics Committee of the First Affiliated Hospital, School of Medicine, Zhejiang University." Because this study is multicenters trial, the approval of the Ethics Committee needs to obtain from all participant units. 7. The Discussion section is too redundant, please concise this section. 8. A total of 87 references seems too many, please to delete some if possible.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 62969

Title: Gut Microbiota Dysbiosis in Chinese Children with Type 1 Diabetes Mellitus: A Case-control Study

Reviewer's code: 01589311

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Full Professor

Reviewer's Country/Territory: Brazil

Author's Country/Territory: China

Manuscript submission date: 2021-01-23

Reviewer chosen by: Jin-Lei Wang

Reviewer accepted review: 2021-01-25 17:15

Reviewer performed review: 2021-01-27 12:01

Review time: 1 Day and 18 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

This is an observational study by Liu and colleagues, examining the potential role of the gut microbiota in the development of type 1 diabetes mellitus (T1DM) in a cohort of Chinese children. The authors found that the fecal bacterial diversity increased significantly in T1DM children, and that several key functional bacteria correlated with fasting blood glucose (FBG). The investigators claim that the microbiota profile found could be used as non-invasive diagnostic biomarker to discriminate T1DM from healthy controls, and that the findings may provide novel insights into the pathogenesis of T1DM. The gut microbiome is suggested to play a role in the pathogenesis of autoimmune disorders including T1DM. Evidence of anti-islet cell autoimmunity in T1DM appears in the first years of life, but little is known regarding the establishment of the gut microbiome in early infancy. In addition, a clear relationship between T1DM and intestinal microbiota is yet to be determined. Although the subject is not entirely new, the investigators performed an extensive and detailed study on the composition of the gut microbiota at various levels, and attempted to correlate the findings with fasting blood glucose. The overall structure of the manuscript is complete, as requested by the Editorial instructions of the journal. The text and figures are well structured and the methods employed are logical and well described. In regard to the ethical considerations, the text appears to be appropriate. Regarding the selection of patients, the authors indicate a multi-center origin, but they still end up with a relatively small number of cases, one of the limitations of this study, acknowledged in the Discussion section.

Major points: 1) The investigators should explain in more detail the origin of the patients and samples. Where are the centers (hospitals) located? Are they in the same city? Or they are from different Districts? How far they are form each other? In the Discussion section, the authors comment on the importance of geography. Therefore, it

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would be interesting to add more details concerning this issue in the manuscript. 2) Regarding limitations of the study, it seems important to acknowledge that the findings of fecal microbiota and FBG do not indicate an obvious clear primary or secondary relationship. Moreover, although the investigators show statistical significance, the isolated findings show relatively weak associations. 3) The investigators should explain in more detail why the findings of this study could be used as "non-invasive diagnostic biomarkers to distinguish between patients with T1DM and healthy controls"? What exactly do authors mean? Since the diagnosis of T1DM does depend on microbial studies, what could we expect regarding the findings? Early predisposition to the development of T1DM? If this were the idea, how practical would be investigating the fecal microbiota of the population? We understand that the findings of this study are much more important in terms disease pathogenesis, and the potential development of microbiota-targeted treatments, as adjuvant therapies or perhaps influencing preventive measures. Minor comments: 1) A general language revision will be necessary. There are many minor mistakes in several parts of the manuscript.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 62969

Title: Gut Microbiota Dysbiosis in Chinese Children with Type 1 Diabetes Mellitus: A Case-control Study

Reviewer's code: 02630177

Position: Peer Reviewer

Academic degree: PhD

Professional title: Associate Professor

Reviewer's Country/Territory: Thailand

Author's Country/Territory: China

Manuscript submission date: 2021-01-23

Reviewer chosen by: Jin-Lei Wang

Reviewer accepted review: 2021-01-25 08:57

Reviewer performed review: 2021-02-01 06:39

Review time: 6 Days and 21 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

To the editors/authors, This case control study indicates that, in Chinese, T1DM displayed bacterial diversities differently from healthy control subjects. Further, some bacteria might predict clinical onset and treatment outcome. Comments 1.Hb1C should be reported and its correlation with some bacteria may be useful more than fasting blood glucose, otherwise supporting each other. 2. Introduction and methods should be concise and referred to previous reports instead. Discussion should not repeat methods and results description and be concise. 3. This study excluded differences in dietary habits and race, the factors that can affect gut microbial diversities. How to apply the prediction result to the general Chinese? A-month dietary control may not be practical. Discussion should be added this concern. 4. English need carefully rechecked and edited.

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 62969

Title: Gut Microbiota Dysbiosis in Chinese Children with Type 1 Diabetes Mellitus: A Case-control Study

Reviewer's code: 02630177
Position: Peer Reviewer
Academic degree: PhD
Professional title: Associate Professor
Reviewer's Country/Territory: Thailand
Author's Country/Territory: China

Manuscript submission date: 2021-01-23
Reviewer chosen by: Jia-Ru Fan
Reviewer accepted review: 2021-02-18 06:31
Reviewer performed review: 2021-02-18 06:55
Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

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No more comments.

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 62969

Title: Gut Microbiota Dysbiosis in Chinese Children with Type 1 Diabetes Mellitus: A Case-control Study

Reviewer's code: 02508010

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Taiwan

Author's Country/Territory: China

Manuscript submission date: 2021-01-23

Reviewer chosen by: Jia-Ru Fan

Reviewer accepted review: 2021-02-18 01:10

Reviewer performed review: 2021-02-18 09:05

Review time: 7 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[Y] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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The revised manuscript reported an original paper in title “Gut Microbiota Dysbiosis in Chinese Children with Type 1 Diabetes Mellitus: A Case-control Study”. The revision results in more concise and clear for this paper. They have answered and revised this manuscript according to the suggestions point to point. No more criticisms to me.

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 62969

Title: Gut Microbiota Dysbiosis in Chinese Children with Type 1 Diabetes Mellitus: A Case-control Study

Reviewer's code: 01589311

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Full Professor

Reviewer's Country/Territory: Brazil

Author's Country/Territory: China

Manuscript submission date: 2021-01-23

Reviewer chosen by: Jia-Ru Fan

Reviewer accepted review: 2021-02-18 01:06

Reviewer performed review: 2021-02-18 20:47

Review time: 19 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

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The authors' repsonses to questions are appropriate, and changes made improved the overall quality of the manuscript.