



PEER-REVIEW REPORT

Name of journal: World Journal of Diabetes

Manuscript NO: 60176

Title: Blood glucose response after oral lactulose intake in type 2 diabetic individuals

Reviewer's code: 02624173

Position: Editorial Board

Academic degree: MD

Professional title: Doctor, Professor

Reviewer's Country/Territory: India

Author's Country/Territory: Austria

Manuscript submission date: 2020-12-03

Reviewer chosen by: Le Zhang

Reviewer accepted review: 2021-01-13 06:27

Reviewer performed review: 2021-01-14 15:48

Review time: 1 Day and 9 Hours

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 Grade E: Do not publish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



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SPECIFIC COMMENTS TO AUTHORS

Nicely presented work. Some queries are: How isomerization process can produce impurities? This information needs to be revised. What is still water? Under exclusion criteria, do other endocrinal disorders need not be excluded?



PEER-REVIEW REPORT

Name of journal: World Journal of Diabetes

Manuscript NO: 60176

Title: Blood glucose response after oral lactulose intake in type 2 diabetic individuals

Reviewer's code: 00503572

Position: Editorial Board

Academic degree: MD, MSc

Professional title: Associate Professor, Professor

Reviewer's Country/Territory: Mexico

Author's Country/Territory: Austria

Manuscript submission date: 2020-12-03

Reviewer chosen by: Le Zhang

Reviewer accepted review: 2021-02-02 16:10

Reviewer performed review: 2021-02-06 00:38

Review time: 3 Days and 8 Hours

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



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SPECIFIC COMMENTS TO AUTHORS

The manuscript entitled “Unaffected blood glucose after oral lactulose intake in type 2 diabetic individuals” sets out the results of a well-designed and well-written study showing that oral lactulose administration in patients with type 2 DM did not lead to impairments in glucose levels and was also well tolerated. The results of this study contrast with the previous assumption that this drug could be the cause of diabetes decompensation in these patients. However, I have the following concerns regarding the results. The study adopted numerous exclusion criteria in diabetic patients for the study. It is known that patients with DM have a high frequency of acute and chronic comorbidities and may also receive a high number of medications. This raises the following question: what was the rate of selection of patients after applying all these selection criteria in this study who may receive the benefits of the medication? Likewise, if the decision of excluding a probably high number of patients could not significantly modify results that might be obtained in the real-life clinical practice. I recommend authors to discuss based on their results which are finally the contraindications of giving lactulose to diabetic patients in general terms. In addition, there are different formulations of lactulose marketed by various laboratories. As a gesture of clarity for readers who want to use lactulose in their diabetic patients in the real-life clinic, what would be the specific recommendations regarding the pharmacological presentation of the lactulose that should be used?



PEER-REVIEW REPORT

Name of journal: World Journal of Diabetes

Manuscript NO: 60176

Title: Blood glucose response after oral lactulose intake in type 2 diabetic individuals

Reviewer's code: 02539650

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Chief Doctor, Consultant Physician-Scientist, Doctor, Senior Researcher

Reviewer's Country/Territory: Hungary

Author's Country/Territory: Austria

Manuscript submission date: 2020-12-03

Reviewer chosen by: Le Zhang

Reviewer accepted review: 2021-02-02 07:20

Reviewer performed review: 2021-02-12 20:50

Review time: 10 Days and 13 Hours

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



SPECIFIC COMMENTS TO AUTHORS

I found the manuscript of the RCT titled “Unaffected blood glucose after oral lactulose intake in type 2 diabetic individuals” interesting. This paper provides valuable information about the effect of lactulose on glycemic parameters which is a useful knowledge in the everyday clinical work. Therefore my opinion is basically supportive due to that the work is relevant for the clinics. Nevertheless there are few (related) issues with this paper that should be addressed prior to publication.

- I found both the title “Unaffected blood glucose after oral lactulose intake in type 2 diabetic individuals” and the statement in the abstract
- “all secondary endpoints, including the maximum increase in glucose from baseline, did not differ between lactulose and water intake in a clinically relevant manner” somewhat exaggerated and overstated.

There is no such thing in medical science that “unaffected blood glucose” and this clearly indicates the problem with the paper:

- If the authors would have had used the appropriate language, e.g. “unchanged blood glucose levels” in the title it would not be true any more. It is simply due to that a significant difference ($p=0.0059$) was observed in the maximum increase in glucose from baseline after the administration of 30g of liquid lactulose vs administration of water.
- Similarly, it is not entirely appropriate to state that “all secondary endpoints, including the maximum increase in glucose from baseline, did not differ between lactulose and water intake in a clinically relevant manner” especially not in the results section.
- It should rather be indicated that there was a significant difference in the maximum increase in glucose from baseline (Treatment Diff in max increase of glucose $cc= 0.63\text{mmol/L}$, $p=0.0059$).
- In the conclusion it may be stated that this significant difference is not too high, therefore it is unlikely to cause major changes in the clinics, however it is again not entirely black and white and not absolutely equivalent with a kind of “zero clinical relevance” as suggested



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by the authors with the current interpretation. Even such a small increase may have clinical relevance, it simply depends on the clinical situation, e.g.: a patient with T2DM have a mean postprandial values in his/her SMBG profile of 7.7 mmol/L after a given meal and when he/she starts to load 30g of liquid lactulose this postprandial glucose level increases up to 8.3 mmol/L (as typically patients do not only consume water) and such a postmeal glucose value (already can again be considered above the target) may trigger changes in therapy. Although it really can be recognized that the increase of 0.6 mmol/L in glucose concentration can be considered minimal which - in the very vast majority of the cases - is unlikely to result in major changes of the therapy and this can be outlined in the discussion/conclusion section. • Therefore I would suggest to change the title to a more relevant one. • I would also suggest to report numerically and clearly the results regarding the treatment difference in max increase of glucose cc (0.63mmol/L, p=0.0059) for 30g liquid lactulose vs water in the results section of the abstract already. • The clinical interpretation of this should not be mentioned in the results section, but in the conclusion/discussion sections and I would suggest to temper down the tone of this interpretation a bit, in particular for the clinics when liquid lactulose is often used in higher doses (in other indications, e.g.: in PSE high doses can be used up to 300 mL lactulose) and if the currently minimal, yet already significant increases in max increase of glucose levels are multiplied with the use of higher doses (in other indication) than the increases in blood glucose levels can already be clinically more relevant. This is not too obvious now from reading the title at this point.



RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Diabetes

Manuscript NO: 60176

Title: Blood glucose response after oral lactulose intake in type 2 diabetic individuals

Reviewer's code: 02539650

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Chief Doctor, Consultant Physician-Scientist, Doctor, Senior Researcher

Reviewer's Country/Territory: Hungary

Author's Country/Territory: Austria

Manuscript submission date: 2020-12-03

Reviewer chosen by: Jia-Ru Fan

Reviewer accepted review: 2021-04-10 16:55

Reviewer performed review: 2021-04-10 17:08

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS



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My comments were answered in detail and the subsequent changes were made thoroughly and appropriately (incl. the title itself after my recommendation). Therefore I would suggest to accept this MS for publication.