



## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Diabetes*

**Manuscript NO:** 72326

**Title:** Clopidogrel delays and can reverse diabetic nephropathy pathogenesis in type 2 diabetic db/db mice

**Provenance and peer review:** Unsolicited manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 05249683

**Position:** Editorial Board

**Academic degree:** BSc, MSc, PhD

**Professional title:** Professor

**Reviewer's Country/Territory:** Egypt

**Author's Country/Territory:** China

**Manuscript submission date:** 2021-10-18

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2021-10-25 09:04

**Reviewer performed review:** 2021-10-26 08:56

**Review time:** 23 Hours

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 Grade E: Do not publish            |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



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|-------------------------------------|---|
| <b>Peer-reviewer<br/>statements</b> | Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous<br>Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
|-------------------------------------|---|

### **SPECIFIC COMMENTS TO AUTHORS**

In this manuscript, the authors have a good finding in type 2 diabetic db/db mice. They found that clopidogrel reduced renal collagen deposition and fibrosis in db/db mice and prevented renal dysfunction. This occurs most likely by inhibiting renal macrophage infiltration and associated inflammation. Furthermore, the results are well-represented, and the units are clearly expressed. Also, the immunohistochemical staining results were achieved with a high level of expertise. On the other hand, the authors have to show the results of blood sugar and insulin assays in their manuscript to know the diabetic state in db/db mice. A complete information of db/db mice must be given in introduction and the written link in page 7 does not have any knowledge about these mice.



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**Reviewer's code:** 05947685

**Position:** Peer Reviewer

**Academic degree:** MD, PhD

**Professional title:** Doctor, Lecturer

**Reviewer's Country/Territory:** Thailand

**Author's Country/Territory:** China

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**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2021-11-02 16:03

**Reviewer performed review:** 2021-11-10 05:12

**Review time:** 7 Days and 13 Hours

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|---------------------------|---|
| <b>Scientific quality</b> | <input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good<br><input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish            |
| <b>Language quality</b>   | <input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing<br><input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
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| <b>Peer-reviewer<br/>statements</b> | Peer-Review: [ <input checked="" type="checkbox"/> ] Anonymous [ <input type="checkbox"/> ] Onymous<br>Conflicts-of-Interest: [ <input type="checkbox"/> ] Yes [ <input checked="" type="checkbox"/> ] No |
|-------------------------------------|---|

### **SPECIFIC COMMENTS TO AUTHORS**

In this manuscript, the authors showed that copidogrel can reduce the pathogenesis of diabetic nephropathy in db/db type 2 diabetic mice. The propose mechanism(s) are via the inhibition of inflammation as well as inhibiting the infiltration of macrophage to renal tissues. Even the research topic and findings are of interest, the results leading to the the authors' conclusion are still weak. Most of the findings are descriptive and may need more investigation to make a convincible and concrete conclusion. The authors may have to consider these following points: Major points: 1. The details of animal experiments need to be given and included in the Materials and Methods, rather than citing the previous publication (as detailed as other researchers could repeat the experiments after reading). The dosage, route, frequency of copidogrel administration mist be given. The graph comparing urinary albumin/creatinine ratio in Fig 3 should be clearly spelled out when the baseline was taken. The statement about the ethic approval with the number of approval should also be included in the section of animal experiments. 2. The authors suggested that copidogrel may inhibit the renal inflammation by demonstrating the reduction of macrophage infiltration and suppressing the expression of several genes, e.g., TNFA, IL1B. However, the supporting evidence to show how copidogrel exerts the activities on these local targets is unclear. There is neither supporting experiments nor the discussion on this point. On the other hand, copidogrel is known to directly affect the platelets. However, the systemic inflammatory cytokines which may be derived from platelets have not been examined yet in this manuscript. The levels of related cytokines in sera of the mice in each group will be strengthen the findings and conclusion of the authors. Minor points: 1. In page



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7, there is a description that diabetic mice had longer bleeding time than in wild type, however, the results in Fig 2 does not show the concordance with the main text. 2. How did the authors prove the hypermutation of membranes. There is no experiment shown but mentioned in "Clopidogrel ameliorated diabetes-associated renal dysfunction, glomerular sclerosis, and collagen fiber deposition in the mice" section. 3. The scale bars should be added into every microscopic photos. 4. The IHC photos in Fig 4 are not clear, especially there is a very high background of Fig 4B. Could these figures be improved? 5. Please check the scale of graph in Fig 1B. The blood glucose levels are to low for the animal to be survive.



## RE-REVIEW REPORT OF REVISED MANUSCRIPT

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**Reviewer's Country/Territory:** Thailand

**Author's Country/Territory:** China

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**Reviewer chosen by:** Jing-Jie Wang

**Reviewer accepted review:** 2022-02-04 12:21

**Reviewer performed review:** 2022-02-05 15:30

**Review time:** 1 Day and 3 Hours

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|---------------------------|---|
| <b>Scientific quality</b> | <input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good<br><input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish            |
| <b>Language quality</b>   | <input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing<br><input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
| <b>Conclusion</b>         | <input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority)<br><input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection             |
| <b>Peer-reviewer</b>      | Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous   |



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statements

Conflicts-of-Interest: [ ] Yes [Y] No

#### **SPECIFIC COMMENTS TO AUTHORS**

The article has been improved. The answers addressed to this reviewer are acceptable and the limitation of the study is acknowledged.



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**Manuscript submission date:** 2021-10-18

**Reviewer chosen by:** Jing-Jie Wang

**Reviewer accepted review:** 2022-02-03 05:23

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**Review time:** 17 Days and 22 Hours

|                           |   |
|---------------------------|---|
| <b>Scientific quality</b> | <input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good<br><input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish            |
| <b>Language quality</b>   | <input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing<br><input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
| <b>Conclusion</b>         | <input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority)<br><input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection             |
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statements

Conflicts-of-Interest: [ ] Yes [Y] No

#### **SPECIFIC COMMENTS TO AUTHORS**

The authors responded to my concerns about blood glucose and insulin levels in the original version with a convincing response. The response isn't in the revised version's or the supplementary file's file.