Baishideng Publishing Group

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

PEER-REVIEW REPORT

Name of journal: *World Journal of Diabetes*

Manuscript NO: 81580

Title: AT1 Receptor downregulation: a mechanism for improving glucose homeostasis in patients with type 2 diabetes mellitus

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 02459759
Position: Associate Editor
Academic degree: MD
Professional title: Professor
Reviewer's Country/Territory: China
Author's Country/Territory: Mexico

Manuscript submission date: 2022-11-15

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-11-16 08:55

Reviewer performed review: 2022-11-29 06:33

Review time: 12 Days and 21 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

Baishideng Publishing Group

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
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
Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

It's a very interesting topic about AT1 receptor downregulation in T2D.

We thank the reviewer for carefully reading our manuscript and for its acceptance suggestion.

Baishideng Publishing Group

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

PEER-REVIEW REPORT

Name of journal: *World Journal of Diabetes*

Manuscript NO: 81580

Title: AT1 Receptor downregulation: a mechanism for improving glucose homeostasis in patients with type 2 diabetes mellitus

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06462052
Position: Peer Reviewer
Academic degree:

Professional title:

Reviewer's Country/Territory: Reviewer_Country

Author's Country/Territory: Mexico

Manuscript submission date: 2022-11-15

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-12-09 05:38

Reviewer performed review: 2022-12-13 15:23

Review time: 4 Days and 9 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

Baishideng Publishing Group

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[ ] Grade A: Priority publishing [ ] Grade B: Minor language polishing [Y] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Present study provided a relatively complete description of the role of AT1R inhibition in regulating the glucose homeostasis in patients with type 2 diabetes mellitus. The perspective of the whole review is relatively complete and in-depth, and the review shall be more referential with the following modifications.

We thank the reviewer for carefully reading our manuscript and for all criticisms to improve it. All changes in the revised manuscript are included in this document highlighted in red.

First of all, the running title should be a brief description of the title, or at least consistent in meaning with the title.

We have reformatted the running title accordingly.

Secondly, the conclusion of the involvement of AT1R inhibition in regulating the glucose homeostasis in patients with type 2 diabetes mellitus is hardly to be made with the figures provided. The authors should provide more evidence to match the theme of the article title. Otherwise, the authors should just use the running title as the title of the

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

whole article. However, it also brings a new problem, that is, the novelty of the whole article is greatly reduced. This should be the biggest problem of this article and I really hope the authors could make up with a good solution.

We agreed with the reviewer's comment, so we modified the main title to associate it with the main text content properly. Also, we had provided further clinical evidence on this matter to strengthen the theme of our manuscript. For this purpose, we have included more bibliographic references from high impact research describing the glucose control improvement associated with AT1 receptor activity downregulation. In fact, the evidence on these aforementioned reports agrees with our findings on the molecular effects that are described in our review. This information has been added on page 6, second paragraph:

"That premise could be supported by Dominguez et al., who reported that patients with T2DM who took ACE inhibitors (drugs that decrease ANG-II levels) had enhanced insulin receptor activation compared to those who took a placebo (45). Furthermore, The DREAM Trial Investigators carried out a clinical trial including 5,269 patients with impaired glucose tolerance; in this double-blind protocol, one treatment group received ACE inhibitors and other group received placebo. After three years of follow-up, T2DM incidence was lower in the group of patients who took ACE inhibitors (46). Likewise, The NAVIGATOR Study group also conducted a randomized clinical trial including 9,306 patients with impaired glucose tolerance. In this study, one group of patients received AT1R antagonists (drugs that bind to AT1R acting as antagonists, thus blocking the action of ANG-II) and the other group received a placebo; after an average follow-up of 5 years, it was demonstrated that patients who received AT1R antagonists had a lower risk of developing T2DM (47)."

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

Thirdly, the authors should check the data comparison in the figures, and the comparison with significant difference should be marked. In addition, as required by the journal, for all manuscripts involving human studies and/or animal experiments, authors must submit the related formal ethics documents that were reviewed and approved by their local ethical review committee.

The footnotes of the figures include the description of the statistical analysis performed. Specifically, on figure 2 the symbol asterisk (*) is incorporated over the bars to highlight that there is a significant statistical difference. The figure 3 does not include any symbol as no statistical difference was found among the groups, although, there is a trend which from a biochemical point of view is related to the data in figure 2, that is addressed on the last paragraph on page 6:

"That premise could be supported by Dominguez et al., who reported that patients with T2DM who took ACE inhibitors (drugs that decrease ANG-II levels) had enhanced insulin receptor activation compared to those who took a placebo (45). Furthermore, The DREAM Trial Investigators carried out a clinical trial including 5,269 patients with impaired glucose tolerance; in this double-blind protocol, one treatment group received ACE inhibitors and other group received placebo. After three years of follow-up, T2DM incidence was lower in the group of patients who took ACE inhibitors (46). Likewise, The NAVIGATOR Study group also conducted a randomized clinical trial including 9,306 patients with impaired glucose tolerance. In this study, one group of patients received AT1R antagonists (drugs that bind to AT1R acting as antagonists, thus blocking the action of ANG-II) and the other group received a placebo; after an average follow-up of 5 years, it was demonstrated that patients who received AT1R antagonists had a lower risk of developing T2DM (47)."

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

Concerning the ethics documents, our institutional Ethics committee approved our protocol in the "Circular Letter number 0985/2017" which is mentioned in the footnotes of figures 2 and 3. The document was submitted along with the manuscript and the Editor in chief confirmed the document has met the basic publishing requirements of the World Journal of Diabetes. We apologize as we do not know if the reviewers have access to this document.

Finally, the grammar of the article should be greatly revised for better understanding.

We thank the reviewer for carefully reading our manuscript, the grammar has been corrected so the language quality has been improved.

Baishideng Publishing Group

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

PEER-REVIEW REPORT

Name of journal: *World Journal of Diabetes*

Manuscript NO: 81580

Title: AT1 Receptor downregulation: a mechanism for improving glucose homeostasis in patients with type 2 diabetes mellitus

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06461797
Position: Peer Reviewer
Academic degree:

Professional title:

Reviewer's Country/Territory: Reviewer_Country

Author's Country/Territory: Mexico

Manuscript submission date: 2022-11-15

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-12-10 14:37

Reviewer performed review: 2022-12-19 17:40

Review time: 9 Days and 3 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

Baishideng Publishing Group

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
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) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Thank you for sending me the manuscript to review. The topic of this manuscript is clinical important and is of interest. The title and abstract well summarized topic and aim of this manuscript.

We thank the reviewer for carefully reading our manuscript and for all criticisms to improve it. All changes in the revised manuscript are included in this document highlighted in red.

The suggestions to improve the manuscript were showed as the following:

1. The main body of this manuscript should focus on demonstrating the correlation between the signaling pathways of ANG-II and insulin resistance. However, the main body mainly separately introduced effects and signaling pathway of insulin, ANG-II , and insulin resistance. Although the introduction was explicit, the clear and logical demonstration to explain the correlation between signaling pathways of ANG-II and insulin resistance was limited in the main body.

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

We appreciate your observation. The review´s aim is to explain the mechanisms by which the chronic activation of ANGII signaling is able to block insulin pathways. Hence, we consider that for didactical purposes it is important to initiate with the physiological context, namely describing the ANGII and insulin signaling pathways and so later establish the pathophysiological correlation among them.

However, following your suggestion we had included a more detailed description of this correlation in the review´s main body to facilitate readers comprehension. In this sense, the main text mentions the insulin resistance mechanisms associated with ANGII, though, following your assertive suggestion, we have improved the clinical evidence of this named association and of its correlation with the molecular pathophysiological mechanisms. This information has been added on page 6, second paragraph:

"That premise could be supported by Dominguez et al., who reported that patients with T2DM who took ACE inhibitors (drugs that decrease ANG-II levels) had enhanced insulin receptor activation compared to those who took a placebo (45). Furthermore, The DREAM Trial Investigators carried out a clinical trial including 5,269 patients with impaired glucose tolerance; in this double-blind protocol, one treatment group received ACE inhibitors and other group received placebo. After three years of follow-up, T2DM incidence was lower in the group of patients who took ACE inhibitors (46). Likewise, The NAVIGATOR Study group also conducted a randomized clinical trial including 9,306 patients with impaired glucose tolerance. In this study, one group of patients received AT1R antagonists (drugs that bind to AT1R acting as antagonists, thus blocking the action of ANG-II) and the other group received a placebo; after an average follow-up of 5 years, it was demonstrated that patients who received AT1R antagonists had a lower risk of developing T2DM (47)."

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

2. In the section "AT1R inhibition improves glucose homeostasis in patients with type 2 diabetes mellitus", the point that glycemic control in patients with HBP and T2DM is easier than those with only T2DM should be cautiously considered, because the research evidences to support this point was not critically discussed. Are all research evidence consistent, or are there any other contrary findings?

As you mentioned, besides the data obtained by our team on glucose homeostasis amelioration through AT1 receptor inhibition, we should provide further evidence on this matter to strengthen our manuscript. Hence, we had included references from high impact publications describing the glucose control improvement associated to AT1 receptor activity downregulation. This information has been added on page 6, second paragraph:

"That premise could be supported by Dominguez et al., who reported that patients with T2DM who took ACE inhibitors (drugs that decrease ANG-II levels) had enhanced insulin receptor activation compared to those who took a placebo (45). Furthermore, The DREAM Trial Investigators carried out a clinical trial including 5,269 patients with impaired glucose tolerance; in this double-blind protocol, one treatment group received ACE inhibitors and other group received placebo. After three years of follow-up, T2DM incidence was lower in the group of patients who took ACE inhibitors (46). Likewise, The NAVIGATOR Study group also conducted a randomized clinical trial including 9,306 patients with impaired glucose tolerance. In this study, one group of patients received AT1R antagonists (drugs that bind to AT1R acting as antagonists, thus blocking the action of ANG-II) and the other group received a placebo; after an average follow-up of 5 years, it was demonstrated that patients who received AT1R antagonists had a lower risk of developing T2DM (47)."

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

3. The "antihypertensive drugs" used in the manuscript could be more precise. Because this manuscript explored the correlation between ANG-II and insulin resistance, the antihypertensive drugs could be more precise, such as angiotensin converting enzyme inhibitor, angiotensin II receptor antagonists.

We agreed with the reviewer's comment about the importance of further emphasis on the mechanisms of action for the antihypertensive drugs mentioned. This information has been added on page 6, second and third paragraphs:

"That premise could be supported by Dominguez et al., who reported that patients with T2DM who took ACE inhibitors (drugs that decrease ANG-II levels) had enhanced insulin receptor activation compared to those who took a placebo (45). Furthermore, The DREAM Trial Investigators carried out a clinical trial including 5,269 patients with impaired glucose tolerance; in this double-blind protocol, one treatment group received ACE inhibitors and other group received placebo. After three years of follow-up, T2DM incidence was lower in the group of patients who took ACE inhibitors (46). Likewise, The NAVIGATOR Study group also conducted a randomized clinical trial including 9,306 patients with impaired glucose tolerance. In this study, one group of patients received AT1R antagonists (drugs that bind to AT1R acting as antagonists, thus blocking the action of ANG-II) and the other group received a placebo; after an average follow-up of 5 years, it was demonstrated that patients who received AT1R antagonists had a lower risk of developing T2DM (47).

In accordance with these reports, our results in clinical practice are represented in figures 2 and 3, which shows two groups of patients who attended to the internal medicine department for consultation to manage their condition, on the one hand patients who only suffer from T2DM and on the other hand patients with HBP and T2DM. As shown in Figure 2, glycemic control in patients with HBP and T2DM is easier than those with just T2DM; as the HbA1c levels are close to therapeutic goals (48-51). This response could be due to the fact that the second group of patients, apart from treatment for T2DM (metformin), received AT1R antagonists (losartan or telmisartan) or ACE inhibitors

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

(captopril or enalapril) as hypertension treatment as either of these drugs decrease the activation of the AT1R (52,53)."