Name of journal: World Journal of Diabetes

Manuscript NO: 95252

Title: Mitigating diabetes-related complications: Empowering metformin with cholecalciferol and taurine supplementation in type 2 diabetic rats

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer’s code: 03831562

Position: Peer Reviewer

Academic degree: PhD

Professional title: Professor

Reviewer’s Country/Territory: India

Author’s Country/Territory: Egypt

Manuscript submission date: 2024-04-06

Reviewer chosen by: Jia-Ru Fan

Reviewer accepted review: 2024-04-22 09:09

Reviewer performed review: 2024-05-01 09:19

Review time: 9 Days

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**SPECIFIC COMMENTS TO AUTHORS**

1. The authors would do well in future prospective studies to study the receptor and binding with reference to the ligand, 1,25 Dihydroxy cholecalciferol, as related to Type 2 diabetes mellitus.
2. Since Vitamin D levels have a role in insulin sensitivity, the authors can include more than one parameter to monitor insulin sensitivity in future studies.
PEER-REVIEW REPORT

Name of journal: World Journal of Diabetes

Manuscript NO: 95252

Title: Mitigating diabetes-related complications: Empowering metformin with cholecalciferol and taurine supplementation in type 2 diabetic rats

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer’s code: 02623966

Position: Editorial Board

Academic degree: MD, MSc, PhD

Professional title: Attending Doctor, Doctor, Research Scientist

Reviewer’s Country/Territory: Greece

Author’s Country/Territory: Egypt

Manuscript submission date: 2024-04-06

Reviewer chosen by: Jia-Ru Fan

Reviewer accepted review: 2024-05-20 17:49

Reviewer performed review: 2024-05-20 17:49

Review time: 1 Hour

| Scientific quality | [ ] Grade A: Excellent | [ ] Grade B: Very good | [ ] Grade C: Good |
| Novelty of this manuscript | [ ] Grade A: Excellent | [ ] Grade B: Good | [ ] Grade C: Fair |
| Creativity or innovation of this manuscript | [ ] Grade A: Excellent | [ ] Grade B: Good | [ ] Grade C: Fair |
**SPECIFIC COMMENTS TO AUTHORS**

It is a well-design study adding new information to the literature. According to my knowledge, it is a novel paper in its field opening new horizons for further evidence. Authors, succeed to present their findings in a clear way. In addition, the object as well as the results are appropriately discussed in the context of previous literature explaining the importance of the manuscript in its field. Authors succeed to present their data in a clear way adding information to the existing literature. Therefore, I have no corrections or further work to propose for the improvement of the manuscript and therefore it can be published unaltered.
Name of journal: World Journal of Diabetes

Manuscript NO: 95252

Title: Mitigating diabetes-related complications: Empowering metformin with cholecalciferol and taurine supplementation in type 2 diabetic rats

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer’s code: 05247977

Position: Peer Reviewer

Academic degree: MD

Professional title: Assistant Professor

Reviewer’s Country/Territory: Saudi Arabia

Author’s Country/Territory: Egypt

Manuscript submission date: 2024-04-06

Reviewer chosen by: Jia-Ru Fan

Reviewer accepted review: 2024-05-20 15:38

Reviewer performed review: 2024-06-01 12:48

Review time: 11 Days and 21 Hours

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SPECIFIC COMMENTS TO AUTHORS

Thank you for the opportunity to review the manuscript "Mitigating Diabetes-Related Complications: Empowering Metformin with Cholecalciferol and Taurine Supplementation in Type 2 Diabetic rats". Summary: This study investigated the effects of supplementing metformin treatment with cholecalciferol and taurine in a rat model of streptozotocin-induced type 2 diabetes. The authors measured various metabolic, biochemical, histological and immunohistochemical parameters. They found that the combination of metformin, cholecalciferol and taurine was more effective than metformin alone in improving glycemic control, lipid profiles, liver function, oxidative stress markers, and pancreatic islet structure and function. The authors conclude that this combination therapy may help prevent diabetes complications by mitigating oxidative stress-induced tissue damage. Originality and Significance: The topic of preventing diabetes complications using combination therapies is clinically important given the increasing global burden of type 2 diabetes. While previous studies have looked at metformin plus either cholecalciferol or taurine, the novelty of this study is evaluating the triple combination. The results, if validated in humans, could lead to
improved treatment approaches for diabetes. However, the manuscript does not sufficiently highlight what is already known on this topic and the key knowledge gaps this study aims to address. The introduction should provide more context on the limitations of current therapies and prior evidence on cholecalciferol and taurine in diabetes. Experimental Design and Methods: The use of the streptozotocin rat model is appropriate for studying type 2 diabetes pathology and treatments. The dosing and administration of the therapeutic agents are clearly described. However, some additional details are needed: - Specify the source/supplier of the streptozotocin - Clarify the timing of the post-STZ glucose measurement used to confirm diabetes (e.g. fasting or random, how many days post-STZ) - Provide more details on the high-fat diet composition - Specify whether the treatment allocations were randomized and if so, the randomization method - Report the housing conditions (individual vs group) which can impact metabolic outcomes - Specify the euthanasia method - Clarify the sample size per group for each outcome, as this is not always consistent in the results. Statistical Analysis: Using one-way ANOVA for most outcomes seems appropriate given the study design. However, the glucose data over time was analyzed by repeated measures of two-way ANOVA, which is the correct test, but this is not mentioned in the methods. Please state the post-hoc test used for pairwise comparisons (Tukey's?). It would also be helpful to justify the sample size - was a power calculation done? Results and Data Interpretation: The results show clear benefits of the cholecalciferol+taurine+metformin combination compared to metformin alone or untreated diabetes across most of the measured outcomes. The figures are informative, but the legends are very long - some of those details (scale bars, etc.) could be moved to the methods. A few specific comments: - Fig 1 - the asterisk and hash symbols are not defined in the legend - Fig 2 - the y-axis units are missing for glucose and insulin - Fig 4 - LDH does not seem to have been mentioned in the methods - Fig 5 - the data suggest an increase in SOD and CAT with the combination
treatment compared to control - this is not physiological and should be discussed - The histology and IHC data are somewhat descriptive - quantification of islet size/number and insulin staining intensity would strengthen the conclusions. - There are quite a few typos and grammatical errors that need to be corrected. Discussion and Conclusions: The discussion summarizes the key findings but is lacking some important elements: - The results should be put in the context of previous related studies on metformin, cholecalciferol, and taurine in animal models and humans - The potential mechanisms of the observed effects should be discussed in more depth - The limitations of the animal model and ex vivo analyses for predicting human responses should be acknowledged - The potential side effects and contraindications of cholecalciferol and taurine in humans should be mentioned - Future directions should be proposed, such as dose-finding studies and clinical trials in patients. In summary, this is an interesting and novel study suggesting promise for cholecalciferol and taurine supplementation as an adjunct to metformin for preventing diabetic complications. However, the manuscript requires major revisions to increase the clarity, rigor and impact of the work. With additional experiments to quantify the histological outcomes, further discussion of the underlying mechanisms and limitations, and an improved introduction and conclusions, this study could make a valuable contribution to the field. I would be willing to re-review a revised version of the manuscript.
RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Diabetes

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Reviewer’s code: 02623966

Position: Editorial Board

Academic degree: MD, MSc, PhD

Professional title: Attending Doctor, Doctor, Research Scientist

Reviewer’s Country/Territory: Greece

Author’s Country/Territory: Egypt

Manuscript submission date: 2024-04-06

Reviewer chosen by: Cong Lin

Reviewer accepted review: 2024-07-01 16:17

Reviewer performed review: 2024-07-01 16:18

Review time: 1 Hour

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SPECIFIC COMMENTS TO AUTHORS

It is an interesting manuscript. Authors succeed to present their data in a clear way adding information to the existing literature. Therefore, I have no corrections to do and the manuscript can be published unaltered.