

Response to Reviewers

Manuscript Title: Bidirectional link between Diabetes Mellitus and COVID-19 leading to cardiovascular disease: A Narrative Review
Manuscript ID: 60644
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Reviewer #1

This review article demonstrates the Bidirectional link between Diabetes Mellitus and COVID-19 leading to cardiovascular disease. Overall, it is well-written and deserves significance. I recommend accept for this article, whereas some suggestions are needed

R1-1. I used search strategy “Diabetes Mellitus[TIAB] AND COVID-19[TIAB] AND cardiovascular disease” and found there are similar articles: the authors shall explain the differences among them: 32219363, 32232218, 32743793

Authors: We thank this reviewer for the inputs regarding the 3 articles that were discovered. We have now added following three references in our revised manuscript with the explanation. Further, we have also explained the difference between them. Thank you.

1. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential Effects of Coronaviruses on the Cardiovascular System: A Review. *JAMA Cardiol.* 2020 Jul 1;5(7):831-840. doi: 10.1001/jamacardio.2020.1286. PMID: 32219363.
2. Emami A, Javanmardi F, Pirbonyeh N, Akbari A. Prevalence of Underlying Diseases in Hospitalized Patients with COVID-19: a Systematic Review and Meta-Analysis. *Arch Acad Emerg Med.* 2020 Mar 24;8(1):e35. PMID: 32232218; PMCID: PMC7096724.
3. Azar WS, Njeim R, Fares AH, Azar NS, Azar ST, El Sayed M, Eid AA. COVID-19 and diabetes mellitus: how one pandemic worsens the other. *Rev Endocr Metab Disord.* 2020 Dec;21(4):451-463. doi: 10.1007/s11154-020-09573-6. PMID: 32743793; PMCID: PMC7395898

Madjid et al. [1] presented a review that highlighted the identification of heart damage through high levels of troponin in the blood due to COVID-19 leading to mortality of the patient. Furthermore, authors showed a role of inflammation of heart due to COVID-19, i.e., myocarditis, vascular inflammation, and cardiac arrhythmias. **Emami et al. [2]** presented a meta-analysis showing the prevalence of pre-existing diseases in COVID-19 patients. The data in their study were pooled from 10 articles having 76,993 patients and showed the prevalence of 7.87% (95% CI 6.57%-9.28%) diabetes, 16.37% (95%CI: 10.15%-23.65%) hypertension, 12.11% (95% CI 4.40%-22.75%) CVD and 7.63% (95% CI 3.83%-12.43%) smoking history, respectively in patients infected with SARS-CoV-2. **Azar et al. [3]** have reported that the presence of pre-existing diseases such as diabetes mellitus, hypertension, and CVD are more likely to be associated with an increased risk of mortality in COVID-19 patients. **Azar et al. [3]** emphasized on the concept of cytokine storm that showed a connection between DM and COVID-19. Further, authors showed that the higher basal levels of proinflammatory cytokines observed in diabetic patients, which results in a cytokine storm with an increase in viral infection. They demonstrated the link between high levels of IL-6 and the AMPK/mTOR signaling pathway and their role in exacerbating diabetes-related complications and insulin resistance.

Both statements in this article support **Pathway VI** (Figure 1) of our article that shows the possibility of aggravating preexisting diabetes or new-onset diabetes in COVID-19 due to cytokine storm. Additionally, they highlighted the role of the angiotensin 2 conversion enzyme (ACE2) receptor during viral binding to the host cell, thereby causing an increased risk of viral uptake in diabetes patients. The work presented by Azar et al. [3] is one of the bases of our hypothesis, where we discuss the two-way relationship between DM and COVID-19, i.e., triggering of COVID-19 on the new onset of DM and worsening glycemic levels of DM. Further, our study demonstrated the importance of early imaging to prevent CVD among all patients with COVID-19. On the contrary, the studies by Majid *et al.* and Emami *et al.* did not directly support the concept of bidirectional relationship.

In lieu of the above discussion, we have now added following paragraph on page 11 and section IV of our revised manuscript.

“As a supporting evidence Madjid et al. [1] study highlights the identification of heart damage through high levels of troponin in the blood due to COVID-19 leading to mortality of the patient. Further, it was shown the role of inflammation of the heart due to COVID-19, i.e., myocarditis, vascular inflammation, and cardiac arrhythmias. Another supporting evidence by Emami et al. [2] is a meta-analysis showing the prevalence of pre-existing diseases in COVID-19 patients. The data in this study were pooled from 10 articles having 76,993 patients and showed the prevalence of 7.87% (95% CI 6.57%-9.28%) diabetes, 16.37% (95%CI: 10.15%-23.65%) hypertension, 12.11% (95% CI 4.40%-22.75%) CVD and 7.63% (95% CI 3.83%-12.43%) smoking history, respectively in patients infected with SARS-CoV-2. Further, Azar et al. [3] have shown that the presence of pre-existing diseases such as diabetes mellitus, hypertension, and CVD are more likely to be associated with an increased risk of mortality in COVID-19 patients. Azar et al. focus on the cytokine storm concept that showed the connection between DM and COVID-19. Further, they showed that the higher basal levels of proinflammatory cytokines are seen in diabetic patients, which results in a cytokine storm with an increase in viral infection. They demonstrated the link between high levels of IL-6 and the AMPK/mTOR signaling pathway and their role in exacerbating diabetes-related complications and insulin resistance. Both statements in the article support Pathway VI of our article, which shows the possibility of aggravating preexisting diabetes or new-onset diabetes in COVID-19 due to cytokine storm. Additionally, they highlighted the role of the angiotensin 2 conversion enzyme (ACE2) receptor during viral binding to the host cell, thereby causing an increased risk of viral uptake in diabetes patients. Azar et al.’s work is one of the bases of our hypothesis, where we discuss the two-way relationship between DM and COVID-19, i.e., triggering of COVID-19 on the new onset of DM and worsening glycemic levels of DM. Further, our study demonstrated the importance of early imaging to prevent CVD among all patients with COVID-19. On the contrary, the studies by Majid *et al.* and Emami *et al.* did not directly support the concept of bidirectional relationship.”

R1-2: The English needs edited by a native speaker.

Authors: We thank this reviewer. We have asked the native reviewer to read our manuscript. Further, Magnum Proof reading services have already given a solid feedback. Thank you so much for the feedback.

R1-3: For a better understanding of background and discussion, please cite the following literature in appropriate sites throughout the manuscript before accept. PMID: CVD: 27815596,32219363,32724831, 32765957

Authors: We thank this reviewer for the inputs and we have now cited the following four more references in our revised version of the manuscript.

1. Li T, Jiang S, Yang Z, Ma Z, Yi W, Wang D, Yang Y. Targeting the energy guardian AMPK: another avenue for treating cardiomyopathy? *Cell Mol Life Sci.* 2017 Apr;74(8):1413-1429. doi: 10.1007/s00018-016-2407-7. Epub 2016 Nov 4. PMID: 27815596. [4]

This article demonstrates how the protein kinase 5'-AMP-activated (AMPK) plays a protective role in cardiovascular disease. Since this paper is in the area of treatment of CVD, we have added this in the general section of page no 13 section 4.

2. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential Effects of Coronaviruses on the Cardiovascular System: A Review. *JAMA Cardiol.* 2020 Jul 1;5(7):831-840. doi: 10.1001/jamacardio.2020.1286. PMID: 32219363. [1]

Added to main article at Page no 10, section 4

3. Sattar Y, Ullah W, Rauf H, Virk HUH, Yadav S, Chowdhury M, Connerney M, Mamtani S, Pahuja M, Patel RD, Mir T, Almas T, Moussa Pacha H, Chadi Alraies M. COVID-19 cardiovascular epidemiology, cellular pathogenesis, clinical manifestations and management. *Int J Cardiol Heart Vasc.* 2020 Jul 14;29:100589. doi: 10.1016/j.ijcha.2020.100589. PMID: 32724831; PMCID: PMC7359794. [5]

Added to main article at Page no 11, section 4

4. Li T, Mu N, Yin Y, Yu L, Ma H. Targeting AMP-Activated Protein Kinase in Aging-Related Cardiovascular Diseases. *Aging Dis.* 2020 Jul 23;11(4):967-977. doi: 10.14336/AD.2019.0901. PMID: 32765957; PMCID: PMC7390518. [6]

This article demonstrates how the protein kinase 5'-AMP-activated (AMPK) plays a protective role in cardiovascular disease and about the myocardial aging and drug effects. Since this paper is in the area of treatment of CVD, we have added this in the general section on Page no 13 section 4.

R1-4. There are some spelling mistakes and format errors.

Authors: We thank this reviewer. We have asked the native reviewer to read this. Further, Magnum Proof reading services have already given a solid feedback. Thank you so much for the feedback.

R1-5. LANGUAGE QUALITIES: Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language will meet our direct publishing needs.

Authors: We thank this reviewer. We have asked the native reviewer to read this. Further, Magnum Proof reading services have already given a solid feedback. Thank you so much for the feedback.

EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

1. The manuscript describes a review study of the diabetes and COVID-19. The topic is within the scope of the WJD. **Summary of the Peer-Review Report:** This review article demonstrates the Bidirectional link between Diabetes Mellitus and COVID-19 leading to cardiovascular disease. Overall, it is well-written and deserves significance. However, there are some issues should be addressed. (i) There are some spelling mistakes and format errors, (ii) The authors need to add the novelty of this review, and (iii) The questions raised by the reviewers should be answered; and

Authors: We thank the editorial team for providing us an opportunity to revise this manuscript. We have asked the native reviewer to read this. Further, Magnum Proof reading services have already given a solid feedback. Thank you so much for the feedback.

2. There are 2 tables and 2 figures. A total of 220 references are cited, including 141 references published in the 2020. There are 8 self-citations. **2 Language evaluation: Classification: Grade B.** A language editing certificate issued by Magnum Proofreading was provided. **3 Academic norms and rules:** The authors need to provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement, and the Institutional Review Board Approval Form. No academic misconduct was found in the CrossCheck detection and Bing search. **4 Supplementary comments:** This is an invited manuscript. The topic has not previously been published in the WJD. The corresponding author has not published articles in the BPG.

Authors: We thank the editorial team for providing us an opportunity to revise this manuscript. We have now uploaded the conflict of interest form on the online portal of this WJD.

3. I found no "Author contribution" section. Please provide the author contributions;

Authors: We thank the editorial team for providing us an opportunity to revise this manuscript. We have now added "Author contribution" in the separate word file. The Author's Contribution is given below for ready reference.

(I) Conception and design: Vijay Viswanathan, Jasjit S. Suri, Anudeep Puvvala, Ankush Jamthikar; (II) Administrative support: Surinder k. Dhanjil, Narendra N Khanna; (III) Manuscript writing: Jasjit S. Suri, Anudeep Puvvula, Ankush Jamthikar; (IV) Critical Evaluation: Amer M. Johri, George D. Kitas, Vikas Agarwal, Durga Prasanna Misra, Surinder k. Dhanjil; (V) Vascular Inputs: Aditya Sharma, Raghu kolluri, Surinder k. Dhanjil, Narendra N Khanna, Ankush Jamthikar, Jasjit S. Suri; (VI) Proofreading: All authors; (VII) Final approval of manuscript: All authors

We have also added the Author's Contribution section on [page number 19 of our revised manuscript](#).

4. I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; and I found the authors did not add the PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout.

Authors: We thank the editorial team for providing us an opportunity to revise this manuscript. All the figures in this manuscript are original, designed by our team (Courtesy: AtherPoint™, Roseville, USA), and not taken from any other source.

References pertaining to this rebuttal

- [1] M. Madjid, P. Safavi-Naeini, S. D. Solomon, and O. Vardeny, "Potential Effects of Coronaviruses on the Cardiovascular System: A Review," *JAMA Cardiol*, vol. 5, pp. 831-840, Jul 1 2020.
- [2] A. Emami, F. Javanmardi, N. Pirbonyeh, and A. Akbari, "Prevalence of Underlying Diseases in Hospitalized Patients with COVID-19: a Systematic Review and Meta-Analysis," *Archives of academic emergency medicine*, vol. 8, pp. e35-e35, 2020.
- [3] W. S. Azar, R. Njeim, A. H. Fares, N. S. Azar, S. T. Azar, M. El Sayed, *et al.*, "COVID-19 and diabetes mellitus: how one pandemic worsens the other," *Reviews in Endocrine and Metabolic Disorders*, vol. 21, pp. 451-463, 2020.
- [4] T. Li, S. Jiang, Z. Yang, Z. Ma, W. Yi, D. Wang, *et al.*, "Targeting the energy guardian AMPK: another avenue for treating cardiomyopathy?," *Cellular and Molecular Life Sciences*, vol. 74, pp. 1413-1429, 2017.
- [5] Y. Sattar, W. Ullah, and H. Rauf, "COVID-19 cardiovascular epidemiology, cellular pathogenesis, clinical manifestations and management," *International Journal of Cardiology. Heart & Vasculature*, vol. 29, 2020.
- [6] T. Li, N. Mu, Y. Yin, L. Yu, and H. Ma, "Targeting AMP-Activated Protein Kinase in Aging-Related Cardiovascular Diseases," *Aging and disease*, p. 0, 2020.