Response

Diabetes Metab J 2024;48:1181-1182
https://doi.org/10.4093/dmj.2024.0675
pISSN 2233-6079 · eISSN 2233-6087

dmj
DIABETES & METABOLISM JOURNAL

Check for updates

Diabetes Promotes Myocardial Fibrosis via AMPK/EZH2/PPAR-γ Signaling Pathway (*Diabetes Metab J* 2024;48:716-29)

Shan-Shan Li, Lu Pan, Shipeng Dang, Ru-Xing Wang

Department of Cardiology, The Affiliated Wuxi People's Hospital of Nanjing Medical University, Wuxi Medical Center, Nanjing Medical University, Wuxi, China

We sincerely appreciate the thoughtful comments by Dr. Lee and Dr. Moon on our recently published article, "Diabetes promotes myocardial fibrosis via AMPK/EZH2/PPAR-γ signaling pathway" [1]. Your insights have enriched the discussion, particularly regarding the complex interplay between AMP-activated protein kinase (AMPK), zeste homolog 2 (EZH2), and peroxisome proliferator-activated receptor γ (PPAR-γ) signaling pathways, and the implications for therapeutic strategies in diabetic heart failure. We also would like to thank the editor for the chance to further discuss our article.

Dr. Lee and Dr. Moon raised several important points that warrant further elaboration. First, the cardioprotective effects of metformin, a well-known AMPK activator, is highly relevant. Indeed, as they noted, metformin has demonstrated multiple beneficial effects in improving diabetic heart failure outcomes, including mortality and hospitalization rates [2]. The parallel between metformin's inhibition of the transforming growth factor-β1-Smad3 pathway and our findings regarding AMPK-mediated EZH2 regulation of PPAR-γ signaling highlights a potential shared mechanism [3]. We agree that further investigation into how metformin influences EZH2 and histone methylation in the context of cardiac fibrosis could provide a more comprehensive understanding of its protective effects in diabetic heart failure. This is an avenue we are actively considering for future studies.

Your second concern regarding the dual-edged effects of PPAR-γ activation is equally important. While rosiglitazone and pioglitazone have shown promise in attenuating cardiac fibrosis, the fluid retention and heart failure risks associated with thiazolidinediones are well-documented [4,5]. Their observation underscores the need for cautious evaluation of PPAR-γ agonists, especially in light of their known effects on sodium reabsorption and peripheral edema. We agree that the potential for novel PPAR-γ agonists, or possibly co-agonists/antagonists targeting additional molecular pathways, could offer a more favorable balance between anti-fibrotic effects and the risk of exacerbating heart failure. Future research should focus on identifying PPAR-γ-targeting therapies that minimize adverse outcomes while improving cardiac function in diabetic patients.

Finally, we also agree that EZH2 inhibitors and their emerging potential in metabolic diseases provides an exciting avenue for exploration. While EZH2 inhibitors like GSK126 have demonstrated efficacy in reducing cardiac fibrosis in our study, their broader potential in metabolic and cardiovascular disorders, as well as their established role in oncology, highlights the

Corresponding authors: Shipeng Dang https://orcid.org/0000-0002-2083-7479
Department of Cardiology, The Affiliated Wuxi People's Hospital of Nanjing Medical University, Wuxi Medical Center, Nanjing Medical University, No. 299 Qingyang Road, Wuxi 214023, China
E-mail: spdang@njmu.edu.cn

Ru-Xing Wang https://orcid.org/0000-0001-7355-5048
Department of Cardiology, The Affiliated Wuxi People's Hospital of Nanjing Medical University, Wuxi Medical Center, Nanjing Medical University, No. 299 Qingyang Road, Wuxi 214023, China
E-mail: ruxingw@aliyun.com

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Copyright © 2024 Korean Diabetes Association https://e-dmj.org

versatility of histone methylation modulators. The promising effects of dual EZH1/2 inhibitors in cancer treatment suggest that EZH2-targeted therapies could be similarly beneficial in the context of diabetic heart failure. However, the safety and efficacy of these inhibitors in non-oncological diseases must be thoroughly evaluated.

In conclusion, we appreciate the valuable comments on our study. The roles of metformin, PPAR-γ activation, and EZH2 inhibitors in diabetic heart failure open new avenues for future investigation. We agree that a more nuanced approach, considering both the benefits and risks of these therapies, is essential for optimizing outcomes in diabetic heart failure patients. We look forward to further studies that explore these mechanisms and potential therapies in greater depth.

Thank you once again for your insightful comments.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Li SS, Pan L, Zhang ZY, Zhou MD, Chen XF, Qian LL, et al. Diabetes promotes myocardial fibrosis via AMPK/EZH2/PPAR-γ signaling pathway. Diabetes Metab J 2024;48:716-29.
2. Eurich DT, Weir DL, Majumdar SR, Tsuyuki RT, Johnson JA, Tjosvold L, et al. Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure: systematic review of observational studies involving 34,000 patients. Circ Heart Fail 2013;6:395-402.
3. Xiao H, Ma X, Feng W, Fu Y, Lu Z, Xu M, et al. Metformin attenuates cardiac fibrosis by inhibiting the TGFbeta1-Smad3 signalling pathway. Cardiovasc Res 2010;87:504-13.
4. Wei WY, Zhang N, Li LL, Ma ZG, Xu M, Yuan YP, et al. Pioglitazone alleviates cardiac fibrosis and inhibits endothelial to mesenchymal transition induced by pressure overload. Cell Physiol Biochem 2018;45:26-36.
5. Loke YK, Kwok CS, Singh S. Comparative cardiovascular effects of thiazolidinediones: systematic review and meta-analysis of observational studies. BMJ 2011;342:d1309.