ISSN 1948-9358 (online)

World Journal of *Diabetes*

World J Diabetes 2024 August 15; 15(8): 1654-1828

Published by Baishideng Publishing Group Inc

World Journal of Diabetes

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The *WJD* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2024 Edition of Journal Citation Reports® cites the 2023 journal impact factor (JIF) for *WJD* as 4.2; JIF without journal self cites: 4.1; 5-year JIF: 4.2; JIF Rank: 40/186 in endocrinology and metabolism; JIF Quartile: Q1; and 5-year JIF Quartile: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Diabetes

ISSN
ISSN 1948-9358 (online)

LAUNCH DATE
June 15, 2010

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Lu Cai, Md. Shahidul Islam, Michael Horowitz

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-9358/editorialboard.htm

PUBLICATION DATE
August 15, 2024

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World J Diabetes 2024 August 15; 15(8): 1654-1658

DOI: 10.4239/wjd.v15.i8.1654

ISSN 1948-9358 (online)

EDITORIAL

Teneligliptin: A potential therapeutic approach for diabetic cardiomyopathy

Ashraf Al Madhoun

Specialty type: Endocrinology and metabolism

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C, Grade C

Novelty: Grade B, Grade C

Creativity or Innovation: Grade B, Grade C

Scientific Significance: Grade B, Grade B

P-Reviewer: Chen X, United States; Zhou X, China

Received: March 12, 2024

Revised: May 14, 2024

Accepted: June 12, 2024

Published online: August 15, 2024

Processing time: 135 Days and 3.7 Hours

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Abstract

In this editorial, we comment on the article by Zhang *et al*. Diabetes mellitus is a chronic disorder associated with several complications like cardiomyopathy, neuropathy, and retinopathy. Diabetes prevalence is increasing worldwide. Multiple diabetes medications are prescribed based on individual patients' needs. However, the exact mechanisms by which many of these drugs exert their protective effects remain unclear. Zhang *et al* elucidates molecular mechanisms undelaying cardioprotective effect of the dipeptidyl peptidase-IV inhibitor, teneligliptin. Briefly, teneligliptin alleviates the activation of NOD-like receptor protein 3 inflammasome, a multiprotein complex that plays a pivotal role in regulating the innate immune system and inflammatory signaling. Suppression of NOD-like receptor protein 3 inflammasome activity reduces the expression of cytokines, oxygen radicals and inflammation. These findings highlight teneligliptin as an anti-diabetic cardioprotective reagent.

Key Words: Teneligliptin; Diabetes mellitus; NOD-like receptor protein 3 inflammasome; Inflammation; Cardiomyopathy

Core Tip: Zhang *et al* provided evidence that teneligliptin mitigated diabetic cardiomyopathy. The authors also clarified the undelaying molecular mechanisms, showing that teneligliptin inhibits NADPH oxidase 4, NOD-like receptor protein 3 inflammasome and activates activated protein kinase to maintain myocyte homeostasis. Researchers are encouraged to implement similar studies on humans to delineate the precise mechanism by which teneligliptin influences activated protein kinase and NOD-like receptor protein 3 signaling.

Citation: Al Madhoun A. Teneligliptin: A potential therapeutic approach for diabetic cardiomyopathy. *World J Diabetes* 2024; 15(8): 1654-1658
URL: https://www.wjgnet.com/1948-9358/full/v15/i8/1654.htm
DOI: https://dx.doi.org/10.4239/wjd.v15.i8.1654

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia. DM increases the risk of microvascular and macrovascular complications including heart disease, retinopathy, neuropathy, and nephropathy. DM is a global health crisis affecting an estimated 425 million individuals worldwide[1]. Diabetic cardiomyopathy (DCM) is a serious complication of DM that affects approximately 12% of patients with DM and leads to heart failure and death[2]. DCM is a chronic progressive myopathy characterized by ventricular chamber dilation and myocyte hypertrophy, leading to impaired systolic function and heart failure[3]. The exact mechanisms underlying DCM are not fully understood; however, chronic hyperglycemia is believed to play a role. One critical pathway implicated in DCM development is the NOD-like receptor protein 3 (NLRP3) inflammasome. The NLRP3 inflammasome is a multiprotein complex that activates inflammatory responses. Recent studies have demonstrated that NLRP3 inflammasome activation contributes to DCM by promoting inflammation and cell death in the heart[4,5].

In the context of glucose homeostasis, dipeptidyl peptidase-4 (DDP-4) plays a key role in the regulation of incretin hormones, including glucagon, glucagon-like peptide (GLP)-1, GLP-2, and gastric inhibitory peptide[6]. These incretins are secreted into the bloodstream and stimulate postprandial insulin secretion and peripheral glucose uptake. The inactivation of these incretins *via* dipeptidyl peptidase-4 (DPP-4) digestion is essential for maintaining glucose homeostasis[7]. In DM characterized by impaired incretin function, DPP-4 inhibition is a therapeutic strategy to enhance incretin activity and improve glycemic control.

DPP-4 inhibitors or gliptins are a class of oral antihyperglycemic drugs that suppress DDP-4 activity, leading to elevated and sustained incretin levels[8]. Several gliptins, including sitagliptin, saxagliptin, linagliptin, alogliptin, and vildagliptin, have been approved for clinical use in Western countries to manage type 2 DM management[9]. Teneligliptin, anagliptin, and trelagliptin are gliptins approved in some Asian markets, but are not yet widely available globally[10]. Omarigliptin was initially used in Japan and is currently undergoing further evaluation in clinical trials[11,12].

Although extensive research has established the efficacy of DPP-4 inhibitors in the management of DM, a comprehensive comparison of all the available gliptins is beyond the scope of this editorial. Here, we focus specifically on the article by Zhang *et al*[13] published in the recent issue of the *World Journal of Diabetes* (PMID: 38680706, DOI: 10.4239/wjd.v15.i4.724) elucidating the potential therapeutic role of teneligliptin in DCM and its unique characteristics compared to other established gliptins.

TENELIGLIPTIN: POTENTIAL THERAPEUTIC ADVANTAGES

Teneligliptin is an orally administered medication belonging to the class of DPP-4 inhibitors. Compared to other DPP4 inhibitors, teneligliptin is relatively cost-effective and economical for patients[14]. Although it shares similar efficacy and safety profiles with other gliptins, teneligliptin exerts unique pharmacokinetic and pharmacodynamic properties owing to its distinct chemical structure. Classified as a class III DPP-4 inhibitor, teneligliptin exhibits a stronger binding affinity to the enzyme than other class II gliptins[15]. This strong binding is attributed to the formation of an additional subsidized bond with DPP-4, potentially leading to more extensive and longer-lasting DPP-4 inhibition[16,17]. However, large-scale clinical trials are needed to investigate whether this translates into significant advantages in glycemic control compared to other gliptins. While a recent meta-analysis suggested favorable efficacy and acceptable safety of teneligliptin compared to other DDP-4 inhibitors, further well-designed clinical trials are warranted to definitively confirm these findings[18]. Interestingly, recent research has suggested that teneligliptin may have additional benefits beyond glycemic control. Previous studies have reported that teneligliptin exerts anti-inflammatory and protective effects on myocardial and neuronal cells[19-22]. These findings suggest that teneligliptin is a potential therapeutic agent for the management of DCM.

INVESTIGATING TENELIGLIPTIN'S EFFECTS ON DCM

To explore the potential therapeutic effects of teneligliptin on DCM and delineate the associated molecular mechanisms, Zhang *et al*[13] conducted a study on streptozotocin-induced diabetes in mice. In this study, one group of diabetic mice was treated with teneligliptin (30 mg/kg) and the other group served as a control. Notably, teneligliptin treatment alleviated the myocardial hypertrophy phenotype observed in streptozotocin-induced diabetic mice, improved heart function parameters, and reduced the cardiomyocyte damage markers (creatine kinase-MB, aspartate transaminase, and lactate dehydrogenase). Mechanistically, the study revealed that teneligliptin inhibited NADPH oxidase 4 and NLRP3 inflammasome activation and the subsequent release of reactive oxygen species and interleukin 1β – key inflammatory

molecules - in diabetic mice.

IN-VITRO CONFIRMATION: TENELIGLIPTIN PROTECTS CARDIOMYOCYTES

To strengthen these findings, Zhang *et al*[13] conducted additional experiments using isolated primary mouse cardiomyocytes. These cells were exposed to high glucose (HG) conditions mimicking the diabetic environment, with or without teneligliptin treatment. Notably, HG exposure triggered NLRP3 inflammasome activation in cardiomyocytes. Teneligliptin treatment effectively suppresses NLRP3 inflammasome activation in these cells. Moreover, teneligliptin significantly reduced the levels of creatine kinase-MB, aspartate transaminase, and lactate dehydrogenase in HG-treated cardiomyocytes, suggesting that it protected against cell damage.

Interestingly, this study also revealed that the beneficial effects of teneligliptin on cardiomyocytes were mediated by the activation of activated protein kinase (AMPK), a cellular energy sensor that plays a crucial role in maintaining metabolic homeostasis. Researchers have found that teneligliptin increases the levels of phosphorylated AMPK, an activated form, in cardiomyocytes exposed to HG levels. Furthermore, blocking AMPK signaling using compound C, a specific inhibitor, abolished the protective effects of teneligliptin[13]. These findings suggested that AMPK activation is a key mechanism underlying the cardioprotective effects of teneligliptin.

PROMISING POTENTIAL OF TENELIGLIPTIN FOR DCM

This preclinical study provides compelling insights into the potential use of teneligliptin in DCM. This study suggests that teneligliptin may exert its effects through the inhibition of NADPH oxidase 4 and the NLRP3 inflammasome, and the activation of AMPK, all of which are key players in reactive oxygen species formation and inflammation[13]. To translate these findings into clinical applications, further research is needed to validate these mechanisms in human patients with DCM, and to elucidate the precise pathways through which teneligliptin influences AMPK and NLRP3 signaling for a complete understanding of its therapeutic potential.

BROADENING THE SCOPE OF TENELIGLIPTIN RESEARCH

While teneligliptin effectively lowers hemoglobin A1c, still need to be clarify the direct trophic effects on β-cell function and mass restoration, or its potential immunomodulatory effects during and after drug administration. This is a crucial aspect, as it could pave the way for type 1 DM intervention trials aimed at better disease management and prevention.

Because teneligliptin is a relatively new DPP-4 inhibitor studied primarily in Asian populations, large-scale multiethnic trials are warranted. These trials should assess the effectiveness of teneligliptin compared to other DPP-4 inhibitors, both as monotherapy and in combination therapy with other DM medications. Additionally, studies should identify the genetic and/or clinical factors influencing patient responses to teneligliptin, enabling personalized treatment approaches, and assessing the causative factors for rare side effects reported with DPP-4 inhibitors. Exploring the potential benefits of teneligliptin in high-risk populations, such as prediabetics and those with metabolic syndrome, is also of interest, considering the current limited focus on patients with DM in clinical trials.

LONG-TERM STUDIES AND INTERNATIONAL COLLABORATION

Long-term follow-up studies utilizing proteomics and metabolomics are necessary to understand the impact of teneligliptin on long-term complications such as neuropathy, nephropathy, and liver disease. Finally, we believe that the involvement of international societies and organizations would be highly beneficial. This collaboration could lead to the implementation of guidelines and a consensus for safer use of teneligliptin and other DPP-4 therapies in managing DM and its associated complications.

CONCLUSION

Zhang *et al*[13] suggested that teneligliptin, a drug for diabetes, may have therapeutic potential in DCM; however, further research is required. In mice, teneligliptin improves heart function and reduces damage markers, potentially by inhibiting inflammatory pathways. Human trials are necessary to confirm these findings and determine the optimal dose of teneligliptin for DCM. Addressing these future directions will bridge the gap between this preclinical study and clinical applications, allowing researchers to explore the full potential of teneligliptin for DCM and potentially broaden diabetes management.

FOOTNOTES

Author contributions: Al Madhoun A designed the overall concept, review of literature, writing, and editing the manuscript.

Supported by the Kuwait Foundation for the Advancement of Sciences and Dasman Diabetes Institute, No. RACB-2021-007.

Conflict-of-interest statement: The author reports no relevant conflicts of interest for this article.

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S-Editor: Wang JJ
L-Editor: A
P-Editor: Wang WB

REFERENCES

1 **Sun H**, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, Stein C, Basit A, Chan JCN, Mbanya JC, Pavkov ME, Ramachandaran A, Wild SH, James S, Herman WH, Zhang P, Bommer C, Kuo S, Boyko EJ, Magliano DJ. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract* 2022; **183**: 109119 [PMID: 34879977 DOI: 10.1016/j.diabres.2021.109119]

2 **Kenny HC**, Abel ED. Heart Failure in Type 2 Diabetes Mellitus. *Circ Res* 2019; **124**: 121-141 [PMID: 30605420 DOI: 10.1161/CIRCRESAHA.118.311371]

3 **Schultheiss HP**, Fairweather D, Caforio ALP, Escher F, Hershberger RE, Lipshultz SE, Liu PP, Matsumori A, Mazzanti A, McMurray J, Priori SG. Dilated cardiomyopathy. *Nat Rev Dis Primers* 2019; **5**: 32 [PMID: 31073128 DOI: 10.1038/s41572-019-0084-1]

4 **Zheng Y**, Xu L, Dong N, Li F. NLRP3 inflammasome: The rising star in cardiovascular diseases. *Front Cardiovasc Med* 2022; **9**: 927061 [PMID: 36204568 DOI: 10.3389/fcvm.2022.927061]

5 **Ding K**, Song C, Hu H, Yin K, Huang H, Tang H. The Role of NLRP3 Inflammasome in Diabetic Cardiomyopathy and Its Therapeutic Implications. *Oxid Med Cell Longev* 2022; **2022**: 3790721 [PMID: 36111168 DOI: 10.1155/2022/3790721]

6 **Barchetta I**, Cimini FA, Dule S, Cavallo MG. Dipeptidyl Peptidase 4 (DPP4) as A Novel Adipokine: Role in Metabolism and Fat Homeostasis. *Biomedicines* 2022; **10** [PMID: 36140405 DOI: 10.3390/biomedicines10092306]

7 **Nauck MA**, Meier JJ. Incretin hormones: Their role in health and disease. *Diabetes Obes Metab* 2018; **20** Suppl 1: 5-21 [PMID: 29364588 DOI: 10.1111/dom.13129]

8 **Makrilakis K**. The Role of DPP-4 Inhibitors in the Treatment Algorithm of Type 2 Diabetes Mellitus: When to Select, What to Expect. *Int J Environ Res Public Health* 2019; **16** [PMID: 31366085 DOI: 10.3390/ijerph16152720]

9 **Deacon CF**. Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review. *Diabetes Obes Metab* 2011; **13**: 7-18 [PMID: 21114598 DOI: 10.1111/j.1463-1326.2010.01306.x]

10 **Saini K**, Sharma S, Khan Y. DPP-4 inhibitors for treating T2DM - hype or hope? an analysis based on the current literature. *Front Mol Biosci* 2023; **10**: 1130625 [PMID: 37287751 DOI: 10.3389/fmolb.2023.1130625]

11 **Kamrul-Hasan ABM**, Alam MS, Talukder SK, Dutta D, Selim S. Efficacy and Safety of Omarigliptin, a Novel Once-Weekly Dipeptidyl Peptidase-4 Inhibitor, in Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. *Endocrinol Metab (Seoul)* 2024; **39**: 109-126 [PMID: 38417828 DOI: 10.3803/EnM.2023.1839]

12 **Burness CB**. Omarigliptin: first global approval. *Drugs* 2015; **75**: 1947-1952 [PMID: 26507988 DOI: 10.1007/s40265-015-0493-8]

13 **Zhang GL**, Liu Y, Liu YF, Huang XT, Tao Y, Chen ZH, Lai HL. Teneligliptin mitigates diabetic cardiomyopathy by inhibiting activation of the NLRP3 inflammasome. *World J Diabetes* 2024; **15**: 724-734 [PMID: 38680706 DOI: 10.4239/wjd.v15.i4.724]

14 **Dahlén AD**, Dashi G, Maslov I, Attwood MM, Jonsson J, Trukhan V, Schiöth HB. Trends in Antidiabetic Drug Discovery: FDA Approved Drugs, New Drugs in Clinical Trials and Global Sales. *Front Pharmacol* 2021; **12**: 807548 [PMID: 35126141 DOI: 10.3389/fphar.2021.807548]

15 **Kishimoto M**. Teneligliptin: a DPP-4 inhibitor for the treatment of type 2 diabetes. *Diabetes Metab Syndr Obes* 2013; **6**: 187-195 [PMID: 23671395 DOI: 10.2147/DMSO.S35682]

16 **Sharma SK**, Panneerselvam A, Singh KP, Parmar G, Gadge P, Swami OC. Teneligliptin in management of type 2 diabetes mellitus. *Diabetes Metab Syndr Obes* 2016; **9**: 251-260 [PMID: 27574456 DOI: 10.2147/DMSO.S106133]

17 **Nabeno M**, Akahoshi F, Kishida H, Miyaguchi I, Tanaka Y, Ishii S, Kadowaki T. A comparative study of the binding modes of recently launched dipeptidyl peptidase IV inhibitors in the active site. *Biochem Biophys Res Commun* 2013; **434**: 191-196 [PMID: 23501107 DOI: 10.1016/j.bbrc.2013.03.010]

18 **Zhu M**, Guan R, Ma G. Efficacy and safety of teneligliptin in patients with type 2 diabetes mellitus: a Bayesian network meta-analysis. *Front Endocrinol (Lausanne)* 2023; **14**: 1282584 [PMID: 38189048 DOI: 10.3389/fendo.2023.1282584]

19 **Yamamoto M**, Ishizu T, Seo Y, Suto Y, Sai S, Xu D, Murakoshi N, Kimura T, Kawakami Y, Aonuma K. Teneligliptin Prevents Cardiomyocyte Hypertrophy, Fibrosis, and Development of Hypertensive Heart Failure in Dahl Salt-Sensitive Rats. *J Card Fail* 2018; **24**: 53-60 [PMID: 28888840 DOI: 10.1016/j.cardfail.2017.09.001]

20 **Imazu M**, Nakano A, Ito S, Hamasaki T, Kitakaze M; TOPLEVEL investigators and study coordinators. Effects of Teneligliptin on the Progressive Left Ventricular Diastolic Dysfunction in Patients with Type 2 Diabetes Mellitus in Open-Label, Marker-Stratified Randomized, Parallel-Group Comparison, Standard Treatment-Controlled Multicenter Trial (TOPLEVEL Study): Rationale and Study Design. *Cardiovasc Drugs Ther* 2019; **33**: 363-370 [PMID: 30850916 DOI: 10.1007/s10557-019-06871-3]

21 **Hashikata T**, Yamaoka-Tojo M, Kakizaki R, Nemoto T, Fujiyoshi K, Namba S, Kitasato L, Hashimoto T, Kameda R, Maekawa E, Shimohama T, Tojo T, Ako J. Teneligliptin improves left ventricular diastolic function and endothelial function in patients with diabetes. *Heart Vessels* 2016; **31**: 1303-1310 [PMID: 26266630 DOI: 10.1007/s00380-015-0724-7]

22 **Zhang L**, Yuan W, Kong X, Zhang B. Teneligliptin protects against ischemia/reperfusion-induced endothelial permeability in vivo and in vitro. *RSC Adv* 2020; **10**: 3765-3774 [PMID: 35492650 DOI: 10.1039/c9ra08810e]

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