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Contents

Monthly Volume 15 Number 10 October 15, 2024

EDITORIAL

REVIEW

ORIGINAL ARTICLE

Retrospective Study

Observational Study

World Journal of Diabetes

Monthly Volume 15 Number 10 October 15, 2024

Contents

World Journal of Diabetes

Monthly Volume 15 Number 10 October 15, 2024

Contents

ABOUT COVER

Peer Review of *World Journal of Diabetes*, Tao-Hsin Tung, PhD, Researcher, Director, Epidemiologist, Evidence-based Medicine Center, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, Taizhou 317000, Zhejiang Province, China. dongdx@enzemed.com .

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EDITORIAL

Potential mechanism of teneligliptin in the treatment of diabetic cardiomyopathy

Jing Guo, Yi Cao, Qing-Yuan Wu, Lu-Sha Cen

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Abstract

Diabetic cardiomyopathy (DCM), a complication of diabetes, poses a significant threat to public health, both its diagnosis and treatment presents challenges. Teneligliptin has promising applications and research implications in the treatment of diabetes mellitus. Zhang *et al* observed the therapeutic effect of teneligliptin on cardiac function in mice with DCM. They validated that teneligliptin's mechanism of action in treating DCM involves cardiomyocyte protection and inhibition of *NLRP3* inflammasome activity. Given that the *NLRP3* inflammasome plays a crucial role in the onset and progression of DCM, it presents a promising therapeutic target. Nevertheless, further clinical validation is required to ascertain the preventive and therapeutic efficacy of teneligliptin in DCM.

Key Words: Teneligliptin; *NLRP3* inflammasome; Diabetes; Diabetic cardiomyopathy; Diabetes complications

Core Tip: Diabetic cardiomyopathy (DCM) is a complication of diabetes, presenting significant challenges in both diagnosis and treatment of DCM. Zhang *et al* observed the therapeutic effect of teneligliptin on cardiac function in mice with DCM. They confirmed that teneligliptin functions by protecting cardiomyocytes and mitigating inflammation by inhibiting *NLRP3* inflammasome activity. This discovery offers clinical management of DCM patients; however, its clinical application necessitates further clinical verification and discussion.

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INTRODUCTION

The number of patients with diabetes mellitus (DM) is expected to reach 783 million by 2045 worldwide[1]. Diabetic cardiomyopathy (DCM), a distinct diabetes-associated cardiac complication, ranks among the primary causes of death in patients with diabetes. DCM is characterized by structural alterations and functional irregularities of the heart, coronary atherosclerosis, significant valvular heart disease, and the absence of hypertension[2]. The pathophysiology of DCM involves various molecular processes, such as hyperglycemia, insulin resistance, accelerated fatty acid oxidation, oxidative stress, mitochondrial dysfunction, and endothelial dysfunction[3]. Given that the progression of DCM correlates with chronic inflammation and cardiomyocyte demise, ultimately leading to heart failure[4], its prevention and treatment merit urgent attention.

DCM AND *NLRP3* INFLAMMASOME

Cardiac inflammation manifests in the early stages of diabetes, with the development of DCM being mainly attributable to the nod-like receptor (NLR) family pyrin domain containing 3 (*NLRP3*) inflammasome. In DCM, activation of the *NLRP3* inflammasome in cardiomyocytes triggers pyroptosis of the heart cells, aggravating the cardiac condition[5]. Using a diabetic mouse model, Song *et al*[6] revealed that sirtuin 3 deficiency aggravated hyperglycemia-induced mitochondrial damage, increased reactive oxygen species accumulation, activated the *NLRP3* inflammasome, and ultimately aggravated DCM. Zhang *et al*[7] discovered that high glucose stimulation in a diabetic cell model activates the *NLRP3* inflammasome, leading to increased secretion of interleukin-1β by neonatal rat ventricular myocytes, and subsequent induction of myocardial injury[8]. Moreover, inhibition or silencing of the *NLRP3* inflammasome gene has shown potential therapeutic effects in DCM. Gao *et al*[9] found that inhibiting the *NLRP3* inflammasome could effectively suppress the pyrodeath of cardiomyocytes. Yang *et al*[10] discovered that metformin demonstrates cardioprotective and anti-inflammatory effects in DCM by activating adenosine 5′-monophosphate-activated protein kinase/autophagy and subsequently inhibiting the *NLRP3* inflammasome. In conclusion, these findings suggest that the *NLRP3* inflammasome represents a promising molecular target in DCM, emphasizing the significance of interventions that can target the activity of this immune system complex for effectively managing the cardiac complications[11].

In clinical practice, DCM treatment includes conventional cardiovascular and anti-glycemic drugs, as well as new therapies such as coenzyme Q10, MicroRNA, and stem cell therapy[12]. However, each method has its limitations: For example, traditional cardiovascular drugs are applied only at the heart of DCM development and have more obvious symptoms when applicable. Conventional hypoglycemic drugs have insignificant efficacy, and sodium-glucose cotransporter-2 inhibitors is the only first-line drug recommended for DCM[13]. Teneligliptin, a dipeptidyl peptidase-4 inhibitor, is a newer drug used in the management of type 2 DM (T2DM). Teneligliptin has promising applications in the treatment of DM and its associated complications and thus warrants further research. Because it can be used in patients with T2DM with renal and/or mild-to-moderate hepatic impairment, it has a unique place in therapy[14]. This drug has the advantages of being inexpensive and safe, improving blood glucose consistently (decreasing the glycated hemoglobin A1c value), and being available to patients with mild to moderate hepatic impairment. More reassuringly, patients with mild, moderate, or severe renal impairment or end-stage kidney disease can safely take the drug without dose adjustment [15,16]. Wang and Zhang[17] showed that teneligliptin attenuated diabetes-related cognitive impairment by inhibiting endoplasmic reticulum stress and the *NLRP3* inflammasome in diabetic mice. Few studies have investigated the effect and mechanism of action of teneligliptin on *NLRP3* inflammatory vesicles. Although the study by Zhang *et al*[7] introduced the concept of applying teneligliptin to treat DCM in patients with kidney damage, the model in that study is more similar to type 1 DM, and the suggested clinical application of this drug requires further research and discussion.

Ultimately, the incidence of cardiac issues correlates closely with the severity of diabetes, and the utilization of hypoglycemic drugs may exert dual effects on both the preventing and treating DCM. The study by Zhang *et al*[7] introduces a novel concept for the clinical management of DCM patients with kidney damage, offering a promising avenue for therapeutic intervention. However, the preventive and therapeutic effects of teneligliptin on DCM require further validation through large-scale clinical trials. Additionally, the question of whether it is covered by medical insurance warrants consideration.

CONCLUSION

Cardiac inflammation contributes to the onset and progression of DCM, which is often associated with *NLRP3* inflammasome activation. Traditional drugs for heart treatment can only be administered when cardiac symptoms are evident, underscoring the importance of identifying preventive measures for DCM. Through in vivo and in vitro experiments, teneligliptin has been shown to inhibit *NLRP3* inflammasome activity and exert anti-inflammatory and protective effects in cardiomyocytes. Although large-scale clinical studies are still needed, the *NLRP3* inflammasome represents a novel target of teneligliptin for the clinical treatment of DCM.

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FOOTNOTES

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