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LETTER TO THE EDITOR

Teneligliptin mitigates diabetic cardiomyopathy through inflammasome inhibition: Insights from experimental studies

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Abstract

This article provides commentary on the article by Zhang *et al*. In this original research, Zhang *et al* investigated the therapeutic potential of teneligliptin for diabetic cardiomyopathy (DCM), which was mediated by targeting the NOD-like receptor protein 3 (NLRP3) inflammasome. Through the use of both *in vivo* and *in vitro* models, the study demonstrated that teneligliptin alleviates cardiac hypertrophy, reduces myocardial injury, and mitigates the inflammatory responses associated with DCM. These findings suggest that teneligliptin's cardioprotective effects are mediated through the inhibition of NLRP3 inflammasome activation, positioning it as a promising therapeutic option for managing DCM in diabetic patients.

Key Words: Diabetic cardiomyopathy; Teneligliptin; Nucleotide-binding oligomerization domain-like receptor 3 inflammasome; Inflammasome inhibition

Core Tip: Teneligliptin can mitigate diabetic cardiomyopathy (DCM) by inhibiting NOD-like receptor protein 3 inflammasome activation and upregulating AMP-activated protein kinase signaling. This study provides insights into the molecular mechanisms underlying the beneficial effects of teneligliptin for the treatment of DCM.

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TO THE EDITOR

Diabetic cardiomyopathy (DCM) is a severe complication of diabetes mellitus (DM); DCM is characterized by structural and functional abnormalities in the myocardium that often lead to heart failure[1]. The activation of inflammatory pathways, particularly those involving the NOD-like receptor protein 3 (NLRP3) inflammasome, plays a central role in the development of DCM and is closely associated with myocardial damage in patients with diabetes[2]. Teneligliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, is a promising therapeutic agent for DCM due to its anti-inflammatory and cytoprotective effects[3]. Zhang *et al*[4] demonstrated that teneligliptin protects against DCM by inhibiting NLRP3 inflammasome activation. Through *in vivo* and *in vitro* models, their study revealed that teneligliptin reduces cardiac hypertrophy, alleviates myocardial injury, and suppresses inflammatory pathways. In a streptozotocin-induced diabetic mouse model, teneligliptin considerably improved cardiac function and reduced the levels of myocardial damage markers[4], indicating its potential to address both the inflammatory and structural aspects of DCM. The rising global prevalence of diabetes and its complications, including DCM, indicates the urgent need for effective treatments. Zhang *et al*[4] indicated that targeting the NLRP3 inflammasome, a key mediator of inflammatory responses, is a novel therapeutic strategy. Teneligliptin, with its dual roles in glycemic control and preventing inflammation, has promising therapeutic potential for DCM[5]. Although these results are encouraging, further research is required to fully elucidate the mechanisms through which teneligliptin inhibits NLRP3 inflammasome activation in DCM. In addition, clinical trials should be conducted to investigate the long-term efficacy and safety of teneligliptin in patients with diabetes and cardiomyopathy [6]. Overall, teneligliptin is a multifaceted therapeutic option that can substantially improve the management of DCM, offering benefits that extend beyond glycemic control to anti-inflammatory and cardioprotective effects[7].

Pathophysiology of DCM

DCM is a distinct form of heart disease that is directly associated with diabetes, and it is independent of other common cardiovascular risk factors, such as atherosclerosis and hypertension[1]. The diabetic state triggers several metabolic disturbances, including chronic hyperglycemia, insulin resistance, and dyslipidemia, which collectively drive the pathophysiology of DCM. These metabolic abnormalities lead to the increased production of reactive oxygen species (ROS), causing oxidative stress and damage to myocardial cells[2]. This oxidative stress initiates inflammation, a key factor in DCM progression. The persistent activation of the NLRP3 inflammasome, a multiprotein complex that detects cellular stress signals, is a crucial driver of this inflammatory response. Upon activation, the NLRP3 inflammasome promotes the release of proinflammatory cytokines, particularly interleukin (IL)-1β and IL-18[4]. These cytokines further increase inflammation, causing widespread myocardial damage and accelerating the progression toward heart failure. Chronic hyperglycemia and insulin resistance also contribute to structural abnormalities in the myocardium in DCM, such as myocardial fibrosis and hypertrophy[6]. Fibrosis, which is characterized by excessive collagen deposition in the myocardial extracellular matrix, leads to stiffening of the heart tissue and impaired contractility. Hypertrophy, or thickening of the heart muscle, arises as a compensatory response to the increased workload, but it ultimately exacerbates cardiac dysfunction and promotes heart failure. Apoptosis, or programmed cell death, further complicates these problems by reducing the number of functional cardiomyocytes, contributing to the decline in cardiac function[3]. Increased glucose levels and ROS activate apoptotic pathways in cardiomyocytes, worsening myocardial cell loss and overall cardiac performance[3]. The interplay between oxidative stress, inflammation, fibrosis, hypertrophy, and apoptosis leads to the structural and functional decline observed in DCM. The NLRP3 inflammasome remains a key therapeutic target because its inhibition can alleviate the harmful effects of inflammation in DCM. Agents such as teneligliptin can reduce NLRP3 activation, decrease cytokine levels, and improve cardiac outcomes in diabetic models[4]. By mitigating both inflammation and oxidative stress, these interventions can delay DCM progression and improve patient outcomes.

NLRP3 inflammasome: A central player in inflammation

The NLRP3 inflammasome plays a critical role in regulating inflammation, particularly in DCM, where its activation substantially accelerates disease progression. As a key sensor of pathogenic signals, the NLRP3 inflammasome is an essential component of the innate immune system. Under diabetic conditions, elevated glucose levels, mitochondrial dysfunction, and advanced glycation end-product accumulation[4] activate the NLRP3 inflammasome[4]. Once activated, the inflammasome mediates the cleavage and release of proinflammatory cytokines, including IL-1β and IL-18, which amplify inflammation and contribute to progressive myocardial damage[2]. Chronic activation of the NLRP3 inflammasome in the diabetic myocardium is closely linked to fibrosis, which is characterized by excessive extracellular matrix

protein deposition; this causes structural remodeling and increased cardiac stiffness[1]. Persistent NLRP3 activity is also associated with pathological changes, including left ventricular hypertrophy, diastolic dysfunction, and eventual heart failure[2]. Inflammation driven by NLRP3 not only accelerates fibrosis but also impairs both systolic and diastolic cardiac functions, worsening the clinical manifestations of DCM[4]. Therapeutic strategies aimed at reducing NLRP3 activation could halt or slow the progression of DCM. Teneligliptin inhibits NLRP3 inflammasome activation and reduces inflammation in the diabetic heart[4]. Studies have demonstrated that teneligliptin reduces the release of IL-1β and IL-18, limits fibrosis, and improves both systolic and diastolic functions, indicating its potential cardioprotective effects for managing DCM[5,8]. In summary, the NLRP3 inflammasome forms a crucial link between metabolic disturbances and immune responses in DCM. Its chronic activation drives structural remodeling and functional decline in the heart. Pharmacological interventions targeting NLRP3, such as teneligliptin, offer significant potential for reducing inflammation and protecting against the progression of diabetic heart disease[1,4].

Teneligliptin as a therapeutic agent

Teneligliptin is widely recognized for its ability to improve glycemic control in type 2 diabetes by enhancing incretin levels, which stimulate insulin secretion and reduce glucagon production[7]. Beyond its glucose-regulating effects, teneligliptin also exerts anti-inflammatory and cardioprotective effects, making it a promising therapeutic agent in DCM [6]. Recent studies have highlighted the role of teneligliptin in mitigating the activation of the NLRP3 inflammasome, a key mediator of inflammation in DCM[4]. Metabolic dysregulation in diabetes triggers NLRP3 inflammasome activation, leading to the release of proinflammatory cytokines, such as IL-1β and IL-18; these cytokines drive chronic inflammation and fibrosis in cardiac tissue, worsening structural remodeling and functional decline[2]. By inhibiting NLRP3 activation, teneligliptin reduces cytokine secretion and limits myocardial damage, effectively alleviating inflammation and preventing fibrosis in the diabetic heart[2,4]. One of the primary mechanisms underlying the cardioprotective effects of teneligliptin is its ability to attenuate cardiac fibrosis, a defining feature of DCM. Fibrosis contributes to the stiffening of the myocardium, leading to left ventricular diastolic dysfunction and eventual heart failure. Through its inhibition of NLRP3-mediated pro-fibrotic signaling pathways, teneligliptin can preserve cardiac structure and function, as demonstrated in preclinical models[4]. Clinical studies, including the TOPLEVEL trial, have further supported the role of teneligliptin in preventing the progression of left ventricular diastolic dysfunction, indicating its potential for protecting the heart in patients with diabetes[6]. In addition to its cardioprotective effects, teneligliptin exhibits broader anti-inflammatory properties. Its inhibition of the NLRP3 inflammasome is associated with decreased pyroptosis, a form of programmed cell death that contributes to tissue injury in DCM[2]. This mechanism highlights the capacity of teneligliptin to protect cardiomyocytes from injury and death, thus maintaining myocardial integrity[2]. Furthermore, the benefits of teneligliptin extend beyond glucose regulation and inflammation. Teneligliptin improves endothelial function and vascular health by modulating circulating endothelial progenitor cells, which play a crucial role in vascular repair and maintenance[9]. These findings suggest that teneligliptin provides comprehensive cardiovascular protection for patients with diabetes; thus, teneligliptin addresses multiple pathways involved in the progression of DCM. In summary, teneligliptin is a multifaceted therapeutic option for managing DCM, exerting both glucose-lowering and cardioprotective effects. By inhibiting NLRP3 inflammasome activation, teneligliptin reduces inflammation, limits fibrosis, and prevents further cardiac damage, making it a valuable agent for mitigating the cardiovascular complications associated with diabetes[4,6].

Mechanisms of NLRP3 inhibition by teneligliptin

Teneligliptin inhibits NLRP3 inflammasome activation through multiple mechanisms involving oxidative stress and metabolic signaling pathways. A key mechanism involves the ability of teneligliptin to reduce oxidative stress by enhancing mitochondrial function and minimizing mitochondrial damage, a major trigger for NLRP3 activation[4]. Mitochondrial dysfunction results in excessive ROS production, a well-established activator of the NLRP3 inflammasome[2]. By improving mitochondrial health and suppressing ROS generation, teneligliptin directly protects against inflammasome activation. Moreover, teneligliptin modulates the AMP-activated protein kinase (AMPK) signaling pathway, which plays a crucial role in regulating cellular energy balance and suppressing inflammation[1]. The activation of AMPK by teneligliptin further inhibits the NLRP3 inflammasome, enhancing its anti-inflammatory effects[4]. The ability of teneligliptin to exert dual modulatory effects on metabolic and inflammatory pathways makes it particularly effective for combating chronic inflammation associated with DCM. Recent studies have suggested that teneligliptin alleviates endoplasmic reticulum (ER) stress, another known trigger for NLRP3 inflammasome activation[5]. By reducing ER stress, teneligliptin addresses this upstream driver of inflammation, adding to its protective effects against diabetic complications. Collectively, these mechanisms highlight teneligliptin's ability to comprehensively inhibit the activation of the NLRP3 inflammasome, offering a multifaceted approach to managing DCM and mitigating inflammatory damage in metabolic disorders[4,5].

Comparison of teneligliptin with other treatments for DCM

Teneligliptin shows considerable promise for the treatment of DCM, which is primarily due to its anti-inflammatory properties. Although all DPP-4 inhibitors are effective for improving glycemic control, teneligliptin has additional cardiovascular benefits, distinguishing it from other agents in its class and from therapies targeting inflammatory pathways. Compared with other DPP-4 inhibitors, teneligliptin demonstrates enhanced cardioprotective effects. Zhang *et al*[4] indicated that teneligliptin mitigates DCM by inhibiting NLRP3 inflammasome activation, reducing inflammation in cardiac tissues. Other DPP-4 inhibitors, such as sitagliptin and saxagliptin, are effective for glycemic control but have not consistently exhibited the same anti-inflammatory effects in DCM. For example, saxagliptin is associated with an increased risk of heart failure in some patients[10], a concern that is less prominent with teneligliptin due to its unique

pharmacological profile. In addition to DPP-4 inhibitors, therapies targeting inflammatory pathways, such as those inhibiting the NLRP3 inflammasome or reducing ER stress, are promising options for managing DCM. The ability of teneligliptin to inhibit pyroptosis and alleviate ER stress positions it favorably compared with other anti-inflammatory treatments, including empagliflozin, which primarily focuses on glucose control but also exhibits some anti-inflammatory properties[2]. Cardiovascular benefits further differentiate teneligliptin from other glucose-lowering therapies. Teneligliptin might improve vascular endothelial function, a critical factor in managing DCM. Akashi *et al*[9] reported that teneligliptin enhances the activity of endothelial progenitor cells, contributing to improved cardiac outcomes. Other DPP-4 inhibitors, such as alogliptin, have demonstrated less pronounced cardiovascular benefits, predominantly providing glycemic control. When compared with sodium-glucose co-transporter-2 (SGLT-2) inhibitors, such as canagliflozin, teneligliptin offers complementary effects. SGLT-2 inhibitors exert strong effects on weight reduction and cardiovascular risk mitigation, particularly in patients with heart failure. Combining teneligliptin with SGLT-2 inhibitors may provide additive benefits. Kadowaki *et al*[7] demonstrated that a combination of teneligliptin and canagliflozin yielded synergistic effects on body weight control and lipid metabolism, highlighting teneligliptin as an effective adjunct therapy for patients needing both glycemic and cardiovascular management. Despite its advantages, teneligliptin has limitations. Although it effectively reduces inflammation and supports cardiovascular health, questions remain regardinh its long-term efficacy and safety, especially regarding bone health and diabetic nephropathy. Shaik *et al*[8] raised concerns about potential bone health problem with teneligliptin in combination therapies, which could limit its use in specific patient subgroups. Furthermore, other anti-inflammatory agents may provide broader protection across multiple organs affected by diabetes, such as the kidneys and nervous system, where teneligliptin's benefits are less well understood. In conclusion, teneligliptin is a unique DPP-4 inhibitor with enhanced anti-inflammatory and cardioprotective effects. Its ability to inhibit NLRP3 inflammasome activation and reduce ER stress makes it a valuable therapeutic option for patients with DCM. Although teneligliptin offers significant advantages over other DPP-4 inhibitors and glucose-lowering therapies, its potential in combination therapies and the need for further research to confirm its long-term safety must be considered.

Clinical relevance and potential implications

Zhang *et al*[4] indicated that teneligliptin mitigates DCM by inhibiting the activation of the NLRP3 inflammasome. Thus, teneligliptin can address the unmet clinical needs of patients with diabetes. DCM, a leading cause of heart failure in diabetic individuals, has traditionally been managed with therapies aimed primarily at glycemic control and general cardiovascular protection. However, the progression of DCM is affected by inflammation, fibrosis, and mitochondrial dysfunction, which often render conventional treatments inadequate for treating advanced disease stages[1,2]. Teneligliptin's ability to inhibit NLRP3 inflammasome activation suggest that it is a novel therapeutic strategy that directly targets the inflammatory mechanisms underlying DCM. This may be especially beneficial for patients with advanced DCM, where traditional therapies have limitations for managing inflammation and fibrosis[4]. The progression of DCM is closely linked to chronic inflammation, mitochondrial dysfunction, and pyroptosis, a form of programmed cell death mediated by the NLRP3 inflammasome[2]. By suppressing these detrimental pathways, teneligliptin offers a more targeted approach that may delay disease progression and improve clinical outcomes. Incorporating teneligliptin into treatment regimens may enhance patient care by addressing both the metabolic and inflammatory components of DCM. Its effects on mitochondrial function, reduction of oxidative stress, and activation of the AMPK signaling pathway lead to superior clinical outcomes compared with traditional glucose-lowering agents alone[6,8]. This multifaceted mechanism highlights teneligliptin's potential to be combined with other therapies for a more comprehensive approach to managing the diverse pathophysiological factors contributing to DCM. These findings have significant clinical implications. By targeting the underlying causes of DCM progression, teneligliptin offers a more tailored therapy that may reduce the need for invasive interventions, such as heart transplantation, or long-term dependence on heart failure medications[4]. However, translating preclinical findings into clinical practice presents challenges, particularly when evaluating the efficacy of treatments such as teneligliptin for DCM. Although animal models provide valuable insights into disease mechanisms, they often do not fully replicate human pathophysiology, limiting their prediction of clinical outcomes. For example, although teneligliptin has been shown to reduce inflammation and prevent DCM by inhibiting NLRP3 inflammasome activation in animal models[4], these results may not always translate directly to humans due to species-specific differences in immune responses and metabolic pathways[2]. To bridge this gap, comprehensive clinical trials are needed to confirm teneligliptin's efficacy and ensure its safety in diabetic patients with DCM. Previous studies, such as the ARISE-HF trial, have provided valuable data on baseline cardiac dysfunction in patients with diabetes[1], offering a foundation for evaluating new treatments in this population. Moreover, trials such as the TOPLEVEL study, which focuses on teneligliptin's impact on diastolic dysfunction, indicate the importance of rigorously controlled studies for determining long-term benefits and potential adverse effects in humans[6]. Although teneligliptin shows promise for targeting inflammatory pathways to mitigate DCM, its long-term safety and efficacy across diverse patient populations must be validated. Kadowaki *et al*[3] highlighted the importance of large-scale post-marketing surveillance, which demonstrated the sustained efficacy of teneligliptin in more than 10000 patients with type 2 diabetes. Such real-world evidence is crucial for understanding the true clinical utility of the drug and identifying any safety concerns that may emerge with prolonged use. In summary, although preclinical findings are encouraging, translating them into clinical practice requires well-designed, large-scale trials that account for the complexity of human physiology and the multifactorial nature of diseases like DCM. These trials are essential to ensuring that teneligliptin can safely and effectively benefit diabetic patients, especially those with complications like DCM.

The safety profile of teneligliptin, as demonstrated in extensive post-marketing surveillance, indicates its potential as a long-term therapeutic option for patients with type 2 DM (T2DM) and cardiovascular complications[3]. Its safety across various patient subgroups, especially those with DCM and other comorbidities should be explored. Teneligliptin's safety in patients with cardiovascular complications is particularly significant for individuals with DCM. Research, including

that of Zhang *et al*[4], highlights the role of teneligliptin in mitigating DCM progression through the inhibition of the NLRP3 inflammasome, a critical mediator of inflammation and cardiac damage. This anti-inflammatory effect offers a dual advantage for patients managing both T2DM and cardiovascular conditions. The ARISE-HF trial's baseline findings emphasize the complex relationship between diabetes and heart failure, further highlighting the need for therapies such as teneligliptin that may positively affect cardiac outcomes[1]. In addition to its cardiovascular benefits, teneligliptin's safety in combination with other antidiabetic agents has been well-explored. The TOPLEVEL trial, for instance, demonstrates its role in controlling progressive diastolic dysfunction when used alongside standard treatments[6]. Similarly, Kadowaki *et al*[3] demonstrated teneligliptin's long-term safety in over 10000 Japanese patients, indicating that it can be safely integrated into existing glycemic control regimens without significant risks of severe adverse effects. Nonetheless, patient monitoring remains crucial, particularly when teneligliptin is combined with agents such as SGLT2 inhibitors, which have different mechanisms of action. Combination therapies, such as those with canagliflozin, have shown additive benefits in metabolic control and weight reduction, but the long-term cardiovascular impact of these combinations requires further investigation[7,11]. Despite its broad therapeutic potential, concerns regarding the long-term use of teneligliptin, particularly in different demographic and clinical contexts, remain. For example, potential side effects such as bone health issues have been noted, particularly in studies exploring the combination of metformin and teneligliptin[8]. Although teneligliptin shows promise in improving glycemic control and reducing cardiovascular risks, especially in patients with DCM, ongoing clinical trials are necessary to assess its long-term efficacy and safety across diverse patient subgroups and in combination with other antidiabetic agents.

CONCLUSION

Zhang *et al*'s study significantly advances the understanding of the role of inflammation in the pathogenesis of DCM and establishes a foundation for future therapeutic research[4]. By highlighting that the activation of the NLRP3 inflammasome and associated inflammatory pathways are involved in the pathogenesis of DCM, this research indicates the critical importance of targeting inflammation to mitigate DCM progression[2,4]. Therapeutic agents such as teneligliptin, which have demonstrated potential for reducing inflammation and improving cardiac function in diabetic conditions[1], is a promising avenue for future clinical applications. These findings offer a valuable framework for the development of new treatments that address both glycemic control and the underlying inflammatory mechanisms contributing to DCM[6,9].

FOOTNOTES

Author contributions: Cheng CY and Hao WR contribute equally to this study as co-first authors; Cheng CY and Hao WR conceptualized the editorial and provided critical insights into the relevance of the study; Liu JC contributed to the analysis and interpretation of the study's findings; Cheng TH supervised the editorial process and provided overall guidance; all of the authors read and approved the final version of the manuscript to be published.

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