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EDITORIAL

Macrophage modulation with dipeptidyl peptidase-4 inhibitors: A new frontier for treating diabetic cardiomyopathy?

Saeed Mohammadi, Ahmed Al-Harrasi

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Abstract

This editorial introduces the potential of targeting macrophage function for diabetic cardiomyopathy (DCM) treatment by dipeptidyl peptidase-4 (DPP-4) inhibitors. Zhang *et al* studied teneligliptin, a DPP-4 inhibitor used for diabetes management, and its potential cardioprotective effects in a diabetic mouse model. They suggested teneligliptin administration may reverse established markers of DCM, including cardiac hypertrophy and compromised function. It also inhibited the NLRP3 inflammasome and reduced inflammatory cytokine production in diabetic mice. Macrophages play crucial roles in DCM pathogenesis. Chronic hyperglycemia disturbs the balance between pro-inflammatory (M1) and anti-inflammatory (M2) macrophages, favoring a pro-inflammatory state contributing to heart damage. Here, we highlight the potential of DPP-4 inhibitors to modulate macrophage function and promote an anti-inflammatory environment. These compounds may achieve this by elevating glucagon-like peptide-1 levels and potentially inhibiting the NLRP3 inflammasome. Further studies on teneligliptin in combination with other therapies targeting different aspects of DCM could be suggested for developing more effective treatment strategies to improve cardiovascular health in diabetic patients.

Key Words: Diabetic cardiomyopathy; Macrophage; Dipeptidyl peptidase-4 inhibitor; Teneligliptin; NLRP3 inflammasome; Glucagon-like peptide-1

Core Tip: Targeting macrophage function could be introduced as a new approach for managing diabetic cardiomyopathy. Chronic hyperglycemia interrupts the balance between pro-inflammatory and anti-inflammatory subtypes of macrophages, promoting inflammation and tissue damage. The dipeptidyl peptidase-4 inhibitors, used for diabetes, might offer cardioprotective benefits by influencing macrophage activity and promoting an anti-inflammatory environment.

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INTRODUCTION

Diabetic cardiomyopathy (DCM) is recognized as a significant public health issue, resulting from the heterogeneous interaction of chronic hyperglycemia, metabolic irregularities, and subsequent changes in heart structure and function[1]. These alterations encompass changes in cellular structure, modifications to the composition of the extracellular matrix, and disruptions in signaling pathways within the heart. Early diagnosis and proactive management of diabetes and its complications are essential to prevent or slow the progression of DCM, which needs regular monitoring, maintaining optimal blood sugar levels, and adopting a healthy lifestyle[2]. However, there remains a need for novel therapeutic targets to address DCM effectively.

A recent study by Zhang *et al*[3], published in the recent issue of the *World Journal of Diabetes*, evaluated a potential therapeutic approach targeting the NLRP3 inflammasome, a critical inflammatory signaling complex known in DCM pathogenesis, by focusing on teneligliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor used for diabetes management, and its potential cardioprotective effects[4]. They revealed that teneligliptin administration markedly reversed established markers of DCM in a streptozotocin-induced diabetic mouse model[3]. The diabetic mice showed characteristics of cardiac hypertrophy and compromised function. Additionally, the elevated cardiac enzymes confirmed the occurrence of heart damage. Teneligliptin treatment effectively reversed these adverse changes, demonstrating its potential to enhance cardiac function and alleviate the progression of DCM. The diabetic mice exhibited elevated NLRP3 activity and interleukin (IL)-1β secretion, demonstrating inflammation[3]. Teneligliptin could efficiently inhibit these inflammatory pathways. The *in vitro* experiments on primary mouse cardiomyocytes showed that teneligliptin inhibited NLRP3 inflammasome activation and reduced the production of damaging cardiac enzymes. An inhibitor of the AMP-activated protein kinase (AMPK) signaling pathway eliminated these beneficial effects. These findings revealed a promising therapeutic option to manage DCM[3]. It is suggested that more research should be conducted to confirm the long-term effectiveness and safety of teneligliptin in patients with DCM. Moreover, investigating the role of immune cells, especially macrophages, in DCM pathogenesis requires more research studies, as Zhang *et al*[3] did not thoroughly investigate this aspect.

THE LINK BETWEEN CARDIOMYOPATHY AND DIABETES: M1 MACROPHAGES PLAY AN IMPORTANT ROLE

Macrophages are versatile innate immune cells that maintain tissue homeostasis and modulate repair processes after injury. Macrophages maintain a balance between pro- (M1) and anti-inflammatory (M2) states in a healthy heart[5]. The M1 macrophages (or classically activated macrophages), activated by bacterial infections or damage-associated molecular patterns, are involved in enhancing immune responses and eliminating pathogens by producing pro-inflammatory cytokines such as IL-1β and tumor necrosis factor-alpha, as well as reactive oxygen species (ROS)[5]. However, their long-lasting activation can lead to collateral tissue damage. The M2 macrophages (or alternatively activated macrophages), activated by factors such as IL-10 and transforming growth factor-beta, enhance tissue repair, the clearance of apoptotic cells, and resolution of inflammation[6]. The M2 macrophages secrete factors that dampen the inflammatory response and facilitate wound healing.

Chronic hyperglycemia, the main feature of diabetes, disrupts this balance. The exposure to elevated blood sugar levels can lead to aberrant M1 polarization and disruption of the M2 polarization process[7]. The activation of signaling pathways, such as nuclear factor-kappaB and mitogen-activated protein kinases, which are responsive to hyperglycemia, may result in the aberrant polarization of macrophages[8]. The M1 macrophages produce inflammatory cytokines and ROS, contributing to cardiac inflammation and damaging the surrounding cardiomyocytes[9]. The classically activated macrophages demonstrate impaired clearance of apoptotic and necrotic cells and promote tissue fibrosis (scarring), which can aggravate the inflammatory response and impair tissue repair[10]. The M1 macrophages can result in excessive collagen deposition by fibroblasts, leading to myocardial fibrosis. Stiffening of the heart muscle significantly compromises its pump function[11]. The impaired removal of apoptotic/necrotic cells by altered macrophages creates a self-amplifying cycle of inflammation[5]. Activation of the NLRP3 inflammasome in macrophages leads to the production of IL-1β, which activates the inflammatory cascade and promotes cardiac dysfunction[12]. Targeting the NLRP3 inflam-

masome, which could be assessed in more detail by Zhang *et al*[3], can offer a promising strategy to modulate macrophage function, reverse inflammation, and ultimately stop DCM progression. Accordingly, we could consider the M1 polarization of macrophages in diabetes as a leading contributor to heart dysfunction. We present an overview of the molecular mechanisms of macrophage dysfunction in DCM in Table 1, which includes related signaling pathways and cellular interactions.

Table 1 Molecular mechanisms of macrophage dysfunction in diabetic cardiomyopathy

Mechanism	Consequence	Effect on heart function	Ref.
Increased M1 polarization by hyperglycemia: Activation of nuclear factor-kappaB and mitogen-activated protein kinases pathways	Increased production of pro-inflammatory cytokines (IL-1β, TNF-α) and enhanced generation of reactive oxygen species	Direct cardiomyocyte damage and impaired contractile function	[8,12]
Impaired M2 polarization by hyperglycemia: Downregulation of IL-10 and TGF-β signaling	Reduced production of anti-inflammatory cytokines and impaired clearance of apoptotic cells and tissue repair	Perpetuation of inflammation and delayed wound healing	[7]
NLRP3 inflammasome activation: Triggered by hyperglycemia and damage-associated molecular patterns	Processing and release of pro-inflammatory cytokine IL-1β	Amplification of inflammatory response and aggravated cardiac dysfunction	[12,13,22]
M1 macrophage-mediated cardiomyocyte injury: Release of pro-inflammatory cytokines and reactive oxygen species	Direct damage to cardiomyocytes	Reduced contractility and pump function	[23]
M1 macrophage-promoted fibrosis: Enhanced collagen deposition by fibroblasts	Myocardial stiffening and fibrosis	Impaired relaxation and filling of heart and decreased pump function	[11]
Impaired apoptotic/necrotic cell clearance: Dysfunctional macrophages	Accumulation of cellular debris	Sustained inflammatory response and hindered tissue repair	[10]

TNF: Tumor necrosis factor; IL: Interleukin; TGF: Transforming growth factor.

EFFECTS OF ANTI-DIABETIC DRUGS ON MACROPHAGE FUNCTION IN DCM

Anti-diabetic drugs, particularly DPP-4 inhibitors, show promise in attenuating DCM by modulating the immune response, specifically through macrophage function. Medications such as metformin may promote the anti-inflammatory M2 polarization, and suppress the production of inflammatory cytokines[13]. The DPP-4 inhibitors might achieve similar results by increasing glucagon-like peptide-1 (GLP-1) levels, which can modulate macrophage function and potentially maintain the balance towards an anti-inflammatory profile[14]. The improved glycemic control, a key benefit of the anti-diabetic drugs, offers another protective mechanism. The anti-diabetic medications can help safeguard endothelial cells from damage by reducing the production of harmful compounds, such as advanced glycation end-products[15]. The DPP-4 inhibitors improve endothelial function through increased nitric oxide (NO) production and reduced inflammation [14]. Drugs such as teneligliptin (DPP-4 inhibitor) and liraglutide (GLP-1 receptor agonist) dampen inflammation through mechanisms involving reduced cytokine production and promoting M2 macrophage polarization[16]. Metformin utilizes a different pathway, activating AMPK to potentially increase M2 polarization[17]. Despite lacking direct evidence on macrophage function, sodium-glucose cotransporter 2 inhibitors might indirectly influence them by improving cardiac function and reducing overall inflammation[18]. The exact mechanisms of action for these drugs are complex and require more investigation. We summarize the suggested effects of anti-diabetic drug classes on macrophage function in DCM in Table 2.

EFFECTS OF DPP-4 INHIBITORS ON IMMUNE CELLS IN DCM

DPP-4 inhibitors, including teneligliptin, are being introduced as potential therapeutic strategies against DCM by modulating macrophage function through several mechanisms (Figure 1). A critical effect is the elevation of GLP-1 levels, which promotes an anti-inflammatory M2 phenotype and reduces oxidative stress[14]. The DPP-4 inhibitors might influence macrophage function by enhancing cholesterol efflux[19]. These combined effects could create a more protective macrophage profile, potentially suppressing inflammation, promoting tissue repair, and reducing the risk of complications associated with DCM.

Regarding the effects of DPP-4 inhibition on other immune cells, some studies suggest that DPP-4 inhibition might modulate T-cell function. The DPP-4 inhibitors might enhance regulatory T cell activity, leading to a more immunosuppressive environment. The inhibition of DPP-4 might influence the differentiation and activation of effector T cells, potentially reducing the production of pro-inflammatory cytokines[20]. Limited data exists on the direct effects of DPP-4

Table 2 Effects of antidiabetic drugs on macrophage function in diabetic cardiomyopathy

Drug class	Drug examples	Effects on macrophages	Related mechanisms	Ref.
Dipeptidyl peptidase-4 inhibitors	Teneligliptin, linagliptin, sitagliptin	Reduce pro-inflammatory cytokine production (IL-1β, IL-6), promote M2 polarization, and inhibit NLRP3 inflammasome activation	Increased glucagon-like peptide-1 levels, reduced oxidative stress, and modulation of nuclear factor-kappaB signaling pathway	[3,14, 24]
Metformin	Metformin	Reduces M1 polarization, increases M2 polarization, suppresses nuclear factor-kappaB signaling, and inhibits mitochondrial dysfunction	AMPK activation, reduced reactive oxygen species generation, and modulation of metabolic pathways	[13, 17]
Sodium-glucose cotransporter 2 inhibitors	Dapagliflozin, empagliflozin	May indirectly affect macrophage function through improved cardiac function and reduced inflammation	Sodium-glucose cotransporter 2 inhibition leads to diuresis and natriuresis, and may improve cardiac remodeling	[18, 25]
Glucagon-like peptide-1 receptor agonists	Liraglutide, dulaglutide	Promote M2 polarization, reduce pro-inflammatory cytokine production, and may improve cardiac contractility	Reduce oxidative stress, and enhance insulin sensitivity	[26-28]
Thiazolidinediones	Pioglitazone	Have anti-inflammatory properties, and improve insulin sensitivity	Peroxisome proliferator-activated receptor-γ activation, and reduced nuclear factor-kappaB signaling	[29, 30]

AMPK: AMP-activated protein kinase; IL: Interleukin.

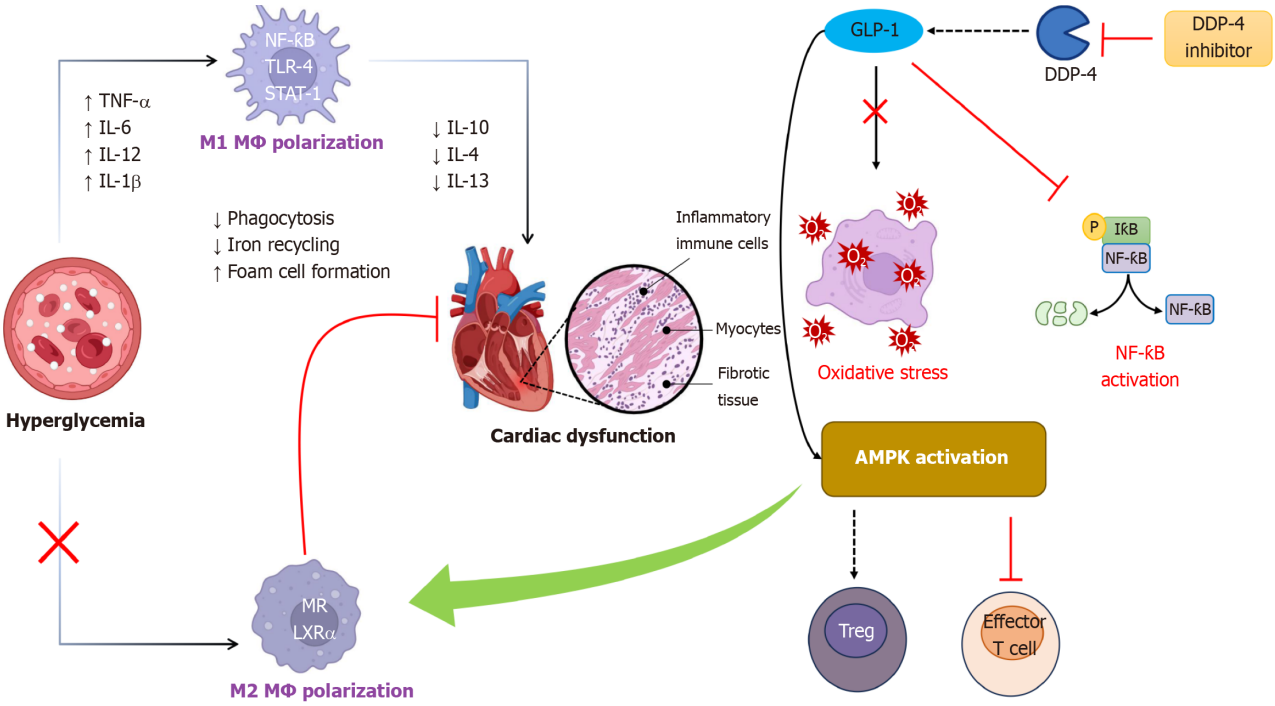

Figure 1 Potential mechanisms by which dipeptidyl peptidase-4 inhibitors modulate macrophage function and protect against diabetic cardiomyopathy. Dipeptidyl peptidase-4 (DPP-4) inhibition elevates glucagon-like peptide-1 (GLP-1) levels, which promotes an anti-inflammatory M2 macrophage phenotype and reduces pro-inflammatory cytokine production. This shift dampens inflammation and promotes tissue repair. GLP-1 signaling reduces oxidative stress in macrophages, protecting them from damage and promoting a healthier phenotype. DPP-4 inhibitors might influence macrophage function by suppressing pro-inflammatory signaling pathways (*e.g.*, nuclear factor kappa B) and enhancing AMP-activated protein kinase activation, which promotes fatty acid oxidation and energy production. GLP-1 signaling may influence cholesterol transporters in macrophages, improving their ability to efflux excess cholesterol and reducing atherogenic potential. NF-κB: Nuclear factor kappa B; AMPK: AMP-activated protein kinase; TNF: Tumor necrosis factor; IL: Interleukin; GLP-1: Glucagon-like peptide-1; DDP-4: Dipeptidyl peptidase-4; Treg: Regulatory T cell; MR: Mannose receptor; LXRα: Liver X receptor alpha; TLR-4: Toll-like receptor 4; STAT-1: Signal transducer and activator of transcription 1; IκB: Inhibitor of kappa B.

inhibitors on B cells. However, some studies suggest that DPP-4 inhibition might indirectly impact B cell function by modulating the activity of other immune cells like T cells, which can influence B cell activation and antibody production (Figure 1)[21]. The potential effects of DPP-4 inhibitors on other immune cells like dendritic cells and natural killer cells are largely unknown[21].

DPP-4 inhibitors (including teneligliptin) present a promising new way for managing DCM by targeting macrophage function[19]. It works through multiple mechanisms, including promoting anti-inflammatory M2 macrophages, po-

tentially inhibiting the NLRP3 inflammasome, and modulating the cytokine profile to favor a more favorable healing environment[22]. These findings suggest that DPP-4 inhibitors might offer a new tool for clinicians in the fight against DCM. However, further research is necessary to confirm its long-term efficacy and safety.

CONCLUSION

Chronic hyperglycemia disrupts the balance between pro-inflammatory M1 and anti-inflammatory M2 macrophages, shifting them towards a pro-inflammatory state contributing to heart damage. Targeting macrophage function may be a promising therapeutic strategy for DCM. Further studies are crucial to increase our understanding of the precise mechanisms by which DPP-4 inhibitors like teneligliptin, alone or in combination with other therapies, influence macrophages and other immune cells in DCM. By understanding the interaction between macrophages, inflammation, and DCM, we can introduce novel therapeutic approaches to manage DCM.

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