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Medical Bulletin

POTENTIAL THERAPEUTIC ROLE OF TENELIGLIPTIN IN THE TREATMENT OF DIABETIC CARDIOMYOPATHY

✤ Introduction

Diabetes mellitus (DM), is a chronic metabolic disorder affecting an estimated 425 million individuals worldwide. Diabetic cardiac diseases comprise ischemic heart disease (IHD), cardiac autonomic neuropathy (CAN) and diabetic cardiomyopathy (DCM).

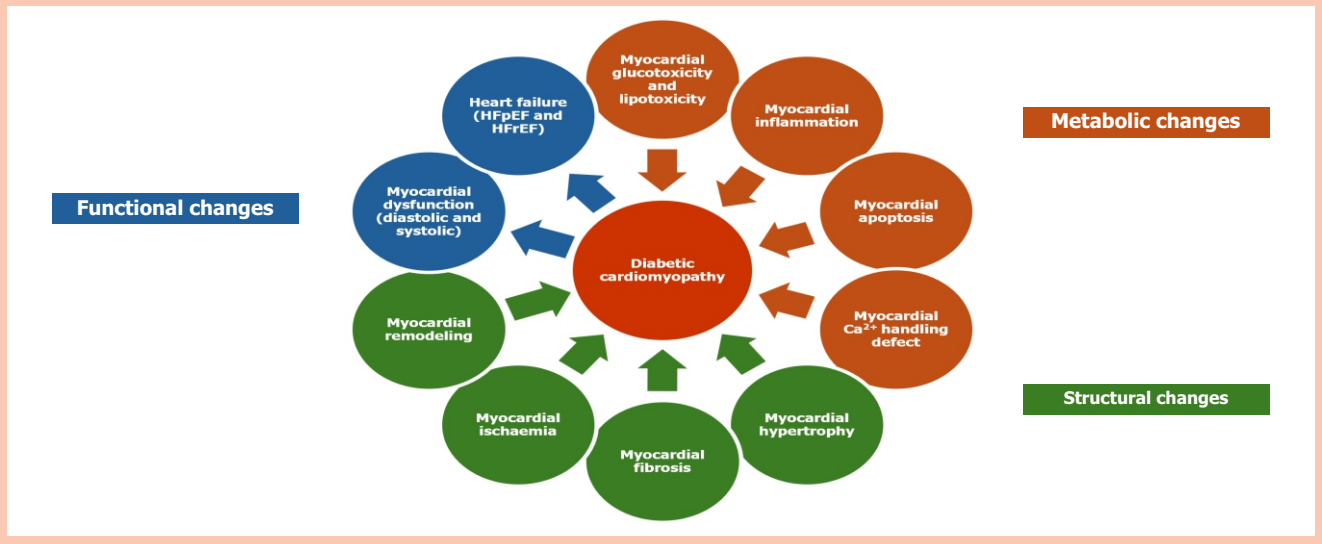
DCM is a myocardial dysfunction occurring in patients with DM, independent of the presence of coronary artery disease (CAD) or systemic hypertension. Studies suggest an incidence of about 30%-40% in the diabetic population. It is defined as the structural, functional and metabolic myocardial changes that result in heart failure (HF) in the absence of CAD, valvular heart disease and conventional cardiovascular risk factors such as hypertension and dyslipidaemia. The resultant HF can either be HF with preserved ejection fraction (HFpEF) or HF with reduced ejection fraction (HFrEF).

It is the most important cause of both diastolic and systolic HF in patients with DM and is associated with significantly higher morbidity and mortality risk.

✤ Pathobiology of DCM

Multiple metabolic, structural and functional alterations have been identified in the etio-pathogenesis of DCM. The pathobiological changes associated with the onset and progression of DCM include chronic hyperglycemia, insulin resistance, hyperinsulinemia, alterations in the pathways controlling intracellular myocardial energy metabolism, increased myocardial fatty acid oxidation (and the consequent mitochondrial dysfunction), diacylglycerol accumulation (with cardiomyocyte lipo-apoptosis), increased reactive oxygen species (ROS) formation (cardiac oxidative stress), increased generation of advanced glycation end products (AGE) (with nuclear factor-κB mediated inflammation), impaired calcium handling and apoptosis (from mitochondrial dysfunction and endoplasmic reticulum stress), altered mitochondrial bioenergetics, overactivation of the renin-angiotensin-aldosterone systems, impaired nitric oxide and endothelium-derived hyperpolarising factor-mediated vasodilation (leading to microvascular dysfunction) and cardiomyocyte apoptosis.

- *Structural changes* associated with DCM include myocardial hypertrophy, fibrosis, ischemia and adverse cardiac remodelling.
- *Functional changes* associated with DCM include the development of diastolic dysfunction, HFpEF, systolic dysfunction and subsequently HFrEF.



✤ Role of NLRP3 Inflammasome in DCM

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. NLRP3 inflammasome is found in both immune and non-immune cells such as macrophages, cardiomyocytes and fibroblasts. It is upregulated in multiple diseases including DCM and atherosclerosis. Activation of the NLRP3 inflammasome has been shown to participate in DCM and the death of cardiomyocytes.

- In response to a variety of pathological factors, the NLRP3 inflammasome and the expression of downstream cytokines are triggered, leading to a cascade of inflammatory reactions and causing damage to myocardial cells.
- Furthermore, NLRP3 activation correlates with ROS production. Under high glucose conditions, ROS levels are elevated, which is important for NLRP3 inflammasome activation.
- In addition, ROS activate the NLRP3 inflammasome mainly by forcing cytochrome C to enter the cytoplasm and bind to NLRP3.

NLRP3 is inactivated by inhibiting ROS production, which alleviates hyperglycaemia-induced myocardial cell damage. Therefore, NLRP3 is a critical target for treating DCM.

✤ Potential of Teneligliptin For DCM

Chronic hyperglycemia induces ROS formation which activates NLRP3 inflammasome and the latter has been implicated in the pathogenesis of DCM; antidiabetic medications may therefore play a role in mitigating DCM.

Teneligliptin is an oral hypoglycemic that belongs to the class of dipeptidyl peptidase-4 (DPP4) inhibitor. Although it shares similar efficacy and safety profiles with other gliptins, Teneligliptin exerts unique pharmacokinetic and pharmacodynamic properties owing to its distinct chemical structure.

Recent research has suggested that Teneligliptin may have additional benefits beyond glycemic control. Studies have reported that Teneligliptin exerts anti-inflammatory and protective effects on myocardial and neuronal cells. These findings suggest that Teneligliptin is a potential therapeutic agent for the management of DCM.

To further strengthen the above, a recent preclinical study explored the potential therapeutic effects of Teneligliptin on DCM.

The following observations were made:

1. Teneligliptin could ameliorate myocardial hypertrophy, improve heart function parameters and reduced the cardiomyocyte damage markers (creatine kinase-MB, aspartate transaminase, and lactate dehydrogenase).

2. The study also revealed that the drug could reduce the activation of NLRP3 inflammasome and the subsequent release of ROS and interleukin 1β, thereby reducing the resultant myocardial injury.

3. It was also found 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.

Therefore, the above preclinical study provides insights into the potential use of Teneligliptin in DCM. Further translation of these findings into clinical applications would help in the management of DCM with a readily available therapeutic option used for treating patients with type 2 DM for several years.

Source: *Zhang GL, et al. World J Diabetes. 2024; 15(4): 724-734, Fernandez CJ, et al. World J Diabetes. 2024; 15(8): 1677-1682*

METFORMIN IN PREDIABETES

Prediabetes, also known as “non-diabetic hyperglycemia” or “intermediate hyperglycemia” is a significant metabolic state related to an increased risk of developing type 2 diabetes mellitus (T2DM). It is the term used for individuals whose plasma glucose levels is below diabetes levels, but above the normal threshold. It includes impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). According to the American Diabetes Association (ADA), IFG 100 to 125 mg/dL and glycosylated hemoglobin (HbA1c) 5.7 to 6.4% are diagnostic of prediabetes. The World Health Organization (WHO) defines an IGT 140 to 199 mg/dL and an IFG 100 to 125 mg/dL as intermediate hyperglycemia. As per the Research Society for Study of Diabetes in India (RSSDI), IFG 110 to 125 mg/dL, IGT 140 to 199 mg/dL and ≥ 5.7%-6.4% is the criteria for prediabetes.

✤ Prevalence of Prediabetes

The prevalence of diabetes is increasing worldwide. According to the ICMR-INDIAB (Indian Council of Medical Research-India Diabetes) data the prevalence of prediabetes in India is 15.3%, which is higher than the prevalence of diabetes (11.4%). This makes prediabetes a bigger problem than T2DM itself.

Prediabetes increases the risk of all-cause mortality and the incidence of CVD outcomes, coronary heart disease, stroke, disease, cancer and dementia.

Risk factors for the development of prediabetes includes age (45 or above), overweight (BMI >25 kg/m^2), physical inactivity, family history, hypertension, history of gestational diabetes mellitus, triglyceride levels >200mg/dL and high density lipoprotein cholesterol (HDL) level < 35 mg/dL.

Given these circumstances, better awareness of prediabetes, timely screening and its proper management / intervention might contribute in preventing T2DM and associated complications.

✤ Pharmacotherapy as an Adjunct to Lifestyle Therapy

Lifestyle modifications & pharmacotherapy may be required and should be based upon severity of the hyperglycemia, individuals more susceptible to worsening dysglycemia, developing diabetes, developing CV complications or having familial history.

The only drug indicated for the prevention or delaying of T2DM is Metformin. Additionally, it has a strong safety record, with positive benefits on lipid levels and BMI.

The Central Drugs Standard Control Organisation (CDSCO) under its Subject Expert Committee (SEC) meeting (held on 26.04.2022 & 29.04.2022 has approved the use of Metformin in the management of prediabetes for

reducing the risk or delay of the onset of T2DM in adult, overweight patients with IGT, and/or IGF, and/or increased HbA1c who are at high risk for developing overt T2DM and still progressing towards T2DM despite implementing intensive lifestyle changes for 3 to 6 months.

✤ Current Guideline Recommendations on the Use of Metformin in Diabetes Prevention

Guideline	Summary of recommendations relating to Metformin
ICMR 2018	• When lifestyle alone is not sufficient and especially in those with combined IFG and IGT where progression to T2DM appears imminent, use of Metformin in addition to lifestyle measures may be considered especially in Indians who progress rapidly to diabetes from the prediabetes stage.
RSSDI 2022	• People with prediabetes failing to achieve any benefit on lifestyle modifications after 6 months may be initiated on oral antidiabetic agents. **Metformin:** In younger individuals with one or more additional risk factors for diabetes, if overweight/obese and having IFG + IGT or IFG + HbA1c >5.7%, Metformin (500 mg twice daily) is recommended.
ADA 2022	• Metformin therapy for prevention of T2DM should be considered in adults with prediabetes, especially those aged 25-59 years with BMI ≥35 kg/m^2, higher fasting plasma glucose (≥110 mg/dL) and higher HbA1c (≥6.0%) and in women with prior gestational diabetes mellitus.

Several studies have provided evidence that Metformin is effective in preventing diabetes;

1. A recently 2024 published meta-analysis analysing the effectiveness of Metformin in delaying the progression prediabetes to T2DM showed a 22% risk reduction with Metformin (n=4328) compared to lifestyle modification or placebo (n=4541).
2. Landmark DPP & DPPOS Trial: The Diabetes Prevention Program (DPP) study found that over a period of 2 year follow up period, Metformin lowered the chance of developing diabetes by 31% compared to placebo. A 10-year follow-up trail called the DPP outcomes trial (DPPOS) showed that Metformin lowered the risk of acquiring diabetes by 18%.
3. A meta-analysis (17 studies, n= 30,474) by Patel D, et al; also highlighted that taking Metformin was associated with a 42% decreased chance of developing diabetes, further supporting the drug's efficacy in avoiding the disease.

These findings demonstrate that Metformin supplementation reduces the likelihood of developing T2DM.

Source: *Das AK, et al. J. Assoc. Physicians India. 2022; 70(12): 11-12, Ghosal S, et al. Clinical Diabetology. 2024, Patel D, et al. Cureus. 2023; 15(9): e46108.*

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