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Review

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Molecular Pathways in Diabetic Cardiomyopathy and the Role of Anti-hyperglycemic Drugs Beyond Their Glucose Lowering Effect

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ABSTRACT

Epidemiological evidence has shown that diabetes is associated with overt heart failure (HF) and worse clinical outcomes. However, the presence of a distinct primary diabetic cardiomyopathy (DCM) has not been easy to prove because the association between diabetes and HF is confounded by hypertension, obesity, microvascular dysfunction, and autonomic neuropathy. In addition, the molecular mechanisms underlying DCM are not yet fully understood, DCM usually remains asymptomatic in the early stage, and no specific biomarkers have been identified. Nonetheless, several mechanistic associations at the systemic, cardiac, and cellular/molecular levels explain different aspects of myocardial dysfunction, including impaired cardiac relaxation, compliance, and contractility. In this review, we focus on recent clinical and preclinical advances in our understanding of the molecular mechanisms of DCM and the role of anti-hyperglycemic agents in preventing DCM beyond their glucose lowering effect.

Keywords: Hypoglycemic agent; Diabetic cardiomyopathy; Diastolic heart failure

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome with a high socioeconomic burden. It is characterized by substantial morbidity and mortality, as well as diminished functional capacity and quality of life. The incidence of HF significantly increases with aging, obesity and diabetes mellitus (DM).[1-3] Patients with type 2 diabetes are more than twice as likely to develop HF as those without, and 30%–40% of patients with HF have diabetes or impaired glucose tolerance.[4] Diabetes is also one of the major risk factors for HF, and patients with HF who also have diabetes have a higher mortality rate than non-diabetic patients.[5] Both type 1 and type 2 diabetes increase the risk of atherosclerosis, which is a cause of ischemic events and HF.[6,7] However, aside from promoting these pathological triggers, longstanding diabetes itself contributes to the development of heart failure with preserved ejection fraction (HFpEF) or heart failure with reduced ejection fraction (HFrEF).[8] One study showed that even

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in patients with diabetes who had no history of ischemic events, the incidence of HF ranged from 11% to 67% varying according to the diagnostic criteria used.[9] This suggests that there is a distinct mechanism of diabetes-induced cardiac remodeling.

In 2013, the American College of Cardiology, the American Heart Association,[10] and the European Society of Cardiology, all in collaboration with the European Association for the Study of Diabetes,[11] defined diabetic cardiomyopathy (DCM) as ventricular dysfunction that occurs in patients with diabetes in the absence of significant coronary artery disease or valvular heart disease and independent of common risk factors for atherosclerosis, such as hypertension and dyslipidemia. Given the prevalence and mortality of DCM, there is consensus on the need to diagnose the disease early and prevent its progression, but until recently, there was no gold standard for diagnosing the disease, which is characterized by decreased left ventricular (LV) relaxation, decreased ejection fraction (EF), LV hypertrophy, and interstitial fibrosis.[12] Moreover, diabetes is often accompanied by vascular disease, such as atherosclerosis, and it is impossible to differentiate HF from vascular disease based on symptoms and signs. The pathophysiological mechanisms underlying DCM are complicated and have not been fully elucidated.[13] Until recently, the only effective treatments for HF were diuretics, beta-blockers, and renin-angiotensin system inhibitors, angiotensin receptor-neprilysin inhibitors, sodium-glucose cotransporter-2 inhibitors (SGLT2i).[14] In context of DCM, there were no options other than controlling serum glucose and lipid concentrations. In particular, there is no specific drugs target the myocardial injury or cardiac remodeling process, which are part of the early changes in DCM. Over the last few years, many clinical trials have shown that several diabetic drugs have significant cardiovascular (CV) benefits including HF (**Table 1**), and there has been considerable interest in their mechanisms by which these medications can prevent or delay the early changes in DCM.

In this review, we summarize the effects of diabetes medications with well-known CV benefits and their known and probable mechanism to provide useful information for drug choices in patients with diabetes at high risk of HF.

Table 1. Main results regarding heart failure outcome of recent cardiovascular outcome trials of anti-hyperglycemic agents in type 2 diabetic patients (2010–2024)

Drug class	Drug name/Control	Study name	HHF results	No. of patients	Study duration
			Hazard ratio (95% CI)		
DPP-4 inhibitors	Sitaglipin/Placebo	TECOS	↔ 1.00 (0.83–1.20)	14,761	36 months
	Saxagliptin/Placebo	SAVOR-TIMI 53	↑ 1.27 (1.07–1.51)	16,492	25 months
	Linagliptin/Placebo	CARMELINA	↔ 0.90 (0.74–1.08)	6,979	26 months
	Linagliptin/Glimepiride	CAROLINA	↔ 1.21 (0.92–1.59)	6,033	76 months
GLP-1 receptor agonists	Lixisenatide/Placebo	ELIXA	↔ 0.96 (0.75–1.23)	6,068	25 months
	Exenatide/Placebo	EXSCEL	↔ 0.94 (0.78–1.13)	14,782	38 months
	Liraglutide/Placebo	LEADER	↔ 0.87 (0.73–1.05)	9,340	45 months
	Semaglutide/Placebo	SUSTATIN 6	↔ 1.11 (0.77–1.61)	3,297	25 months
	Albiglutide/Placebo	HARMONY	↔ 0.85 (0.70–1.04): HHF or CV death composite	9,463	19 months
	Efpeglenide/Placebo	AMPLITUTE-O	↓ 0.63 (0.49–0.81): MACE, any death, HF, kidney outcomes	4,076	22 months
	Dulaglutide/Placebo	REWIND	↔ 0.93 (0.77–1.12)	9,901	65 months
SGLT2i	Canagliflozin/Placebo	CANVAS	↓ 0.67 (0.52–0.87)	10,142	43 months
	Empagliflozin/Placebo	EMPA-REG OUTCOME	↓ 0.65 (0.50–0.85)	7,020	37 months
	Dapagliflozin/Placebo	DECLARE-TIMI 58	↓ 0.73 (0.61–0.88)	17,160	50 months
	Ertugliflozin/Placebo	VERTIS CV	↓ 0.70 (0.54–0.90)	8,246	36 months
	Sotagliflozin/Placebo	SOLOIST-WHF	↓ 0.61 (0.45–0.84)	1,222	9 months

HHF, hospitalization for heart failure; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon like peptide-1; CV, cardiovascular; MACE, major adverse cardiovascular events; HF, heart failure; SGLT2i, sodium-glucose cotransporter-2 inhibitors.

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DCM AS EMERGING DIABETIC COMPLICATIONS

1. Epidemiology

In 1972, Rubler et al.[15] reported a distinct type of cardiomyopathy characterized by the absence of coronary artery or valvular disease in patients with diabetes. Their findings were based on postmortem histopathologic examinations, and they postulated that microangiopathy or abnormal myocardial metabolism may be the underlying mechanism.[15] The Framingham Heart Study reported a higher rate of HF in diabetic men (2.4-fold) and women (5.0-fold) than in age-matched individuals without diabetes, independent of other comorbidities such as obesity, hypertension, dyslipidemia, or coronary artery disease.[16,17] Another epidemiologic study, the Strong Heart Study, similarly reported a 1.5-fold higher incidence of HF in patients with than without diabetes.[18] Moreover, the incidence of HF among patients with diabetes is closely associated with the blood glucose level. One study showed that in patients with type 1 diabetes, the risk of HF increased by 30% for every 1% increase in the hemoglobin A1C (HbA1c) concentration.[19] Other studies revealed that in patients with type 2 diabetes, each 1% increase in HbA1c level resulted in an 8%–16% increase in the risk of HF after adjustment for other risk factors.[20,21]

Large, randomized controlled trials investigating the CV safety of SGLT2i recently showed that the rate of hospitalization for HF in patients with diabetes was 8–15 per 1,000 patient-years.[22,23] Additionally, among patients with diabetes, the survival rate was significantly lower among those with than without incident HF.[24] A recent meta-analysis showed that among diabetic patients, diastolic dysfunction was more common than systolic dysfunction, with HFpEF having a higher incidence than HFrEF (7% vs. 4%, respectively).[4]

2. Diagnosis and management of DCM

There is no effective and accurate diagnostic method for DCM, possibly because molecular mechanisms are not fully elucidated, and it remains asymptomatic for many years. DCM is initially characterized by myocardial fibrosis, dysfunctional remodeling, and associated diastolic dysfunction, later by systolic dysfunction, and eventually by clinical HF (**Fig. 1**). According to the 2021 European Society of Cardiology guidelines, the diagnosis of HF should be based on the presence of cardinal symptoms (breathlessness, fatigue, ankle swelling, etc.) or signs (elevated jugular vein pressure, pulmonary crackle, peripheral edema). After checking the risk factors for HF and electrocardiographic findings, echocardiography should be performed if HF is considered likely. This can confirm the presence of diastolic dysfunction and EF and diagnose the presence and type of HF.[14] However, these diagnostic algorithms cannot detect early changes in heart caused by diabetes, such as myocyte hypertrophy, myocardial inflammation or fibrosis.

The most accurate way to identify myocardial injury, one of the early changes in DCM, is endomyocardial biopsy, but it is invasive and not easily accessible in a general practice setting.[25] Otherwise, cardiac MRI can be used to detect metabolic changes in the early stage of DCM. Phase-contrast MRI can visualize fluid movement and measure its velocity, providing various parameters of diastolic dysfunction.[26] Speckle tracking echocardiography is also one way to diagnose DCM. By quantitatively and qualitatively measuring the movement or deformation of cardiac tissue, it can detect changes in DCM at relatively early time points and has proven to be a useful tool for identifying ventricular dysfunction in many animal models of diabetes.[12] Global longitudinal strain (GLS) is a key parameter measured using speckle tracking echocardiography. GLS is measured as a percentage and represents the

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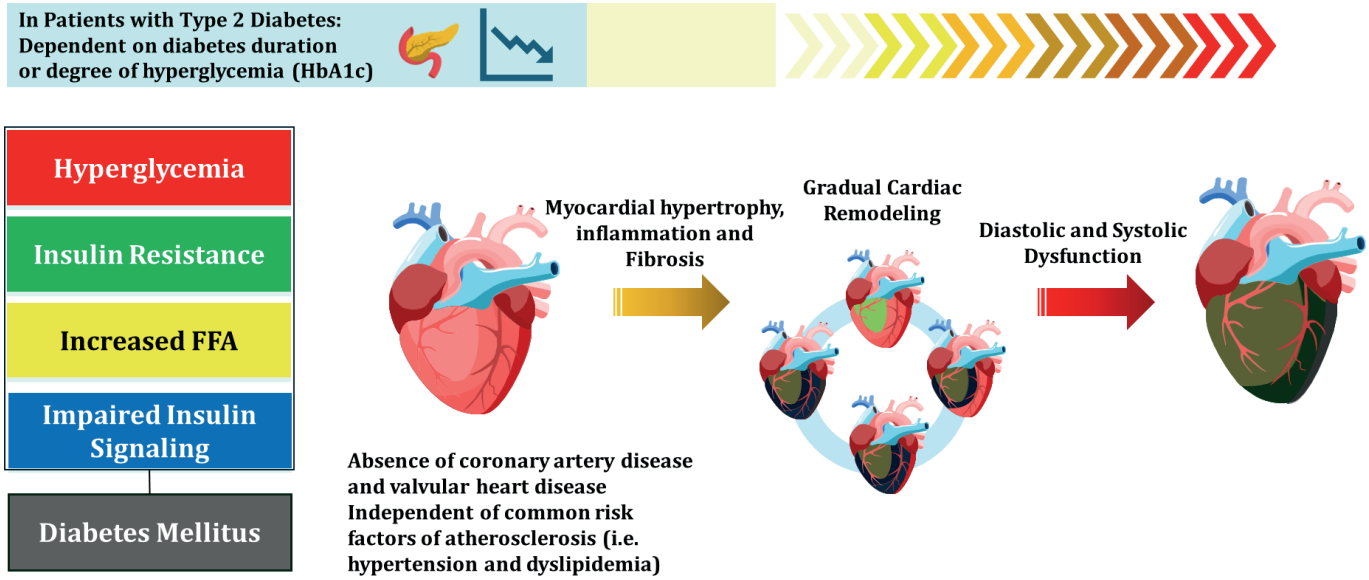

Fig. 1. Schematic representation of the progression diabetic cardiomyopathy.
The changes in diabetic cardiomyopathy are initiated by hyperglycemia, hyperinsulinemia, elevated fatty acids, and impaired insulin signaling. Diabetic cardiomyopathy is defined as ventricular dysfunction that occurs in patients with diabetes in the absence of significant coronary artery disease or valvular heart disease and independent of common risk factors for atherosclerosis. The incidence increases with blood glucose and duration of diabetes. After an initial asymptomatic period that begins with fibrosis of cardiomyocytes, cardiac remodeling progresses, leading to symptomatic diastolic and systolic heart failure.
FFA, free fatty acid; HbA1c, hemoglobin A1C.

degree of myocardial deformation during systole. In patients with diabetes, GLS is often reduced compared to non-diabetic individuals. This reduction in GLS indicates impaired LV function even when the LVEF remains normal (GLS).[13] However, these tools also have limitations and cannot clearly diagnose DCM and are not commonly performed in general practice due to methodology and cost.

Ideally, treatment for DCM should be able to reverse the pathophysiologic changes of the disease. However, there is no specific treatment for these DCMs at this time. If early DCM with preserved EF is suspected, SGLT2i and diuretics (if symptomatic) can be considered according to treatment guideline for HFpEF.[14] As DCM progresses and EF declines, additional medications such as beta-blockers, mineralocorticoid receptor antagonist, and inhibition of the renin-angiotensin system, beta-blockers and those inhibit the renin-angiotensin system can be added.[14]

3. Pathophysiology of DCM

Some of the pathogenesis of DCM is relatively well established and has been the subject of many review articles. Hyperglycemia in diabetes increases metabolites such as advanced glycation end products, which affect cardiomyocytes and endothelial cells. Insulin resistance (IR) reduces the amount of glucose available in the cardiomyocyte by decreasing the expression of glucose transporter (GLUT) 1 and 4 on cell membrane, causing metabolic shift in the cardiomyocyte. IR also promotes hepatic lipolysis, lipogenesis, which increase the amount of free fatty acids, allowing them to be used as an energy source to compensate the insufficient glucose in the cardiomyocytes. However, over time, the limit of free fatty acids β-oxidation is reached. The excess free fatty acids are then metabolized into ceramide and diacylglycerol (DAG), which is the main cause of lipotoxicity. It induces mitochondrial dysfunction, which not only decreases ATP production but also increases the production of

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reactive oxygen species (ROS), resulting in increasing oxidative stress in the cardiomyocyte. This cascade of responses leads to cardiomyocyte death, cardiac hypertrophy, inflammation and progressive fibrosis (**Fig. 2**, **Table 2**).

IR

IR is the main pathogenesis of diabetes and is also caused by factors such as chronic inflammation and oxidative stress. In addition, IR can be increased in HF due to increased adrenergic tone, and IR is known to be an independent risk factor in stable patients with chronic HF.[27] First, IR is associated with an increase in hepatic lipolysis, lipogenesis, and gluconeogenesis, resulting in a change in the energy source of cardiomyocytes.[28] Excess energy sources lead to glucotoxicity and lipotoxicity, which increases the production of ROS,[29] and also affects signaling pathways such as phosphatidylinositol (phosphatidylinositol 3-kinase [PI3K]/protein kinase B [Akt]), which leads to cardiomyocyte hypertrophy and reduced distensibility.[30] PI3Ks have been suggested to regulate cardiac injury during diabetes and seem to be a key factor in cardiac impairment in diabetic rats.[31] PI3Ks are primarily involved in the regulation of cardiac insulin signaling and energy metabolism.[32] Normal myocardial insulin signaling activates PI3K/Akt, which stimulates GLUT4 translocation from intracellular vesicles to the sarcolemma and subsequent glucose uptake in cardiac tissue. The PI3K pathway also stimulates CD36 translocation to the sarcolemma, which leads to an increase in fatty acid uptake.[32] Reduced PI3K/Akt signaling and GLUT4 expression have been observed in myocardial tissue from patients with type 2 diabetes.[33] Impaired activation of the

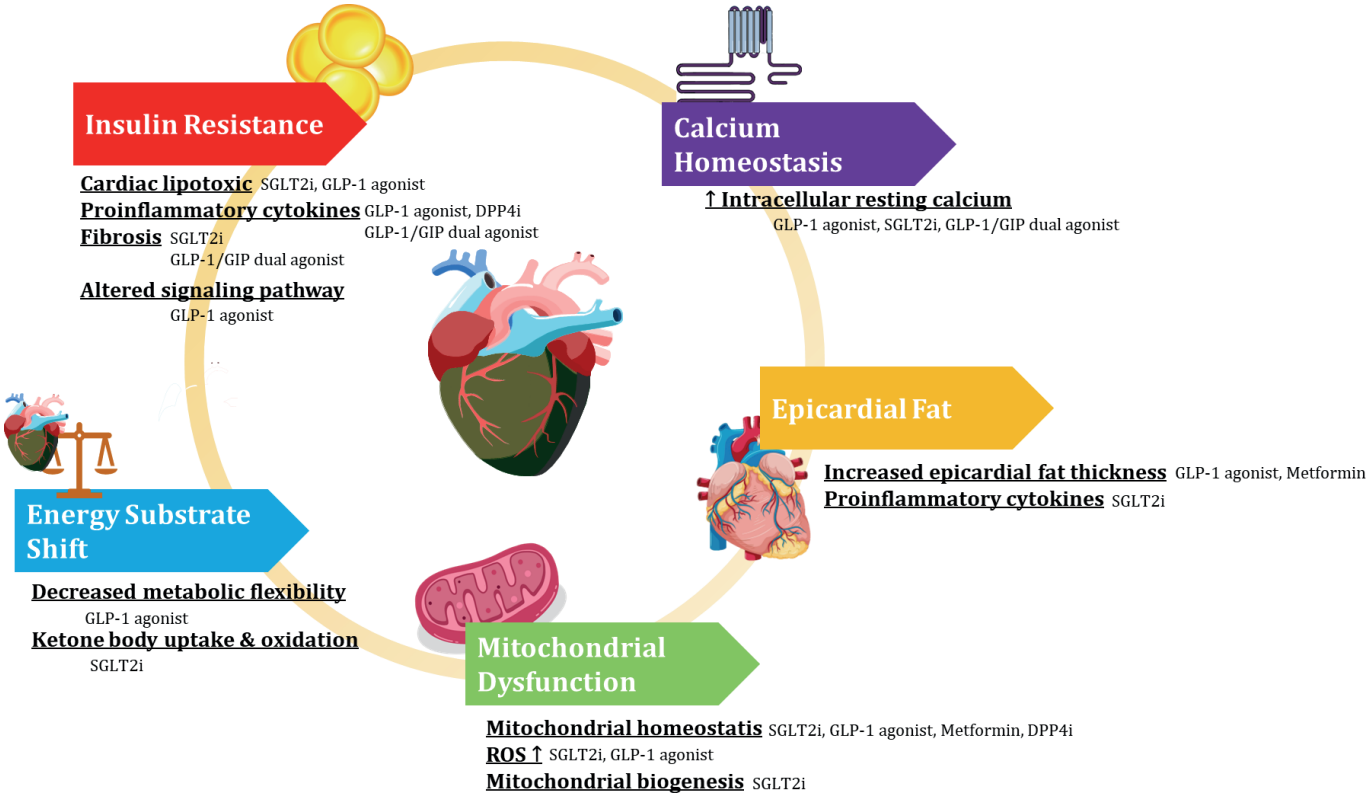

Fig. 2. Molecular pathogenesis of diabetic cardiomyopathy and the action of anti-hyperglycemic agents.
Summarize the molecular mechanisms involved in insulin resistance, energy substrate shift, mitochondrial dysfunction, calcium homeostasis and epicardial fat in diabetic cardiomyopathy and the potential targets for inhibition by currently used anti-hyperglycemic agents.
ROS, reactive oxygen species; SGLT2i, sodium-glucose cotransporter-2 inhibitors; GLP-1, glucagon like peptide-1; DPP4i, dipeptidyl peptidase-4; GIP, glucose-dependent insulinotropic polypeptide.

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Table 2. Summary of mechanisms of action of diabetes medications related to possible pathogenesis of DCM

Possible pathophysiology	Drug's mechanism of action
Insulin resistance	
Increased inflammatory cytokines	
TNF-α, IL-6, IL-8	GLP-1 agonist (↓), DPP-4inhibitor (↓), GLP-1/GIP dual agonist (↓)
Lipotoxicity	
CD36	GLP-1 agonist (↓)
Increased lipid metabolites	GLP-1 agonist (↓)
Altered signaling pathway	
PI3K/Akt	GLP-1 agonist (↓)
Fibrosis	
TGF-β1	SGLT2i (↓)/ GLP-1/GIP dual agonist (↓)
Energy substrate disorder	
Decreased metabolic flexibility	GLP-1 agonist (↑ cardiomyocyte glucose uptake)
	GLP-1 agonist (↑ glucose oxidation)
	GLP-1 agonist (↑ pyruvate influx to TCA cycle)
Ketone bodies	
Increased ketone bodies	SGLT2i (↑)
Ketone body oxidation	SGLT2i (glucose/fatty acid → ketones)
Mitochondrial dysfunction and oxidative stress	
Mitochondrial homeostasis	
AMPK	SGLT2i (↑)/GLP-1 agonist (↑)/Metformim (↑)
PGC-1α	SGLT2i (↑)/GLP-1 agonist (↑)/DPP-4inhibitor (↑)/Metformin (↑)
Mitochondrial biogenesis	SGLT2i (↓fission)
Oxidative stress	
ROS production	SGLT2i (↑sirtuin 3/SOD, ↓AGEs)/GLP-1 agonist (↓)
Calcium homeostasis	
Elevated intracellular resting Ca	
RyR2	GLP-1 agonist (↓)
SERCA2a	Tirzepatide (↑)
Na^+/H^+ exchanger	SGLT2i (↓)
Epicardial fat	
Increased epicardial fat thickness	GLP-1 agonist (↓), Metformin (↓)
Inflammatory cytokines	SGLT2i (↓)

DCM, diabetic cardiomyopathy; TNF, tumor necrosis factor; IL, interleukin; GLP-1, glucagon like peptide-1; DPP-4, dipeptidyl peptidase-4; GIP, glucose-dependent insulinotropic polypeptide; PI3K, phosphatidylinositol 3-kinase; TGF, transforming growth factor; SGLT2i, sodium-glucose cotransporter-2 inhibitors; TCA, tricarboxylic acid; AMPK, adenosine 5′ -monophosphate-activated protein kinase; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1α; ROS, reactive oxygen species; AGEs, advanced glycation end-products; SERCA2a, sarco/ER Ca^{2+}-ATPase 2a.

insulin-mediated PI3K pathway ultimately reduces glucose utilization; this makes the heart dependent on fatty acid β-oxidation for ATP production and leads to cardiac insufficiency and the development of DCM. In addition, long-term downregulation of insulin/PI3Kα/Akt signaling is associated with cardiac hypertrophy, reduced cardiac contractility, and increased cardiomyocyte death.[32] Cardiac-targeted PI3K gene therapy using active PI3K(I) viral constructs has been shown to inhibit cardiac remodeling and rescue cardiac dysfunction in diabetic mice.[34]

Long-term exposure to hyperglycemia increases the amounts of inflammatory cytokines such as tumor necrosis factor [TNF]-α, interleukin [IL]-6, IL-8, etc.) in cardiomyocytes.[35] It stimulates immune cells within the myocardium to increase pro-inflammatory M1 macrophages (decrease anti-inflammatory M2)[36] and increase the activity of NOD-like receptor family, pyrin domain containing (NLRP) and caspase-1 in association with the inflammasome, which also leads to increased macrophage infiltration and sustain inflammatory reaction.[37-39] This process is accompanied by mitogen-activated protein kinase (MAPK) activation, and a series of signaling pathways such as Erk1/2, p38 MAPK, and JNK are involved in cardiac hypertrophy, remodeling.[40] Glucotoxicity and lipotoxicity also contribute to the inflammatory response by enhancing nuclear factor (NF)-κB through Toll-like receptor (TLR) 2 or 4.[41]

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These inflammatory responses increase the expression of transforming growth factor (TGF)-β1 and accumulation of extra-cellular matrix (ECM).[42] TGF-β is one of the most thoroughly studied cytokines in the field of fibrosis,[43] and its gene expression is also increased by hyperglycemia.[44] Binding TGF-β to its receptors trigger formation of a heterotetrameric complex, composed of 2 type I and 2 type II receptor molecules. Subsequently, this complex activates canonical Smad signaling and/or Smad-independent signaling pathways such as MAPK and small guanosine 5′-triphosphatases such as RhoA.[45] The eight known Smad proteins are divided into 3 main groups. Smad 1, 2, 3, 5, and 8 are receptor-regulated Smads (R-Smad) that are activated by TGF-β1 type 1 receptor kinase. After activation by TGF-β1 type 1 receptor, R-Smad dissociates from the receptor and form trimeric complexes with Smad 4 (common Smad). One Smad 4 molecule can bind to 2 molecules of the same R-Smad or may form a mixed complex (Smad 2 and 3 or Smad 1 and 3). These R-Smad/Smad 4 complexes then translocate into the nucleus, where they regulate transcription of the target genes. Smad 6 and 7 are inhibitory Smad, which act competitively with R-Smad and block the TGF-β1-induced signaling pathway.[46] In addition to the canonical Smad pathway above-mentioned, TGF-β1 also acts through a non-canonical Smad pathway.[47] It initiates its intracellular action mainly by activating the MAPK pathway, TGF-β-activated kinase 1, Rho GTPase, PI3K/Akt, focal adhesion kinases extracellular receptor-regulated kinase 1/2 signaling pathway.[48]

Energy substrate disorder

Under normal physiological conditions, >90% of ATP is generated in mitochondria. Of this ATP, approximately 60%–90% is generated through the oxidation of FFAs, with the remaining portions being derived from other substrates such as glucose, lactate, ketones, and amino acids, albeit to a lesser extent.[49] The proportion of utilization between energy sources is regulated by the Randle cycle, which is mainly determined by glucose availability.

In DM, the expression of glucose transporters on the cell surface, GLUT1 and especially GLUT4, is reduced, and the expression of peroxisome proliferator-activated receptor-α is increased, leading to increased activity of enzymes involved in fatty acid degradation. This results in a higher utilization of fatty acids than under normal conditions, contributing to IR.[50] Prolonged periods of this condition can lead to mitochondrial uncoupling, which requires more oxygen to produce a given amount of ATP. Excess fatty acids are metabolized to ceramide and DAG beyond their capacity for β-oxidation capacity, which are major contributors to lipotoxicity.[12] Due to the lack of glucose transporter, glucose that cannot be assimilated in the cell is converted into polyols and hexoamines, which are pro-oxidant, pro-inflammatory, and contribute to glucotoxicity by producing advanced glycation end-products (AGEs).[12]

The normal heart is metabolically flexible, making it relatively easy to shift between energy substrates. However, as HF progresses, metabolic flexibility decreases and ATP production decreases, leading to energy deficiency.[51,52] Finally, in the end-stage of HF, ATP production is reduced by approximately 30% from normal.[53,54] A compensatory response to reduced mitochondrial oxidative metabolism and ATP production in HF is an induction of glycolysis.[55] In this process, glucose uptake is increased via an increase in GLUT1 expression, but glucose oxidation is decreased, resulting in the accumulation of polyols and hexosamine in the cytoplasm as byproducts. These metabolites contribute to the progression of HF by activating the cardiac remodeling pathway.[56] Compensation by increased glycolysis does not increase ATP production enough and eventually leads to an energy deficiency.[57] Furthermore, this process induces the accumulation of H^+ in the cytosol, which triggers the activation of the

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Na/H exchanger. This, in turn, increases the action of the Na/Ca exchanger, leading to the accumulation of Ca in the cytosol.[58]

Ketone bodies are recognized as an important source of energy for the heart.[59,60] In a fasting state, the concentration of ketone bodies in the body is usually increased,[61,62] and this response is exacerbated in patients with HF.[63] Recent reports have shown that ketone body oxidation in cardiomyocytes is increased in HFrEF[64-66] but not in HFpEF.[67] In terms of efficiency, ketone bodies produce more ATP per carbon than glucose, but the amount of ATP produced relative to oxygen consumed is less than glucose,[68] so more research is needed to determine whether the role of ketone bodies in HF is compensatory or causative.

Mitochondrial dysfunction and oxidative stress

The heart weighs 0.5% of the body but produces 8% of total ATP.[69] To keep the heart contracting, it requires an efficient and stable system to produce large amounts of energy, and when this process is compromised by any cause, HF develops. In diabetes or IR, there is also a progressive mitochondrial dysfunction in cardiomyocytes, leading to intracellular lipid accumulation. This generates large amounts of ROS, increasing oxidative stress and accelerating the progression of DCM. One of the mechanisms by which ROS contributes to the progression of DCM is by reducing the activity of adenosine 5′-monophosphate-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), resulting in decreased mitochondrial biogenesis, diminished cardiac autophagy, more severe cardiac impairment, and increased mortality in diabetic mice.[70] Treatment with the AMPK activator metformin has been shown to improve cardiac function by promoting autophagy.[71] In addition, activation of the AMPK pathway ameliorates cardiac hypertrophy by inhibiting the nutrient-sensing mammalian target of rapamycin (mTOR) C1 pathway.[72] Excessive ROS production also facilitates protein kinase C signaling and the hexosamine pathway and inhibits endothelial nitric oxide synthase (eNOS) and prostacyclin synthase activity, contributing to the development of cardiomyopathy.[73,74] PGC-1α promotes the synthesis of new mitochondria and enhances oxidative phosphorylation, which is essential for energy production.[75] PGC-1α expression is regulated by numerous factors, including insulin, glucagon, and exercise.[76] In diabetic conditions, impaired insulin signaling leads to decreased PGC-1α activity, which causes mitochondrial dysfunction. This leads to decreased ATP production, increased ROS generation, and inadequate antioxidant defense.[77] PGC-1α also regulates the metabolic flexibility of cardiomyocytes by modulating the switch between glucose and fatty acid utilization.[78] Experimental studies have shown that PGC-1α deletion can exacerbate cardiac metabolic imbalance; this leads to lipotoxicity and accumulation of lipid intermediates, which are detrimental to cardiac function.[79] By contrast, moderate PGC-1α overexpression in the mouse heart reduces cardiac remodeling and has a beneficial effect on cardiac function.[80,81]

Mitochondrial dysfunction includes impaired mitochondrial respiratory capacity, increased mitochondrial oxidative stress, as well as altered mitochondrial ultrastructure.[82-86] Mitochondria are dynamic organelles that constantly undergo fusion and fission. These processes are necessary for mitochondrial biogenesis and contribute to mitochondrial energy regulation and ROS homeostasis.[87] Mitochondrial fusion results in the formation of elongated tubular mitochondria under nutrient-poor or energy-demanding conditions, whereas fission promotes smaller fragmented mitochondria in environments of caloric excess.[88] These processes also allow damaged segments of mitochondria to be separated and removed through mitophagy.[89] Deletion of fission protein Drp 1 in the heart (cardiac-specific

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Drp1 knockout mice) can result in the development of cardiomyopathy.[90] One study showed that incubating H9C2 rat cardiomyoblasts in high-glucose medium induced mitochondrial fragmentation and ROS production.[91] This indicates that chronic exposure to a high glucose environment alters mitochondrial dynamics, which leads to an imbalance between fusion and fission. Fission in turn generates more ROS, leading to a vicious circle. ROS scavenging might help disrupt this circle and restore normal mitochondrial dynamics.

Calcium and sodium homeostasis disorder

Calcium (Ca^{2+}) is an important messenger coupling electrical signaling in the heart to contraction of the myocardium. When cardiomyocytes depolarize, a small influx of Ca^{2+} through sarcolemmal L-type Ca^{2+} channels (LTCCs) triggers a large release of Ca^{2+} from the sarcoplasmic reticulum (SR) to the cytosol, resulting in cardiomyocyte contraction.[92] At the end of the contraction cycle in cardiomyocytes, Ca^{2+} in the cytosol is reuptake into the SR, primarily via sarco/ER Ca^{2+}-ATPase 2a (SERCA2a), and a small amount of Ca^{2+} a is removed by the Na^{+}/Ca^{2+} exchanger.[92] Elevated cytosolic Ca^{2+} also stimulates Ca^{2+} uptake in mitochondria, leading to increased ATP production.[93]

As previously mentioned, diastolic dysfunction develops early in DCM due to a number of causes, including hyperglycemia, IR and oxidative stress. Ventricular relaxation abnormalities are associated with abnormalities in Ca^{2+} homeostasis in cardiomyocytes[94] and one of the accompanying electrophysiologic changes in the myocardium is a prolongation of action potential.[95] This involves an elevated intracellular resting Ca^{2+}, slowed Ca^{2+} transients, the reduction of (SR) Ca^{2+} reuptake.[96] There are also reports of decreased expression of SERCA2 or LTCC in diabetes,[97,98] which reduces cytoplasmic Ca^{2+} clearance, decreases Ca^{2+} loading of the SR, resulting in a prolonged action potential and contributing to diastolic dysfunction.[99]

Epicardial fat

Epicardial fat is the visceral fat around the heart, located in the atrioventricular and intraventricular grooves in normal adults.[100] When comparing HFpEF patients with similar body mass index (BMI), those with comorbid DM have a larger epicardial adipose tissue (EAT) mass than those without.[101,102] There is no muscle fascia between the EAT and myocardium, so they share the same microvasculature and interact via paracrine or vasocrine secretion.[103,104] In the presence of IR, such as diabetes and obesity, the body secretes fatty acids or proinflammatory cytokines such as leptin, TNF-α, IL-1β, and IL-6, which contribute to the development of HF.[105,106] It has already been reported that proinflammatory cytokines increase macrophage infiltration, leading to cardiac tissue fibrosis,[107] which is partly responsible for the development of atrial arrhythmias.[108,109] In addition to affecting diastolic dysfunction,[110] the release of inflammatory mediators can cause systemic inflammation, which can contribute to multiple organ dysfunction.[111]

The increased EAT mass is located in the cardiac fossa and is often accompanied by biventricular hypertrophy, and the pericardium is not sufficiently expanded, resulting in an increase in intracardiac pressure.[112,113] This leads to an increase in pericardial pressure and LV end-diastolic pressure, and an increase in pulmonary capillary hydrostatin pressure, which also causes dyspnea.[114]

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POTENTIAL TREATMENT OF DCM

1. SGLT2i

Recent studies have demonstrated that SGLT2i exhibit antioxidant, anti-inflammatory, anti-fibrotic and vascular protective effects aside from anti-diabetic effects in several rodent models of diabetes. These effects are thought to mediate the beneficial CV effects based on the results of many clinical trials, but the exact mechanisms are not fully understood. Researchers have proposed various hypotheses for the action of SGLT2. We herein focus on those that are closely related to the pathogenesis of DCM.

In a rat model of T2DM, administration of dapagliflozin and metformin reduced myocardial fibrosis and endothelial-to-mesenchymal transition (EndMT) compared with the control group.[115] The study also showed that treatment of human umbilical vein endothelial cells and primary cardiac fibroblasts with dapagliflozin inhibited high-glucose induced increases in EndMT, as well as TGF-β/Smad signaling and AMPK activity. Another report published in 2022 showed that dapagliflozin treatment reduced serum/glucocorticoid regulated kinase 1 (SGK-1) expression and ameliorated cardiac fibrosis and LV dysfunction in a rat model of diabetes using alloxan.[116] SGK-1 is an important regulator of fibroblast activation by TGF-β1 and has been reported to modulate cardiac fibrosis through FoxO3a.[117] Therefore, dapagliflozin is expected to prevent DCM by inhibiting EndMT and fibroblast activation through AMPK mediated TGF-β/Smad signaling.

SGLT2i may affect the utilization of energy in cardiomyocyte, increasing energy efficiency in patients with a failing heart. In a non-diabetic porcine model, empagliflozin increased myocardial ketone uptake and improved myocardial energetics and LV reverse remodeling .[118] The utilization of ketone bodies may be inhibited in the myocardium of patients with diabetes because of mitochondrial dysfunction which impairs the conversion of ketone bodies to acetyl-CoA.[119] Mice with deletion of succinyl-CoA:3 ketoacid-CoA transferase, the enzyme involved in the last step of ketone body oxidation, exhibit an increase in fatty acid oxidation and ROS production, changes in myocardial mitochondrial and myofilament microstructure, and deformation of the myocardium over time.[120] Ketone bodies are elevated in patients with SGLT2i, suggesting that in HF, SGLT2i may shift myocardial fuel metabolism from fatty acid/glucose oxidation to a more energy-efficient fuel such as ketones in HF.[121]

As mentioned above, mitochondrial dysfunction, which produces more harmful ROS and less ATP, plays an important role in DCM and HF; however, the mechanism is uncertain. Many studies have shown that SGLT2i have beneficial effects on mitochondrial function.[122] In rat with T2DM, empagliflozin treatment resulted in a significantly higher survival rate after acute myocardial infarction, as well as increased expression of myocardial sirtuin 3 and superoxide dismutase 2, which are associated with reduced oxidative stress and increased respiration.[123] Another study revealed that empagliflozin inhibits mitochondrial fission via AMPK activation, thereby reducing the generation of ROS and maintaining the function of the cardiac microvascular endothelial cell barrier.[124] There are also reports that empagliflozin improves mitochondrial biogenesis and balance between fusion and fission in rats with diabetes,[125] prevents decreases in mitochondrial size, and maintains mitochondrial numbers.[126] Empagliflozin may also enhance mitochondrial function by increasing the expression of PGC-1α in rats with diabetes.[127]

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Treatment with SGLT2i reduces cardiac oxidative stress by inhibiting the production of AGEs within the myocardium and aorta.[128] AGEs and activation of AGE receptors are associated with increased NF-κB signaling which increases collagen synthesis and promotes proinflammatory signaling in DCM.[129,130] The anti-inflammatory effect of SGLT2i may be enhanced by activation of the AMPK pathway with downstream inhibition of Na^+/H^+ exchanger isoform 1, thereby decreasing inflammation and apoptosis pathway activity.[131] Activation of the AMPK pathway also suppresses the mTOR pathway, which enhances autophagy in the myocardium and activates PGC-1α, thus improving mitochondrial function.[132] By enhancing the AMPK pathway, empagliflozin reduced the expression of IL-6 and TNF-α[133] and increased autophagy[134] in the myocardium of diabetic rat. These anti-inflammatory effects also suppress profibrotic TGF-β/Smad signaling, which alleviates cardiac fibrosis and remodeling.[115]

By inhibiting Na^+/H^+ exchanger, SGLT2i exerts a homeostatic function, normalizing intracellular sodium and calcium levels. This improves the availability of calcium for myocardial contraction. Dapagliflozin reduced diastolic Ca^{2+} and Na^+ overload and increased Ca^{2+} transient amplitude in ventricular cardiomyocytes.[135] Reported a decrease in mRNA expression of NHE11 in empagliflozin-treated mice, suggesting that NHE11 in cardiac tissue may be a potential target for SGLT2i.[136]

In addition, dapagliflozin has been shown to significantly reduce EAT thickness in patients with DM and/or obesity, and some studies have concluded that this is independent of weight loss.[137,138] Mechanisms such as decreased local proinflammatory chemokines (e.g. CCL2) and improved insulin sensitivity of EAT cells have also been suggested as possible mechanisms for decreased EAT thickness independent of weight loss.[139]

2. Glucagon like peptide-1 (GLP-1) receptor agonists

GLP-1 receptor agonists have been shown to exhibit potential cardioprotective properties which may be derived from their attenuation of CV risk factors including hyperglycemia, high blood pressure, obesity, and unfavorable lipid profiles. While other effects on the myocardium are plausible, the precise pharmacological or physiological mechanisms by which these agents reduce CV events remain uncertain.

A mechanistic investigation showed that the GLP-1 receptor agonist liraglutide directly suppresses the activation of PI3K/Akt1 and stimulates AMPKα signaling pathways in cardiomyocytes, thereby inhibiting angiotensin II and pressure overload induced cardiac remodeling.[140] Several studies have shown that treatment with GLP-1 receptor agonists reduces myocardial ischemia/reperfusion injury and prevents cardiac remodeling in various animal models of ischemic heart disease.[141-143] Other studies also demonstrated that treatment with GLP-1 analogues, including exenatide, not only reduced LV stiffness, diastolic dysfunction, and cardiac remodeling but also improved the survival of rats that developed HF following aortic banding or coronary artery ligation.[144,145] In a human study, GLP-1 receptor agonists or infusion of GLP-1 was shown to improve LV function and prevent the progression of cardiac remodeling in patients with acute myocardial infarction after successful angioplasty.[146,147]

Preclinical studies have reported an increase in myocardial glucose uptake with GLP-1 agonists.[148,149] and albiglutide-treated rats exhibited increased myocardial glucose uptake as well as alterations in glucose and lactate oxidation after ischemia/reperfusion injury.[150] GLP-1 also improves energy efficiency due to energy substrate shift in the HF. Liraglutide increased

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the rate of myocardial glucose oxidation in rats with diabetes, which may contribute to improved cardiac efficiency and alleviate diastolic dysfunction.[151] Metabolomics studies of semaglutide-treated mice have reported increased pyruvate influx into the tricarboxylic acid cycle and increased fatty acid oxidation, suggesting that increased efficiency of ATP production is one of the mechanisms involved.[152]

In HL-1 cardiomyocytes, liraglutide treatment reduces IL-1β-induced ROS production, ameliorates lipotoxicity by reducing lipid accumulation, and improves mitochondrial function by activating AMPK, PGC-1α, and others.[153] A study in which novel oral GLP-1 was administered to diabetic rats also reported improvements in cardiac function, including LVEF, and suggested that the mechanisms may be a reduction in oxidative stress through a decrease in the oxidative stress marker malondialdehyde, an increase in the mRNA expression of SOD1, and an improvement in mitochondrial function, leading to improvement in myocardial hypertrophy and fibrosis.[154]

Liraglutide modulates intracellular calcium homeostasis to reduce reperfusion injury in cardiomyocytes.[155] Furthermore, exendin-4 also shows anti-arrhythmic effects by reducing phosphorylation of RyR2 and attenuating CaMK-II activity, thereby reducing calcium leak from the SR.[156] These results suggest that GLP-1 agonists are involved in calcium homeostasis in cardiomyocytes, which may contribute to delay the progression of HF.

Unlike subcutaneous fat, EAT has a GLP-1 receptor.[157] It has been proposed that GLP-1 agonist administration may alter adipocyte formation or metabolism of EAT. Cohort studies in type 2 diabetes patients have reported a dose-dependent reduction in EAT thickness with semaglutide and dulaglutide once weekly,[158] and a reduction in EAT with metformin and liraglutide has also been reported, along with reductions in HbA1c and BMI.[159] This mechanism may explain some of the favorable CV outcomes seen with GLP-1 agonist administration.

3. Dipeptidyl peptidase-4 (DPP-4) inhibitor

In large clinical outcome trials, DPP-4 inhibitors have demonstrated CV safety without risk reduction.[160] However, an increased incidence of hospitalization for HF was noted in some clinical trials.[161-163] Intriguingly, translational data from animal models have nevertheless revealed potential cardioprotective effect of DPP-4 inhibitors in DCM. The effectiveness and mechanisms of DPP4 inhibitors in HF are not widely studied.

Linagliptin attenuated cardiac dysfunction in diabetic mice with sepsis by inhibiting the NF-κB pathway.[164] Treatment with evogliptin also attenuated cardiac systolic/diastolic dysfunction, hypertrophy, and fibrosis by reducing the accumulation of lipid droplets in the myocardium and alleviating mitochondrial injury by activating PGC-1α/NRFs/TFAM signaling in diabetic *db/db* mice.[165]

In contrast, DPP-4 inhibitors can repress the degradation of stromal cell-derived factor 1, substance P and neuropeptide Y, increases sympathetic tone,[166-169] which may aggravate HF. Neuropeptide Y1 and substance P may also aggravate HF by inducing cardiac fibrosis and cardiomyocyte apoptosis.[170,171] These conflicting results led the Consensus Report of the American Diabetes Association of 2022 to recommend against DPP-4 inhibitor therapy in patients with diabetes who develop stage B and C HF.[172]

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The effect of DPP-4 inhibitors on EAT is also controversial. Some have reported anti-inflammatory properties of EAT through administration of DPP-4 inhibitors. They thought that DPP-4 inhibitors downregulated the receptor for AGEs,[173] reduced ROS generation, and decreased ICAM-1 expression.[174] Conversely, there are also reports that DPP-4 inhibitors may accentuate CXCL12 or mineralocorticoid receptor signaling to trigger a proinflammatory response, which requires further clinical studies and investigation of the mechanisms.

4. Metformin

Numerous preclinical studies have provided promising results regarding the effect of metformin on treatment of DCM. Metformin is a well-known 5-AMPK pathway activator. The activated AMPK pathway provides cardioprotective effects by increasing glucose uptake and glycolysis, inducing autophagy via suppression of mTOR signaling, reducing cardiomyocyte apoptosis, promoting PGC-1α (which improves mitochondrial function), and increasing eNOS activity in endothelial cells.[71,175,176] In addition, the AMPK pathway inhibits oxidative stress and inflammatory responses and attenuates cardiac fibrosis by suppressing the TGF-β/Smad 3 signaling pathway.[177-179] In a recent study, metformin attenuated hyperglycemia-induced collagen type I gene expression in the fibroblasts of heart and vascular adventitia by inhibiting discoidin domain receptor 2, a collagen receptor tyrosine kinase.[180]

Metformin is a classic diabetes medication that helps with weight loss, and recent meta-analyses have shown that it is associated with reduced mortality in HFpEF patients,[137] as well as a 10% reduction in EAT thickness after 3 months of metformin alone.[181,182] The exact mechanisms are not well understood, but it has been suggested that it increases fat oxidation and increases thermogenesis.[183]

5. GLP1/glucose-dependent insulinotropic polypeptide (GIP) dual agonist and GLP1/GIP/glucagon triple agonist

Results from the CV outcome trials of tirzepatide, a GLP-1/GIP dual agonist, and retatrutide, a GLP-1/GIP/glucagon triple agonist, have not yet been reported. The results of SURPASS-CVOT (NCT04255433) comparing tirzepatide to dulaglutide in CV outcomes are expected to be reported soon, and we expect CV efficacy to be better than that of GLP-1 agonists, based on the previously documented benefits of tirzepatide, including improved glycemia, weight loss, blood pressure reduction, and improvement in CV risk factors, including lipid profile.[184] However, there are conflicting reports on the CV effect of GIP,[185-187] so we need to confirm the results of this trial in the future.

The results of several nonclinical studies with tirzepatide are promising. In the AC16 cardiac cell line exposed to high glucose, mRNA expression associated with fibrosis, such as TGF-β and matrix metalloproteinase-9, is increased; however, when treated with tirzepatide, their expression is significantly reduced. In addition, mRNA expression of SERCA2a is significantly increased, suggesting that tirzepatide may be effective in delaying the progression of DCM.[188] In mice treated with lipopolysaccharide, tirzepatide significantly improves cardiac function, including LVEF and LV fractional shortening, and is associated a decrease in inflammatory cytokines such as IL-1β, IL-6, and TNF-α, suggesting a beneficial effect by inhibiting the activation of TLR4/NLRP3 inflammasome signaling pathways.[189]

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CONCLUSION

In this review, we focused on molecular rather than neurohumoral mechanisms in the pathogenesis of DCM and summarized how anti-diabetic medications such as SGLT2i, GLP-receptor agonists, and metformin may impact the early pathological changes in DCM beyond their glucose-lowering effects. Recent studies have highlighted the potential of SGLT2i to mitigate cardiomyocyte fibrosis, improve mitochondrial function, and reduce oxidative stress and inflammation, suggesting their role in reversing some of the early molecular changes in DCM. GLP-1 receptor agonists have also shown promise in improving cardiac efficiency and reducing myocardial ischemia and remodeling. Metformin, through activation of the AMPK pathway, exhibits cardioprotective effects by enhancing autophagy, reducing oxidative stress, and inhibiting fibrosis. Despite advances in this mechanical understanding and clinical studies confirming the HF reduction effects of some drugs, there remains a need for further research to fully elucidate the specific mechanisms by which these medications exert their cardioprotective effects in the context of DCM. Future studies should aim to conduct a long-term clinical trial to assess the sustained impact of SGLT2i, GLP-1 receptor agonists, and other antidiabetic agents on cardiac function and structure in diabetic patients. By addressing these areas, we can improve our understanding of DCM and enhance therapeutic strategies, ultimately improving the prognosis for diabetic patients at high risk of HF.

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