Diabetes Mellitus and Heart Failure: Mechanistic Insights, Therapeutic Advances, and Multidisciplinary Approaches for Optimal Management

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Abstract

Diabetes mellitus and heart failure are intricately linked through shared pathophysiological mechanisms, including insulin resistance, oxidative stress, and lipotoxicity, which collectively contribute to diabetic cardiomyopathy. This unique cardiac complication results in both systolic and diastolic dysfunction, further complicating the management of heart failure in diabetic patients. Glycemic control plays a pivotal role in mitigating cardiovascular risks, with antidiabetic medications like SGLT2 inhibitors and GLP-1 receptor agonists demonstrating significant benefits beyond glucose regulation, including reductions in heart failure hospitalizations and improved overall cardiovascular outcomes. The complexity of managing diabetes-related heart failure necessitates a multidisciplinary approach, integrating expertise from cardiology and endocrinology to develop individualized treatment strategies, enhance patient education, and ensure adherence to therapeutic regimens. Furthermore, advancing our understanding of the interplay between diabetes and heart failure requires ongoing research into long-term effects of combined interventions, encompassing lifestyle modifications, pharmacological innovations, and emerging therapies. This review emphasizes the importance of collaboration and innovation in addressing the multifaceted relationship between these conditions. Effective management strategies not only improve clinical outcomes but also enhance the quality of life for individuals with diabetes, ultimately reducing the global burden of heart failure.

Keywords: Diabetic cardiomyopathy, Heart failure, SGLT2 inhibitors, Glycemic control, Multidisciplinary care

Significance | This review discusses the understanding diabetes-related heart failure mechanisms and therapies, including SGLT2 inhibitors, enables personalized, multidisciplinary care to enhance patient outcomes.

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1. Introduction

Heart failure (HF) is a significant complication of diabetes mellitus (DM), a condition that not only exacerbates HF risk but also serves as an independent risk factor for its development. The Framingham Study reported that the incidence of coronary artery disease is approximately twice as common in men with diabetes and five times as common in women with diabetes compared to non-

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diabetic individuals (Kannel et al., 1974). Furthermore, the prevalence of diabetes among individuals with HF is estimated to be 30–40%, underscoring the close association between these two conditions.

The interplay between diabetes and HF extends beyond complications arising from ischemic heart disease to include metabolic disturbances such as glucose and lipid toxicity driven by insulin resistance. These factors contribute to vascular to vascular endothelial dysfunction, microcirculatory abnormalities, and capillary failure (Wang & Hill, 2015; Jia et al., 2018). Multiple mechanisms have been implicated in this complex relationship. The term "diabetic cardiomyopathy" has been introduced to describe cardiac dysfunction in the absence of substantial hypertension, coronary artery disease, or valvular heart disease, though its recognition has been debated for years (Lee & Kim, 2017; Dillmann, 2019; Bando & Murohara, 2014). The American Heart Association (AHA) and the 2013 Heart Failure Guidelines from the American College of Cardiology (ACC) have acknowledged diabetic cardiomyopathy as a distinct entity (Yancy et al., 2013).

Contrastingly, recent guidelines from the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD) have yet to formally establish diabetic cardiomyopathy as a separate clinical diagnosis, signaling the need for further research and consensus (Cosentino et al., 2020). This comprehensive review examines the evidence regarding diabetic cardiomyopathy and its clinical implications, aiming to inform healthcare professionals about its practical significance. The syndrome may also overlap with conditions like lipotoxic myocardium or obesity-related myocardium, reflecting the shared pathophysiological traits observed in individuals with obesity, insulin resistance, and dyslipidemia (Nakamura & Sadoshima, 2020).

2.Pathophysiology and Mechanisms of Heart Failure Related to Diabetes

Heart failure (HF) is a common complication of diabetes, with various forms linked to the condition. Beyond coronary artery disease, the prevalence of left ventricular diastolic dysfunction among individuals with diabetes is estimated to range between 40% and 60% (Rubler et al., 1972; Regan et al., 1977; Redfield et al., 2003; Paulus & Tschope, 2013). Notably, approximately 40% of patients with heart failure with preserved ejection fraction (HFpEF) also have diabetes, implicating the condition as a key contributor to HFpEF pathogenesis (Paulus & Tschope, 2013). The hallmark of diabetic cardiomyopathy is left ventricular diastolic dysfunction, while left ventricular systolic dysfunction and coronary artery disease associated with reduced ejection fraction (HFrEF) generally emerge as the disease progresses.

Hyperglycemia and hyperinsulinemia in diabetes contribute to capillary damage, cardiac fibrosis, and myocardial hypertrophy, accompanied by mitochondrial dysfunction (Boudina & Abel, 2007; Ritchie & Abel, 2020; Sugawara et al., 2021). Additionally, lipotoxicity—characterized by abnormal lipid accumulation in cardiomyocytes—has been observed, with further evidence indicating oxidative stress and chronic inflammation leading to cardiac fibrosis and hypertrophy (van de Weijer et al., 2011; Russo & Frangogiannis, 2016).

3. Lipotoxicity in the Myocardium

Elevated circulating free fatty acids in diabetes and obesity primarily accumulate as triglycerides in adipose tissue but can also deposit ectopically in organs such as the liver, pancreas, skeletal muscle, and heart. This ectopic lipid deposition disrupts mitochondrial function and contributes to cellular dysfunction, a condition known as lipotoxicity (Shimabukuro, 2009). In the liver and skeletal muscle, lipotoxicity exacerbates chronic inflammation, insulin resistance, glucose intolerance, dyslipidemia, and hypertension.

In the heart, adipose tissue surrounds the myocardium and includes pericardial and epicardial fat deposits. Epicardial fat, located within the myocardium adjacent to the epicardium, has been identified as a predictor of cardiovascular disease onset (Mahabadi et al., 2013). Elevated levels of free fatty acids increase intracellular lipid accumulation in cardiomyocytes, forming lipid droplets, triglycerides, diacylglycerol, and ceramide. Diacylglycerol induces oxidative stress and insulin resistance via protein kinase C (PKC) activation, correlating with reduced Akt activity in failing myocardium (Chokshi et al., 2012). Meanwhile, ceramide promotes mitochondrial dysfunction and oxidative stress. For instance, C6-ceramide decreases Akt activity and elevates brain natriuretic peptide expression, while inhibition of ceramide synthesis mitigates lipotoxic cardiomyopathy (Park et al., 2008). Collectively, these mechanisms contribute to diastolic dysfunction, left ventricular hypertrophy, and ultimately heart failure (Basu et al., 2009).

4.The Mechanism by Which Diabetes Elevates Oxidative Stress

Diabetic cardiomyopathy is characterized by distinct metabolic and molecular alterations that result in cardiac dysfunction. A critical component of this pathology involves elevated oxidative stress caused by diabetes. One of the primary mechanisms underpinning this phenomenon is the increased stimulation of peroxisome proliferator-activated receptor α (PPARα) by elevated fatty acids. This activation enhances fatty acid absorption via CD36 and induces lipotoxicity (van de Weijer et al., 2011). In hypertrophic and non-diabetic failed hearts, PPARα activity is reduced, which leads to a decline in fatty acid β-oxidation and energy shortages. While this provides some insight, the relationship between heart

failure and diabetes remains contentious, necessitating further exploration (Kannel et al., 1974; Wang & Hill, 2015).

Oxidative stress in diabetes is driven by multiple mechanisms, including (1) dysregulation of the mitochondrial electron transport chain (ETC), (2) heightened activity of the renin-angiotensin system (RAS) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and (3) accumulation of advanced glycation end products (AGEs) (Jia et al., 2018). AGEs contribute to oxidative stress by promoting the formation of reactive oxygen species (ROS). These extracellular AGEs activate NADPH oxidase through interactions with cell surface receptors for advanced glycation end products (RAGE), which further elevates oxidative stress and inflammation (Bodiga et al., 2014). Increased oxidative stress subsequently induces myocardial fibrosis and hypertrophy, contributing to the pathogenesis of diabetic cardiomyopathy (Jia et al., 2018; Russo & Frangogiannis, 2016).

Elevated glucose levels also suppress antioxidant activation mediated by nuclear factor erythroid 2-related factor 2 (Nrf2) and sirtuin 1 (Sirt1). Simultaneously, they activate inflammatory pathways, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which synergistically enhance ROS generation and inflammatory mediators. This exacerbates cardiac remodeling and dysfunction (Lee & Kim, 2017). Hydrogen sulfide (H2S), an important gasotransmitter, plays a significant role in cardiovascular health. H2S deficiency exacerbates mitochondrial injury, ROS accumulation, necroptosis, and NLRP3 inflammasome activation, thereby worsening diabetic cardiomyopathy (Sugawara et al., 2021).

5.The Role of Insulin Resistance and Mitochondrial Dysfunction

Insulin resistance is a hallmark of diabetes that reduces glucose utilization and oxidative metabolism, causing an imbalance in fatty acid absorption and oxidation. This results in mitochondrial dysfunction and lipid accumulation in cardiomyocytes, exacerbating ROS production and oxidative stress. These mechanisms further impair cardiac function, promoting the progression of diabetic cardiomyopathy (Tong et al., 2019). Mitophagy, a selective form of autophagy targeting damaged mitochondria, plays a dual role in diabetic cardiomyopathy. While mitophagy eliminates dysfunctional mitochondria to reduce oxidative stress and apoptosis, excessive mitophagy may aggravate cardiac damage (Tong et al., 2019). Key signaling pathways regulating mitophagy include PINK1/parkin, AMPK-mTOR, and Wnt signaling.

5.1 Inflammation and the NLRP3 Inflammasome

Diabetes induces a chronic inflammatory state, partly mediated by the nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome. This inflammasome is closely associated with the progression of diabetic cardiomyopathy (Ritchie & Abel, 2020). Elevated free fatty acids (FFAs), disrupted insulin signaling, and hyperglycemia activate NLRP3, which promotes the production of interleukin-1 beta (IL-1β) and interleukin-18 (IL-18), leading to localized tissue inflammation. ROS-mediated activation of thioredoxin-interacting protein (TXNIP) further facilitates NLRP3 activation, contributing to caspase-1-mediated pyroptosis—a regulated form of necrotic cell death observed in diabetic myocardium. Silencing NLRP3 has been shown to reduce inflammation, pyroptosis, fibrosis, and improve cardiac function in animal models (Sugawara et al., 2021).

5.2 Calcium Dysregulation and Cardiac Autonomic Neuropathy

Type 2 diabetes impairs cardiac contractility and relaxation due to elevated intracellular resting calcium (Ca2+) levels, prolonged Ca2+ transients, and diminished sarcoplasmic reticulum Ca2+ pumping and absorption (Nakamura & Sadoshima, 2020). Additionally, cardiac autonomic neuropathy—characterized by abnormalities in heart rate regulation and vascular dynamics—results from hyperglycemia-induced oxidative stress, toxic glycosylation products, and neuronal cell death (Quinaglia et al., 2019).

5.3 Vascular Endothelial Dysfunction

Another significant pathological contributor to diabetic cardiomyopathy is vascular endothelial dysfunction. The vascular endothelium regulates capillary wall contraction, inflammatory cell adhesion, vascular permeability, and hemostasis. Nitric oxide (NO), synthesized by endothelial nitric oxide synthase (eNOS), is crucial for maintaining vascular tone. Endothelial dysfunction, observed in diabetic patients, correlates with increased mortality risk and the development of heart failure (Cosentino et al., 2020). Factors such as hyperglycemia, hyperinsulinemia, and postprandial hyperlipidemia contribute to endothelial dysfunction by enhancing oxidative stress, activating protein kinase C (PKC), and promoting AGE formation (Ritchie & Abel, 2020).

Under hyperglycemic conditions, glucose uptake by endothelial cells via glucose transporter 1 (GLUT1) is increased. This leads to PKC activation, metabolic disturbances, and endothelial cell damage. Insulin resistance further impairs the phosphoinositide 3-kinase/Akt (PI3K/Akt) pathway, which compromises NO production and exacerbates vascular dysfunction (Cosentino et al., 2020). Hypoglycemia also contributes to endothelial dysfunction through increased ROS, catecholamines, and inflammatory cytokines. Notably, glycemic variability and postprandial hyperglycemia induce greater oxidative stress and inflammatory mediator production compared to chronic hyperglycemia, leading to more pronounced vascular endothelial dysfunction (Boudina & Abel, 2007).

5.4 Impact of Non-Fasting Hyperlipidemia

Non-fasting hyperlipidemia, characterized by elevated triglyceride-rich lipoproteins such as chylomicrons and very low-density

lipoproteins (VLDL), plays a significant role in endothelial dysfunction. Obesity and insulin resistance prolong the clearance of these lipoproteins, leading to postprandial hypertriglyceridemia. This condition enhances inflammatory mediator production, oxidative stress, and eNOS inhibition, thereby impairing endothelial function (Mahabadi et al., 2013). High-fat meals further exacerbate this dysfunction by elevating triglycerides, ApoB-48, and remnant-like lipoprotein cholesterol levels, peaking approximately four hours post-ingestion. During this period, brachial artery flow-mediated dilatation (FMD) significantly declines, reflecting diminished vascular endothelial function (Mahabadi et al., 2013).

Diabetes elevates oxidative stress through a complex interplay of mechanisms involving mitochondrial dysfunction, chronic inflammation, endothelial impairment, and lipid metabolism abnormalities. Advanced glycation end products (AGEs), insulin resistance, and glycemic variability exacerbate ROS production and inflammatory signaling, further compromising cardiac and vascular function. While mitophagy and antioxidant pathways provide some protective effects, their dysregulation in diabetes contributes to the progression of diabetic cardiomyopathy. Understanding these molecular and cellular mechanisms offers opportunities for targeted therapeutic interventions to mitigate the cardiovascular complications of diabetes.

6. Therapeutic Intervention

The management of heart failure is consistent between patients with and without hyperglycemia. However, the effects of antidiabetic medications on heart failure vary, emphasizing the need to prioritize treatments that are both safe and effective in reducing heart failure-related events (Cosentino et al., 2020). This review explores the effects of various medications on diabetic myocardium, a unique condition characterized by complex cardiovascular outcomes. The U-curve relationship between glycated hemoglobin (HbA1c) and mortality in diabetic individuals with cardiac failure underscores the challenge of improving prognosis solely through blood glucose reduction. Furthermore, hypoglycemia may adversely impact the cardiovascular system via sympathetic nerve activation and inflammation, highlighting the importance of preventing hypoglycemic episodes (Kannel et al., 1974).

The efficacy of strict glucose management in preventing heart failure remains controversial. A meta-analysis comparing intensive glycemic control to standard control showed no significant reduction in heart failure hospitalizations with intensive therapy (Cosentino et al., 2020). Moreover, intensive glucose-lowering regimens can exacerbate heart failure. A meta-analysis of 13 trials involving 34,533 patients with type 2 diabetes revealed that intensive glucose-lowering therapy did not reduce cardiovascular events and increased heart failure risk by 47% (Cosentino et al., 2020). Hypoglycemia, a side effect of intensive therapy, may trigger sympathetic nervous system activation, worsening cardiovascular outcomes.

Lifestyle modifications, including dietary and exercise interventions, form the cornerstone of diabetes management. In patients with concurrent hypertension or heart failure, sodium intake should be further restricted. Caloric intake can be estimated using the formula: "appropriate daily energy requirement (kcal) = average weight (kg) × level of physical activity." Studies in healthy individuals suggest that caloric restriction enhances health-related quality of life and reduces oxidative damage (Sugawara et al., 2021). While caloric restriction has shown promise in model organisms such as yeast and mice, its efficacy as a therapeutic strategy for human heart disease remains unproven.

Certain antidiabetic medications, such as sulfonylureas, may increase the risk of heart failure. A retrospective study comparing various diabetic therapies found that sulfonylureas raised total mortality by 24–61% and cardiovascular disease risk by 18–30% compared to metformin monotherapy (Cosentino et al., 2020). Insulin, essential for patients with type 1 diabetes and some with type 2 diabetes, may exacerbate fluid retention and worsen heart failure due to increased renal sodium retention (Bando & Murohara, 2014).

Pioglitazone, a thiazolidinedione, has been associated with an increased risk of heart failure and is contraindicated in such patients. Pioglitazone enhances sodium reabsorption and fluid retention via activation of sodium transporters in renal epithelial cells (Boudina & Abel, 2007). Despite its potential adverse effects, pioglitazone offers protective benefits against cardiovascular events and is often used for secondary prevention. To mitigate fluid retention, it should be combined with mineralocorticoid receptor antagonists or thiazide diuretics.

The role of dipeptidyl peptidase-4 (DPP-4) inhibitors in heart failure prevention remains unclear. Studies suggest that DPP-4 inhibitors do not significantly affect left ventricular diastolic function in diabetic patients (Nakamura & Sadoshima, 2020). Long-term cardiovascular safety trials have shown no significant increase in heart failure risk with DPP-4 inhibitors compared to control groups (Cosentino et al., 2020). However, the SAVOR-TIMI 53 trial reported a higher rate of heart failure hospitalization in the saxagliptin group than in the placebo group (Bando & Murohara, 2014). DPP-4 inhibitors degrade glucagon-like peptide-1 (GLP-1) and other bioactive peptides, such as neuropeptide Y, which may elevate sympathetic nerve activity and contribute to heart failure development (Sugawara et al., 2021). While definitive conclusions about DPP-4 inhibitors' impact on heart failure risk are lacking, their protective role in reducing heart failure risk in diabetic patients appears limited.

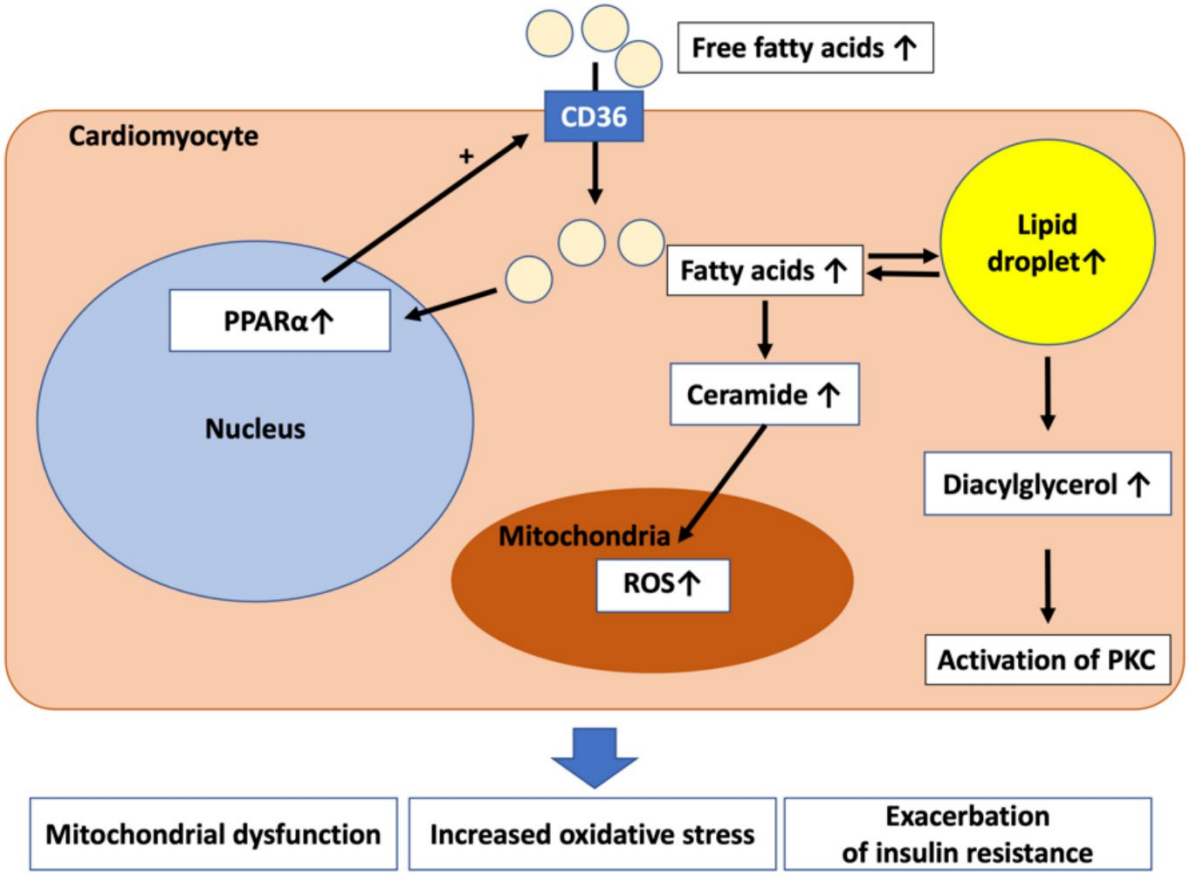

Figure 1. Lipotoxicity in the myocardium associated with diabetic cardiomyopathy.

Managing heart failure in diabetic patients requires a careful balance of glycemic control, lifestyle interventions, and medication selection to minimize adverse cardiovascular outcomes. Further research is needed to clarify the optimal therapeutic strategies for this complex patient population.

The 2021 ESC guidelines for diagnosing and treating chronic and acute cardiovascular diseases emphasize that metformin is considered safe for individuals with heart failure, unlike insulin and sulfonylureas, as evidenced by observational studies (McDonagh et al., 2021). However, metformin is contraindicated in patients with an estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m^2 due to the risk of lactic acidosis. Despite this, no randomized controlled trials have been conducted to establish its efficacy definitively (McDonagh et al., 2021).

Metformin's primary mechanism involves activating AMP-activated protein kinase (AMPK), an enzyme regulating energy metabolism in multiple organs, including the coronary artery, liver, and skeletal muscles. Studies have demonstrated that metformin enhances left ventricular performance and extends the lifespan of mice with ischemic heart failure (Gundewar et al., 2009; Andersson et al., 2010). Additionally, metformin improved cardiac function in a canine model of pacing-induced coronary artery disease through AMPK activation (Sasaki et al., 2009). These findings suggest that metformin provides direct cardiac protection and benefits in heart failure independently of its blood glucose-lowering effects.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors improve heart failure outcomes via two primary mechanisms: metabolic and hemodynamic. Metabolic benefits include hypoglycemia, reduced lipotoxicity, weight loss, elevated blood ketones, decreased insulin levels, and improved insulin sensitivity (Takata & Isomoto, 2021). Hemodynamic effects involve diuresis and blood pressure reduction. SGLT2 inhibitors mitigate lipotoxicity by decreasing lipid accumulation in visceral fat and promoting adipose tissue lipolysis. However, the exact cardioprotective mechanisms against lipotoxicity remain unclear and warrant further investigation. Blood pressure reductions of approximately −3 mmHg and prevention of cardiac hypertrophy have been observed in patients (Kimura et al., 2019).

Another potential mechanism involves reducing sympathetic nerve stimulation. Persistent sympathetic nervous system activation is a hallmark of type 2 diabetes mellitus (T2DM). SGLT2 inhibitors enhance circadian regularity of sympathetic responses in metabolic syndrome models and reduce high-fat diet-induced increases in tyrosine hydroxylase and norepinephrine levels in renal and myocardial tissues (Rahman et al., 2017). Elevated heart rates (HR) in T2DM patients are associated with increased mortality and cardiovascular risks. In patients with resting HR >70 beats per minute, SGLT2 inhibitors, such as luseogliflozin, significantly reduced HR, contributing to better cardiovascular outcomes (Sano et al., 2018).

Recent studies have highlighted that empagliflozin decreases late myocardial sodium channel activity (late-INa), which plays a critical role in cardiovascular disease pathogenesis and arrhythmias. Pharmacological agents blocking late-INa, such as ranolazine, reduce diastolic calcium overload in heart failure and long QT syndrome models (Makielski, 2016; Nie et al., 2019). Empagliflozin's interaction with Nav1.5, similar to local anesthetics and ranolazine, suggests a potential molecular target for its cardioprotective effects (Philippaert et al., 2021).

Clinical trials have further underscored the benefits of SGLT2 inhibitors in heart failure. In patients with heart failure with reduced ejection fraction (HFrEF), dapagliflozin significantly lowered the primary composite endpoint of worsening heart failure or cardiovascular death compared to controls, regardless of diabetes status (DAPA-HF trial) (Packer et al., 2020). Similarly, empagliflozin reduced the primary endpoint of cardiovascular mortality or heart failure hospitalization in HFrEF patients, irrespective of diabetes status (EMPEROR-Reduced trial) (Anker et al., 2021).

For patients with heart failure with preserved ejection fraction (HFpEF), biomarkers such as brain natriuretic peptide (BNP) decreased after initiating luseogliflozin or voglibose therapy in T2DM patients with HFpEF (MUSCAT-HF trial) (Kimura et al., 2019). Sotagliflozin has been shown to reduce the risks of cardiovascular-related mortality, heart failure hospitalizations, and urgent visits for heart failure in patients with diabetes experiencing recent exacerbations of HFrEF or HFpEF (Solomon et al., 2022). Furthermore, empagliflozin demonstrated a significant reduction in the composite endpoint of cardiovascular mortality or heart failure hospitalization in HFpEF patients, irrespective of diabetes status (EMPEROR-Preserved trial) (Anker et al., 2021). The diuretic effect of SGLT2 inhibitors likely contributes to their benefits, as evidenced by the findings of EMPEROR-Preserved, where a 21% reduction in the composite outcome was largely attributed to fewer heart failure hospitalizations, although no significant change in cardiovascular mortality was observed (Anker et al., 2021).

Comparatively, SGLT2 inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists have been shown to reduce all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, and renal failure. However, GLP-1 receptor agonists have minimal or no effect on heart failure hospitalizations, emphasizing the unique benefits of SGLT2 inhibitors in this context (White et al., 2013; Green et al., 2015).

These findings underscore the evolving therapeutic landscape for heart failure, particularly with the integration of SGLT2 inhibitors and metformin. While metformin provides direct cardiac benefits

through AMPK activation, SGLT2 inhibitors offer a multifaceted approach, addressing both metabolic and hemodynamic pathways. However, further research is essential to elucidate the underlying mechanisms, optimize therapeutic strategies, and expand the understanding of these agents' role in cardiovascular disease management.

7. Conclusion

The intricate relationship between diabetes mellitus and heart failure demands a nuanced understanding of the shared pathophysiological mechanisms, such as insulin resistance, oxidative stress, and lipotoxicity, that underlie diabetic cardiomyopathy. These factors contribute significantly to the onset and progression of heart failure, complicating its management by inducing both systolic and diastolic dysfunction.

This review underscores the pivotal role of effective glycemic control in mitigating cardiovascular risks, highlighting the efficacy of SGLT2 inhibitors and GLP-1 receptor agonists in reducing heart failure hospitalizations and enhancing overall outcomes. A multidisciplinary approach involving cardiologists and endocrinologists is crucial to tailoring patient-specific treatment plans, improving adherence, and facilitating timely interventions.

Future research should prioritize exploring long-term effects of integrated strategies, including pharmacological advancements, lifestyle modifications, and novel therapies, to address the complex interplay between these conditions. By fostering collaboration and innovation, we can significantly enhance patient care, reduce the burden of heart failure, and improve the quality of life for individuals living with diabetes.

Author contributions

R.F.R.A., B.A.A., S.A.A., and B.Z.M.A. contributed to the conceptualization and study design. B.B.A. and A.A.A. were involved in data collection and initial drafting of the manuscript. A.A.A. and S.M.A. contributed to data analysis and interpretation. A.M.A. and M.T.A. provided critical revisions and intellectual input. T.S.A.A.-S. and T.A.S.A.-S. coordinated the research process and ensured the integrity of the study. S.A.A., A.A., and N.S.D.A. worked on literature review and manuscript editing. A.M.A. supervised the project and provided final approval of the manuscript for submission.

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Competing financial interests

The authors have no conflict of interest.

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