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Diabetes and Heart Failure: What's the Connection

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Abstract. Diabetes mellitus and heart failure are two common chronic conditions that frequently coexist, producing outcomes worse than either disease alone. This paper investigates how diabetes directly impairs the myocardium, leading to a distinct syndrome often termed diabetic cardiomyopathy, and examines the reciprocal influence of both disorders. Evidence from clinical and experimental studies highlights altered myocardial metabolism, oxidative stress, glycation pathways, calcium dysregulation, mitochondrial injury, inflammatory signaling, and autonomic imbalance as contributors to structural and functional decline. Analysis of pharmacological data shows that sodium–glucose cotransporter-2 inhibitors consistently improve outcomes across heart failure phenotypes, while glucagon-like peptide-1 receptor agonists offer benefits mainly in obesity-related HFpEF. By contrast, several older glucose-lowering drugs may worsen congestion or remain neutral in prognosis. The review concludes that diabetes and heart failure form a complex, self-reinforcing network, and that targeted treatment strategies grounded in mechanistic understanding are critical for advancing patient care and clinical outcomes.

Keywords: Diabetic cardiomyopathy, Reactive oxygen species, SGLT2 inhibitors, GLP-1 receptor agonists

1. Introduction

Diabetes mellitus and heart failure are two major chronic diseases whose prevalence continues to rise in parallel with global aging and the obesity epidemic. Their coexistence is particularly concerning given the profound impact on morbidity, mortality, and healthcare burden. Epidemiological data consistently demonstrate that patients with diabetes have a markedly elevated risk of developing HF, while those with HF and coexisting diabetes experience earlier onset, more severe symptoms, and worse outcomes compared to non-diabetic HF patients [1]. Clinically, such patients often present with dyspnea, reduced exercise tolerance, orthopnea, and peripheral edema. Imaging studies further reveal higher rates of diastolic dysfunction, left ventricular hypertrophy, and myocardial fibrosis, abnormalities that cannot be fully explained by hypertension or coronary artery disease alone [2].

The concept of diabetic cardiomyopathy (DCM), first introduced by Rubler et al. in 1972, underscores that diabetes itself can cause myocardial damage independent of other cardiovascular comorbidities [3]. Since then, mechanistic studies have elucidated a multifactorial pathophysiology involving metabolic reprogramming, ROS overproduction, AGEs–RAGE signalling, calcium

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handling abnormalities, mitochondrial dysfunction, impaired autophagy, chronic inflammation, immune cell infiltration, and autonomic imbalance [4,5].

From a therapeutic perspective, the emergence of SGLT2 inhibitors and GLP-1 receptor agonists has reshaped the treatment paradigm for patients with diabetes and HF. Large-scale clinical trials have shown consistent benefits of SGLT2 inhibitors across the HF spectrum, while GLP-1 receptor agonists demonstrate promising effects, particularly in obesity-related HFpEF. Conversely, older classes of glucose-lowering drugs such as TZDs and insulin pose challenges due to fluid retention and increased HF risk. Against this backdrop, this paper aims to synthesize epidemiological, mechanistic, and pharmacological evidence on the interplay between diabetes and HF while offering a critical appraisal of current findings and their clinical implications.

2. Pathophysiological mechanisms of diabetic cardiomyopathy

Diabetic cardiomyopathy (DCM) arises from a multifactorial and multi-pathway interplay. Its defining pathological hallmarks include myocardial metabolic reprogramming, mitochondrial dysfunction, excessive generation of reactive oxygen species (ROS), accumulation of advanced glycation end-products (AGEs), interstitial fibrosis, and abnormalities in calcium homeostasis. Within the milieu of chronic hyperglycemia and insulin resistance, these mechanisms amplify one another, ultimately resulting in structural and functional cardiac impairment.

Metabolic reprogramming and ROS overproduction are among the earliest recognised mechanisms. Under physiological conditions, the heart flexibly utilizes glucose and fatty acids as energy substrates. In diabetes, however, myocardial glucose utilization declines significantly, with a compensatory over-reliance on fatty acid oxidation. This imbalance decreases ATP production efficiency and increases oxygen consumption, forcing the myocardium to expend greater metabolic effort for the same energetic output [4]. Simultaneously, excessive fatty acid oxidation leads to excessive ROS production. ROS damages mitochondrial DNA and membrane proteins, further promoting cardiomyocyte apoptosis and dysfunction [6]. This “metabolic–oxidative stress cycle” is considered the energetic foundation of DCM.

AGEs–RAGE signaling also accelerates myocardial fibrosis. Chronic hyperglycemia promotes irreversible glycation of proteins and lipids, leading to AGE accumulation. These AGEs bind to their receptor (RAGE), activating downstream signalling pathways such as NF-κB and TGF-β/Smad. The result is the release of inflammatory cytokines and profibrotic factors, promoting collagen deposition and interstitial stiffening [7]. This mechanism is particularly prominent in patients with HFpEF, where diastolic dysfunction and ventricular stiffness are central pathophysiological features.

In addition, calcium-handling abnormalities represent another key characteristic of DCM. Myocardial calcium cycling depends on precise regulation by sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2a) and the Na^{+}–Ca^{2+} exchanger (NCX). In diabetes, SERCA2a expression and activity are reduced, leading to impaired diastolic calcium reuptake and limited myocardial relaxation [5]. Concurrently, CaMKII is aberrantly activated in hyperglycemic and oxidative stress environments, further disrupting calcium homeostasis and increasing arrhythmic risk [8].

Recent studies highlight the role of mitochondrial dynamics and impaired autophagy in DCM. Diabetes disturbs the balance of mitochondrial fusion proteins (Mfn1/2) and fission proteins (Drp1), resulting in abnormal mitochondrial morphology. Simultaneously, impaired mitophagy allows the accumulation of damaged mitochondria, reducing myocardial bioenergetic capacity while amplifying ROS production and pro-inflammatory signalling [9].

Furthermore, inflammatory and immune mechanisms also contribute significantly. Hyperglycemia ignites the NLRP3 inflammasome, unleashing IL-1β and IL-18 that drive

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cardiomyocyte death and myocardial fibrosis. In diabetic hearts, robust infiltration of monocytes and macrophages parallels progressive left-ventricular dysfunction [10]. Yet clinical trials that blunt IL-1β signaling [11] have failed to improve outcomes, underscoring that neutralizing a single inflammatory axis is inadequate against the multifaceted pathophysiology of diabetic heart failure.

Autonomic dysfunction is another pervasive feature of diabetes. Sustained sympathetic hyperactivation with reduced parasympathetic activity decreases heart rate variability, increases arrhythmia risk, and promotes hypertrophy and fibrosis, thereby accelerating HF progression [12].

However, although experimental studies have revealed multiple mechanisms underlying DCM, most evidence derives from animal models that fail to capture the full complexity of human disease. Patients with diabetes typically present with comorbidities, such as obesity, hypertension, and chronic kidney disease, factors that are oversimplified in preclinical models. Moreover, it remains uncertain which mechanisms dominate at different stages of disease. For instance, whether metabolic abnormalities drive early disease while fibrosis and inflammation prevail in later stages remains unproven due to a lack of longitudinal clinical evidence.

3. Antidiabetic drugs and heart failure

The advent of new anti-diabetic therapies has reshaped the management of diabetes with coexisting HF, particularly with SGLT2 inhibitors and GLP-1 receptor agonists (GLP-1 RAs). These agents not only improve glycemic control but also demonstrate significant cardiovascular benefits in large-scale clinical trials. However, their mechanisms, clinical efficacy, and therapeutic roles differ substantially.

SGLT2 inhibitors were originally designed to lower blood glucose via urinary glucose excretion but have shown profound cardiovascular benefits. In the DAPA-HF trial, dapagliflozin reduced HF hospitalisation and cardiovascular mortality in patients with HFrEF, regardless of diabetes status [13]. The EMPEROR-Preserved trial further demonstrated that empagliflozin benefits patients with HFpEF, extending therapeutic efficacy across the HF spectrum [14]. Mechanistically, SGLT2 inhibitors reduce cardiac preload through natriuresis and osmotic diuresis, decrease afterload by lowering blood pressure, and improve renal hemodynamics by mitigating glomerular hyperfiltration, thereby strengthening the heart–kidney axis [15]. Additionally, they shift substrate metabolism toward ketone body utilization, providing a more efficient fuel source [16]. Preclinical studies further suggest inhibition of the myocardial Na^+/H^+ exchanger, reducing intracellular sodium–calcium overload and improving contractility [17]. Despite these benefits, uncertainties remain regarding their long-term ability to reverse structural remodeling, and ethnic variations in efficacy and safety are not well studied.

GLP-1 RAs have proven effective in reducing major atherosclerotic events (MACE) in diabetes, as shown in the LEADER and SUSTAIN-6 trials [18,19]. However, their effects on HF are heterogeneous. The EXSCEL trial showed that exenatide did not reduce HF hospitalizations [20], suggesting limited benefit in HFrEF. By contrast, the STEP-HFpEF trials demonstrated that semaglutide significantly improved exercise capacity and quality of life in obesity-related HFpEF patients [21,22]. These benefits are thought to derive from weight reduction, improved insulin sensitivity, and reduced pericardial fat and inflammation. Nevertheless, in HFrEF, GLP-1 RAs may increase heart rate and myocardial oxygen demand, offsetting potential benefits. Thus, their use must be phenotype-specific rather than generalised.

Beyond SGLT2i and GLP-1 RAs, other glucose-lowering agents display varied effects in HF. Thiazolidinediones (TZDs), such as pioglitazone, improve insulin sensitivity but cause fluid retention and increase HF risk [23]. DPP-4 inhibitors are largely cardiovascularly neutral, though

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saxagliptin has been associated with increased HF hospitalisations [24]. Insulin, though indispensable for glycemic control, can exacerbate sodium retention and sympathetic activation, potentially worsening HF outcomes [25]. These findings highlight that glucose-lowering therapy in HF requires careful drug selection, and current guidelines remain insufficiently nuanced in stratifying patients by HF risk.

4. Critical issues and public health perspective

From a social medicine perspective, the coexistence of diabetes and HF imposes a substantial healthcare and societal burden. Patients with both conditions face nearly double the healthcare costs and markedly higher readmission risks compared with those with a single disease [26]. With global aging, the prevalence of this high-risk group will continue to rise, straining health system sustainability. Also, the population-level differences add complexity. Women with diabetes are more likely to develop HFpEF, whereas men more commonly progress to HFrEF [27]. Yet, most clinical trials have not adequately stratified patients by sex or obesity, potentially underestimating risks in specific subgroups.

Furthermore, randomized controlled trials (RCTs) often enroll healthier and more adherent patients, whereas real-world populations are multimorbid and exposed to polypharmacy. Real-world data show higher discontinuation rates of SGLT2 inhibitors due to adverse effects such as urinary tract infections and dehydration [28], findings not fully captured in RCTs. These discrepancies highlight the need to contextualize trial evidence for practical application.

Critically, lots of research emphasizes average treatment effects, neglecting interindividual variability. In practice, HF phenotype (HFpEF vs. HFrEF), sex, obesity status, and renal comorbidities may substantially influence therapeutic efficacy. Future research and clinical care must emphasize precision stratification over uniform strategies.

5. Conclusion

In conclusion, the association between diabetes and heart failure represents a complex, bidirectional disease network that extends beyond a simple comorbidity. Epidemiological evidence highlights diabetes as a major risk factor for HF, while HF itself worsens insulin resistance and glycemic control. Pathophysiological studies have shown that diabetic cardiomyopathy arises through multiple mechanisms, including metabolic reprogramming, oxidative stress, AGEs–RAGE signaling, calcium dysregulation, mitochondrial dysfunction, inflammation, immune activation and autonomic imbalance. These mechanisms converge to shape distinct HF phenotypes, with HFpEF particularly prevalent in diabetes, though some patients progress to HFrEF.

Therapeutic advances have significantly altered the management landscape. SGLT2 inhibitors provide robust, consistent benefits across both HFpEF and HFrEF, establishing themselves as a cornerstone of therapy. GLP-1 receptor agonists demonstrate clear cardiovascular benefits in diabetes and obesity and show potential in obesity-related HFpEF, though results in HFrEF remain inconclusive. In contrast, older glucose-lowering drugs such as TZDs, DPP-4 inhibitors, and insulin must be used with caution given their neutral or adverse profiles in HF.

In summary, the interplay between diabetes and heart failure should be understood as a systemic interaction between metabolic and cardiovascular dysfunctions. A deeper understanding of the pathophysiological mechanisms, alongside evidence-based therapeutic strategies, is essential to improve outcomes in this high-risk population.

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References

[1] Dunlay SM, Givertz MM, Aguilar D, et al. (2019) Type 2 Diabetes Mellitus and Heart Failure: A Scientific Statement From the American Heart Association and the Heart Failure Society of America: This statement does not represent an update of the 2017 ACC/AHA/HFSA heart failure guideline update. Circulation. 140(7): e294-e324. doi: 10.1161/CIR.0000000000000691

[2] From A.M, Scott C.G, Chen H.H. (2010) The development of heart failure in patients with diabetes mellitus and pre-clinical diastolic dysfunction a population-based study. J Am Coll Cardiol. 55(4): 300-305. doi: 10.1016/j.jacc.2009.12.003

[3] Rubler S., Dlugash J., Yuceoglu Y.Z., Kumral T., Branwood A.W., Grishman A. (1972) New type of cardiomyopathy associated with diabetic glomerulosclerosis. Am J Cardiol. 30(6): 595-602.

[4] Jia G., Hill M.A., Sowers J.R. (2018) Diabetic Cardiomyopathy: An Update of Mechanisms Contributing to This Clinical Entity. Circ Res. 122(4): 624-638.

[5] Ritchie R.H., Abel E.D. (2020) Basic Mechanisms of Diabetic Heart Disease. Circ Res. 126(11): 1501-1525. doi: 10.1161/CIRCRESAHA.120.315913

[6] Boudina S., Abel E.D. (2007) Diabetic cardiomyopathy revisited. Circulation. 115(25): 3213-3223. doi: 10.1161/CIRCULATIONAHA.106.679597

[7] Yang P., Feng J., Peng Q., Liu X., Fan Z. (2019) Advanced Glycation End Products: Potential Mechanism and Therapeutic Target in Cardiovascular Complications under Diabetes. Oxid Med Cell Longev. 2019: 9570616. doi: 10.1155/2019/9570616

[8] Anderson M.E., Brown J.H., Bers D.M. (2011) CaMKII in myocardial hypertrophy and heart failure. J Mol Cell Cardiol. 51(4): 468-473. doi: 10.1016/j.yjmcc.2011.01.012

[9] Bugger H., Abel E.D. (2014) Molecular mechanisms of diabetic cardiomyopathy. Diabetologia. 57(4): 660-671. doi: 10.1007/s00125-014-3171-6

[10] Ramesh P., Yeo J.L., Brady E.M., McCann G.P. (2022) Role of inflammation in diabetic cardiomyopathy. Ther Adv Endocrinol Metab. 13: 20420188221083530.

[11] Ridker P.M., Everett B.M., Thuren T., et al. (2017) Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med. 377(12): 1119-1131.

[12] Vinik A.I., Maser R.E., Mitchell B.D., Freeman R. (2003) Diabetic autonomic neuropathy. Diabetes Care. 26(5): 1553-1579. doi: 10.2337/diacare.26.5.1553

[13] McMurray J.J.V., Solomon S.D., Inzucchi S.E., et al. (2019) Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 381(21): 1995-2008.

[14] Anker S.D., Butler J., Filippatos G., et al. (2021) Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021; 385(16): 1451-1461.

[15] Heerspink H.J.L., Stefánsson B.V., Correa-Rotter R., et al. (2020) Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 383(15): 1436-1446. doi: 10.1056/NEJMoa2024816

[16] Saucedo-Orozco H., Voorrips S.N., Yurista S.R., de Boer R.A., Westenbrink B.D. (2022) SGLT2 Inhibitors and Ketone Metabolism in Heart Failure. J Lipid Atheroscler. 11(1): 1-19.

[17] Baartscheer A., Schumacher C.A., Wüst R.C., et al. (2017) Empagliflozin decreases myocardial cytoplasmic Na+through inhibition of the cardiac Na+/H+ exchanger in rats and rabbits. Diabetologia. 60(3): 568-573. doi: 10.1007/s00125-016-4134-x

[18] Marso S.P., Daniels G.H., Brown-Frandsen K., et al. (2016) Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 375(4): 311-322. doi: 10.1056/NEJMoa1603827

[19] Marso S.P., Bain S.C., Consoli A., et al. (2016) Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 375(19): 1834-1844. doi: 10.1056/NEJMoa1607141

[20] Holman R.R., Bethel M.A., Mentz R.J., et al. (2017) Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 377(13): 1228-1239.

[21] Kosiborod M.N., Abildstrøm S.Z., Borlaug B.A., et al. (2023) Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. N Engl J Med. 389(12): 1069-1084.

[22] Kosiborod M.N., Petrie M.C., Borlaug B.A., et al. (2024) Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes. N Engl J Med. 390(15): 1394-1407.

[23] Dormandy J.A., Charbonnel B., Eckland D.J., et al. (2005) Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 366(9493): 1279-1289. doi: 10.1016/S0140-6736(05)67528-9

[24] Scirica B.M., Bhatt D.L., Braunwald E., et al. (2013) Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 369(14): 1317-1326.

DOI: 10.54254/2753-8818/2025.LD27050

[25] Eurich D.T., Majumdar S.R., McAlister F.A., Tsuyuki R.T., Johnson J.A. (2005) Improved clinical outcomes associated with metformin in patients with diabetes and heart failure. Diabetes Care. 28(10): 2345-2351. doi: 10.2337/diacare.28.10.2345
[26] Shah K.S., Xu H., Matsouaka R.A., et al. (2017) Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction: 5-Year Outcomes. J Am Coll Cardiol. 70(20): 2476-2486.
[27] Lam C.S.P., Arnott C., Beale A.L., et al. (2019) Sex differences in heart failure. Eur Heart J. 40(47): 3859-3868c. doi: 10.1093/eurheartj/ehz835
[28] Goldman A., Fishman B., Twig G., et al. (2023) The real-world safety profile of sodium-glucose co-transporter-2 inhibitors among older adults (≥ 75 years): a retrospective, pharmacovigilance study. Cardiovasc Diabetol. Jan 24, 22(1): 16.