

Diabetic Cardiomyopathy: Molecular Pathogenesis, Metabolic Remodeling, and Emerging Pharmacological Targets

Amira Sobhy Mahmoud , Heba Sabry Ahmed, Nevertyty Mohamed Mahmoud, Dalia M. Abd El Motteleb

Clinical Pharmacology Department, Faculty of Medicine - Zagazig University

Corresponding author: Amira Sobhy Mahmoud, amirasobhy034@gmail.com

ABSTRACT

Background: Diabetic cardiomyopathy (DCM) describes myocardial structural and functional abnormalities associated with diabetes that cannot be explained solely by coronary artery disease, hypertension, or valvular disease. Its biology is complex and includes altered insulin signaling, substrate inflexibility, mitochondrial dysfunction, oxidative stress, inflammation, endoplasmic reticulum stress, impaired calcium handling, autonomic imbalance, microvascular dysfunction, cell death, and progressive fibrosis. **Aim:** To integrate the principal molecular mechanisms of DCM with current and emerging pharmacological strategies capable of modifying myocardial injury and heart-failure risk. **Methods:** Mechanistic studies, experimental models, clinical investigations, outcome trials, and contemporary cardiovascular-diabetes guidance were synthesized with emphasis on AMPK/SIRT1/PGC-1 α signaling, PI3K/Akt/GLUT4, mitochondrial quality control, TGF- β /Smad, mTOR, inflammatory pathways, apoptosis, and the cardiac effects of major glucose-lowering drug classes. **Results:** DCM often begins with subclinical diastolic dysfunction and myocardial metabolic remodeling before overt systolic impairment. Insulin resistance increases fatty-acid dependence and oxygen cost, while mitochondrial ROS, advanced glycation, neurohormonal activation, and defective autophagy amplify myocardial stress. SGLT2 inhibitors have the strongest clinical evidence for reducing heart-failure events across the diabetic heart-failure spectrum, while GLP-1 receptor agonists, metformin, renin-angiotensin-aldosterone system blockade, and selected metabolic interventions may contribute through complementary mechanisms. Several experimental targets, including sirtuins, AMPK, Nrf2, TGF- β /Smad, ER stress, and regulated cell-death pathways, remain translationally attractive. **Conclusion:** DCM is best considered a multidimensional metabolic myocardial disorder requiring early detection and mechanism-informed cardio-metabolic therapy.

Keywords: Diabetic cardiomyopathy, Mitochondrial dysfunction, AMPK, Cardioprotection

INTRODUCTION

Diabetes mellitus is one of the most significant global public health challenges, characterized by rapidly increasing prevalence, substantial morbidity and mortality, and escalating healthcare costs. Despite advances in pharmacological therapies and evidence-based clinical guidelines, diabetes outcomes remain suboptimal in many populations, with marked disparities observed across socioeconomic, educational, and ethnic groups. These persistent gaps highlight the limitations of biomedical approaches alone and emphasize the need to address broader social determinants that shape disease outcomes [1].

Diabetes confers a high risk of heart failure that cannot be explained completely by atherosclerotic coronary disease or hypertension. The term diabetic cardiomyopathy was introduced to describe primary myocardial abnormalities occurring in diabetes in the absence of other dominant causes of cardiomyopathy. Modern understanding has moved away from a single lesion toward a network model in which insulin resistance, altered substrate selection, mitochondrial injury, oxidative stress, inflammation, microvascular dysfunction, fibrosis, calcium-handling abnormalities, autonomic imbalance, and cell death evolve together. The phenotype may remain subclinical for years before manifesting as heart failure with preserved or reduced ejection fraction. [1]

Aim

To review the molecular and pharmacological basis of diabetic cardiomyopathy, linking the major signaling pathways of myocardial injury with established and emerging therapeutic strategies.

Definition and Clinical Spectrum

DCM is generally defined as myocardial structural and functional impairment associated with diabetes that is not attributable to significant coronary artery disease, uncontrolled hypertension, congenital heart disease, or major valvular pathology. Early disease is often characterized by impaired relaxation, increased left-ventricular stiffness, subtle strain abnormalities, and left-atrial remodeling. Later stages may show hypertrophy, interstitial fibrosis, systolic dysfunction, and clinical heart failure. Because patients with diabetes frequently have coexisting hypertension and coronary disease, DCM is best approached as a mechanistic construct within a mixed real-world phenotype rather than as an easily isolated diagnosis. [2]

Epidemiology and Heart-Failure Risk

Diabetes is strongly associated with incident heart failure, recurrent hospitalization, and adverse prognosis. The relationship is bidirectional: heart failure itself can worsen insulin resistance through neurohormonal activation, reduced activity, inflammation, and altered skeletal-muscle metabolism. Women with diabetes may lose more of the usual sex-related protection from cardiovascular disease than men, and the burden increases with duration of diabetes, poor glycemic control, obesity, chronic kidney disease, and microvascular complications. This epidemiological pattern supports the view that myocardial injury begins before clinical heart failure and should be addressed early. [3]

Insulin Resistance and PI3K/Akt/GLUT4 Signaling

Normal myocardial insulin signaling promotes glucose uptake through insulin receptor substrate proteins, PI3K, Akt, and GLUT4 translocation. In diabetes, inhibitory phosphorylation of insulin-signaling intermediates reduces glucose transport and shifts the heart toward greater fatty-acid utilization. Although fatty acids provide substantial ATP, they require more oxygen per unit of ATP generated and promote accumulation of lipotoxic intermediates when supply exceeds oxidative capacity. Impaired Akt signaling also influences nitric oxide availability, growth pathways, and cell-survival signaling, linking metabolic insulin resistance to mechanical and vascular dysfunction. [4]

Substrate Inflexibility and Lipotoxicity

The healthy heart is metabolically flexible, switching among fatty acids, glucose, lactate, ketones, and amino acids according to workload and hormonal state. Diabetes reduces this flexibility. Increased adipose lipolysis and myocardial fatty-acid uptake drive β -oxidation, while glucose oxidation becomes relatively suppressed. Lipid intermediates such as ceramides and diacylglycerols can impair insulin signaling, activate stress kinases, disturb mitochondrial membranes, and promote apoptosis. This metabolic inflexibility increases oxygen demand and decreases energetic efficiency, so the diabetic heart becomes less capable of adapting to ischemia, pressure load, or other stress. [5]

Mitochondrial Dysfunction and Oxidative Stress

Mitochondria sit at the center of DCM because they integrate substrate oxidation, ATP production, redox signaling, calcium handling, and apoptosis. Excess delivery of fatty acids and glucose increases electron leakage and reactive oxygen species generation. Oxidative injury damages mitochondrial DNA, respiratory proteins, and membrane lipids, further decreasing oxidative phosphorylation and increasing ROS. Mitochondrial permeability transition, altered fusion-fission balance, and impaired mitophagy then allow dysfunctional mitochondria to accumulate. The result is a self-sustaining cycle of energetic inefficiency, oxidative stress, inflammation, and cardiomyocyte injury. [6]

AMPK-SIRT1-PGC-1 α -SIRT3 Axis

AMPK and sirtuins coordinate cellular responses to energetic stress. AMPK activation promotes glucose uptake, fatty-acid oxidation, autophagy, and inhibition of energetically expensive anabolic pathways. SIRT1 can activate PGC-1 α , a major regulator of mitochondrial biogenesis and oxidative metabolism, while mitochondrial SIRT3 modifies enzymes involved in respiration and antioxidant defense. Experimental DCM studies show that disruption of this network accompanies mitochondrial dysfunction, whereas restoration of AMPK-SIRT1-PGC-1 α signaling can improve energetic adaptation and reduce oxidative injury. This axis has therefore become a major pharmacological framework for interpreting metformin and several experimental cardioprotective interventions. [7]

Advanced Glycation End Products and RAGE Signaling

Persistent hyperglycemia promotes nonenzymatic glycation of proteins and formation of advanced glycation end products. Cross-linking of extracellular matrix proteins such as collagen increases myocardial stiffness and reduces compliance. Binding of AGEs to the receptor for advanced glycation end products activates oxidative and inflammatory signaling, including NF- κ B-related pathways, and contributes to endothelial dysfunction and fibrosis. AGE-related matrix changes are slow to reverse, which may partly explain why myocardial risk persists after late improvement in glucose control and why early prevention of chronic hyperglycemia remains important. [8]

Inflammation and Toll-Like Receptor Signaling

Metabolic inflammation contributes to both myocardial and vascular injury in diabetes. Free fatty acids, advanced glycation products, gut-derived signals, and damaged-cell molecules can activate innate immune receptors, including toll-like receptors, with downstream NF- κ B signaling and cytokine production. TNF- α , interleukin-6, and related mediators impair insulin signaling, alter calcium handling, activate fibroblasts, and promote cardiomyocyte apoptosis. Inflammatory pathways therefore connect systemic metabolic disease to local myocardial remodeling and represent attractive experimental targets, although broad immune suppression is not a standard treatment for DCM. [9]

Endoplasmic Reticulum Stress and CHOP

The cardiomyocyte endoplasmic reticulum regulates protein folding and calcium storage. Diabetes increases protein-folding demand and exposes cells to lipid and oxidative stress, activating the unfolded protein response. Adaptive signaling initially attempts to restore ER homeostasis, but persistent activation can induce CHOP and caspase-related apoptotic pathways. ER stress also communicates bidirectionally with mitochondrial dysfunction and inflammation. Experimental activation of AMPK and other cytoprotective pathways can suppress maladaptive ER-stress signaling, supporting the concept that organelle-to-organelle stress communication is a key feature of diabetic myocardial injury. [10]

Autophagy and mTOR Signaling

Basal autophagy removes damaged proteins and organelles and is essential for long-lived cardiomyocytes. Diabetes can disrupt this process through nutrient excess, insulin signaling abnormalities, oxidative stress, and mTOR activation. Both insufficient and excessive autophagic flux can be harmful, so the therapeutic objective is restoration of balanced quality control rather than indiscriminate stimulation. AMPK promotes autophagy partly through inhibition of mTOR and activation of autophagy-initiating proteins. Metformin-related AMPK signaling and several experimental interventions improve autophagic markers in diabetic hearts, linking energy sensing with organelle quality control. [11]

Calcium Handling and Contractile Dysfunction

Normal contraction and relaxation depend on tightly regulated calcium cycling through L-type calcium channels, ryanodine receptors, sarcoplasmic reticulum calcium ATPase, and the sodium-calcium exchanger. Diabetes alters these proteins through

oxidative modification, glycation, changes in phosphorylation, and energetic failure. Slower calcium reuptake contributes to impaired relaxation, while abnormal sarcoplasmic reticulum calcium release can promote arrhythmia and contractile instability. Because ATP is required for both calcium reuptake and myofilament cycling, mitochondrial dysfunction magnifies calcium-handling defects and links metabolic failure directly to mechanical dysfunction. [12]

Fibrosis and TGF- β /Smad Signaling

Interstitial and perivascular fibrosis are prominent structural features of DCM. Hyperglycemia, angiotensin II, aldosterone, oxidative stress, inflammatory mediators, and mechanical stress activate cardiac fibroblasts. TGF- β signaling through Smad2/3 increases extracellular matrix synthesis and suppresses matrix degradation, leading to collagen accumulation and ventricular stiffness. AMPK can oppose some TGF- β /Smad effects, while renin-angiotensin-aldosterone system blockade reduces pro-fibrotic signaling clinically. Fibrosis therefore represents both a downstream consequence of metabolic injury and a mechanism sustaining diastolic dysfunction even when glycemia later improves. [13]

Apoptosis and Regulated Cell Death

Cardiomyocyte loss occurs gradually in diabetic hearts through apoptosis and other forms of regulated cell death. Mitochondrial outer-membrane permeabilization and the balance between BAX and BCL2 influence cytochrome-c release and caspase activation. Oxidative stress, ER stress, inflammatory signaling, and impaired survival pathways converge on this machinery. More recent work also implicates ferroptosis, pyroptosis, and necroptosis in diabetic cardiac injury. The relative importance of each pathway in human DCM remains uncertain, but their convergence on mitochondrial and inflammatory biology supports multi-target rather than single-pathway therapeutic strategies. [14]

Microvascular and Endothelial Dysfunction

Diabetes damages the coronary microcirculation through endothelial insulin resistance, reduced nitric oxide bioavailability, oxidative stress, inflammation, capillary rarefaction, and basement-membrane remodeling. These changes impair coronary flow reserve and limit oxygen delivery during increased demand even in the absence of obstructive epicardial coronary disease. Microvascular dysfunction also promotes fibroblast activation and contributes to the heart-failure-with-preserved-ejection-fraction phenotype. Restoration of endothelial function is therefore an important but sometimes overlooked component of myocardial protection in diabetes. [15]

Autonomic Dysfunction

Cardiac autonomic neuropathy alters heart-rate variability, resting heart rate, exercise response, and vascular regulation. Sympathetic predominance may increase myocardial oxygen demand and arrhythmic risk, while impaired parasympathetic tone reduces adaptive reserve. Autonomic dysfunction also interacts with sleep disorders, hypoglycemia, and renal disease. Although it is often discussed separately from DCM, it can amplify hemodynamic and electrical consequences of myocardial metabolic injury and may partly explain why symptoms do not always reflect the severity of structural disease. [16]

Diagnosis and Imaging

No single test establishes DCM. The clinical approach combines exclusion or quantification of competing causes with assessment of myocardial structure and function. Echocardiography may reveal left-ventricular hypertrophy, diastolic dysfunction, increased left-atrial volume, or reduced ejection fraction. Speckle-tracking strain can identify subclinical systolic abnormalities despite preserved ejection fraction. Cardiac magnetic resonance adds tissue characterization, extracellular-volume assessment, and detection of diffuse fibrosis. Biomarkers such as natriuretic peptides and high-sensitivity troponin assist in risk assessment but are not specific for DCM. [17]

Glycemic Control and the Timing Question

Chronic hyperglycemia contributes to DCM, but intensive glucose lowering alone does not uniformly prevent heart failure, especially when initiated after years of established disease. Early good glycemic control reduces microvascular complications and may produce long-term cardiovascular benefit, yet the relationship between HbA1c and heart failure is modified by treatment choice, hypoglycemia, weight gain, kidney disease, and underlying myocardial phenotype. The pharmacological objective is therefore not simply the lowest achievable HbA1c; it is durable metabolic control using agents that do not worsen heart failure and, when possible, directly reduce cardiovascular and renal events. [18]

Metformin

Metformin improves hepatic and peripheral insulin sensitivity and influences AMPK-related signaling, mitochondrial metabolism, oxidative stress, and inflammation. Observational studies have generally supported its cardiovascular safety in stable heart failure when renal function is adequate. Experimental models of DCM show reductions in fibrosis, oxidative stress, and maladaptive mTOR signaling, although these mechanistic observations should not be interpreted as proof of a specific human

DCM indication. In contemporary practice metformin remains useful for glycemic management, but its presence is not required before initiation of drugs with established heart-failure or kidney benefit. [19]

SGLT2 Inhibitors

SGLT2 inhibitors represent the most important pharmacological advance for heart-failure prevention in diabetes. Their benefits occur rapidly and cannot be explained by glucose lowering alone. Proposed mechanisms include natriuresis, reduction in plasma and interstitial volume, improved renal hemodynamics, lower blood pressure, altered myocardial substrate use, reduced inflammation, improved endothelial function, and favorable effects on cellular sodium and calcium handling. Clinical trials consistently show reduced hospitalization for heart failure in people with T2DM, and benefits extend to patients with heart failure regardless of diabetes status. [20]

GLP-1 Receptor Agonists

GLP-1 receptor agonists reduce atherosclerotic cardiovascular events and body weight, and these effects are highly relevant to patients with diabetes at risk of myocardial disease. Their direct role in established DCM is less clear than that of SGLT2 inhibitors, but weight loss, lower blood pressure, improved glycemia, reduced inflammation, and potential endothelial benefits can lessen upstream myocardial stress. In obese patients with symptomatic HFpEF, newer evidence has strengthened the role of GLP-1-based therapy for symptom and weight reduction, making metabolic phenotype increasingly important when selecting cardiovascular diabetes treatment. [21]

Renin-Angiotensin-Aldosterone System and Mineralocorticoid Signaling

Activation of the renin-angiotensin-aldosterone system promotes vasoconstriction, sodium retention, oxidative stress, hypertrophy, inflammation, and fibrosis. ACE inhibitors and angiotensin receptor blockers remain central when hypertension, albuminuric kidney disease, or heart failure provides a conventional indication. Mineralocorticoid receptor antagonism is established in selected heart-failure populations and can reduce fibrosis-related signaling. Finerenone, a nonsteroidal mineralocorticoid receptor antagonist, has additionally demonstrated cardiovascular and renal benefit in T2DM with chronic kidney disease, illustrating how cardio-renal pharmacology can indirectly modify the milieu that drives diabetic myocardial injury. [22]

Lipid Lowering, Blood Pressure, and Multifactorial Risk Reduction

Because DCM rarely exists in isolation, myocardial protection also depends on aggressive treatment of associated cardiovascular risk. Statins reduce atherosclerotic events and thereby decrease ischemic stress superimposed on the diabetic myocardium. Blood-pressure control reduces afterload and limits hypertrophic and fibrotic remodeling. Smoking cessation, physical activity, weight reduction, and treatment of sleep apnea can improve the hemodynamic and metabolic environment. A mechanism-based DCM strategy therefore complements rather than replaces conventional cardiovascular prevention. [23]

Experimental Targets: Nrf2, Sirtuins, and Mitochondrial Quality Control

Preclinical studies have identified several targets capable of interrupting oxidative and metabolic injury. Nrf2 activation enhances antioxidant and phase-II detoxifying responses. SIRT1 and SIRT3 influence mitochondrial biogenesis, deacetylation of metabolic enzymes, and antioxidant defense. Interventions that improve mitochondrial fission-fusion balance, mitophagy, or permeability transition may preserve energetic function. These approaches are biologically coherent and often effective in animal models, but translation requires demonstration that target engagement improves meaningful human outcomes without interfering with essential cellular stress responses. [24]

Future Pharmacology and Translational Priorities

Future DCM pharmacology is likely to combine phenotyping with pathway-directed therapy. Patients dominated by obesity and HFpEF may require a different strategy from those with advanced systolic dysfunction, severe kidney disease, or predominant microvascular dysfunction. Omics-based biomarkers, cardiac imaging, and circulating markers may help identify mechanistic subgroups. The strongest research priorities are early detection, clarification of how SGLT2 and incretin therapies modify myocardial biology, development of reliable human markers of mitochondrial and fibrotic injury, and testing of targeted approaches against inflammation, ER stress, ferroptosis, and impaired autophagy. [25]

Conclusion

Diabetic cardiomyopathy develops through the interaction of metabolic inflexibility, impaired insulin signaling, mitochondrial dysfunction, oxidative and ER stress, inflammation, disturbed calcium handling, microvascular disease, cardiomyocyte loss, and fibrosis. These mechanisms explain why glucose lowering alone is insufficient once myocardial disease is established. Current management should integrate early metabolic control with therapies that improve cardiovascular and renal outcomes, particularly SGLT2 inhibitors, together with appropriate use of GLP-1-based therapy and conventional heart-failure and risk-reduction

treatment. Future progress will depend on identifying mechanistically distinct DCM phenotypes and translating promising targets such as AMPK-sirtuin signaling, mitochondrial quality control, Nrf2, TGF- β /Smad, and regulated cell-death pathways into clinically validated interventions

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