

Diabetic Cardiomyopathy: Recent Advances in Pathophysiology, Clinical Phenotypes, Diagnostic Approaches and Emerging Therapeutic Strategies: A Comprehensive Review

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DOI: <https://doi.org/10.5281/zenodo.22970377>

Received: 31 August 2026, Revised: 14 September 2026, Accepted: 22 September 2026, Online First: 25 September 2026

ABSTRACT

Diabetes mellitus is now recognized as a significant and independent contributor to myocardial disease, extending well beyond its established role in coronary artery disease. Diabetic cardiomyopathy (DCM) refers to structural and functional abnormalities of the myocardium that result from diabetes itself, diagnosed once other major causes such as significant coronary artery disease or valvular disease have been reasonably excluded. The condition typically develops gradually. Early metabolic disturbances and subclinical myocardial changes often precede diastolic dysfunction, ventricular hypertrophy, and fibrosis, and in some patients this progresses further to systolic dysfunction and overt clinical heart failure (Dillmann, 2019; Huo et al., 2023). At the cellular level, chronic hyperglycemia and insulin resistance alter how the heart utilizes metabolic substrates. This promotes glucotoxicity, lipotoxicity, mitochondrial dysfunction, oxidative stress, low-grade inflammation, abnormal calcium handling, endoplasmic reticulum stress, and eventual loss of cardiomyocytes. These changes are further compounded by the accumulation of advanced glycation end products, overactivation of the renin-angiotensin-aldosterone system, endothelial and microvascular dysfunction, cardiac autonomic neuropathy, and remodeling of the extracellular matrix, all of which add to the overall burden of myocardial injury (Jia et al., 2018; Tan et al., 2020). Advances in cardiac imaging have made it possible to detect these abnormalities at an earlier stage than was previously achievable. Strain-based echocardiography and cardiac magnetic resonance imaging can now identify myocardial dysfunction well before any measurable decline in conventional left ventricular ejection fraction occurs (Huo et al., 2023; Tadic et al., 2025). This allows for the possibility of earlier clinical intervention. As a result, the management of DCM can no longer be limited to glycemic control alone. It requires a broader approach that includes comprehensive cardiovascular risk reduction along with evidence-based heart failure therapy. Sodium-glucose cotransporter-2 inhibitors have shown clear and clinically meaningful benefit across the different phenotypes of heart failure. Glucagon-like peptide-1 receptor agonists, along with newer dual incretin-based therapies, are also gaining importance, particularly in patients with obesity-related and cardiometabolic forms of heart failure with preserved ejection fraction (American Diabetes Association Professional Practice Committee, 2026). This review outlines the biological basis, clinical progression, diagnostic approach, and current as well as emerging treatment strategies for diabetic cardiomyopathy. It also highlights the ongoing gap between the strong mechanistic and experimental evidence regarding the same.

Keywords: *Diabetic Cardiomyopathy, Diabetes Mellitus, Myocardial Fibrosis, Oxidative Stress, Mitochondrial Dysfunction, Lipotoxicity, Heart Failure, SGLT2 Inhibitors, GLP-1 Receptor Agonists*

INTRODUCTION

Diabetes mellitus is increasingly recognised as a major and independent driver of myocardial disease that extends well beyond its established association with coronary artery disease, and the term diabetic cardiomyopathy (DCM) is now used to describe myocardial structural and functional abnormalities that are attributable to diabetes in the absence of an alternative primary explanation such as significant coronary artery disease, hypertensive heart disease or valvular disease (Dillmann, 2019; Huo et al., 2023; Jia et al., 2018). The disorder usually evolves in a gradual and insidious fashion, with metabolic disturbances and subclinical myocardial abnormalities preceding the development of diastolic dysfunction, left ventricular hypertrophy and interstitial fibrosis, and, in a proportion of patients, progressing to overt systolic dysfunction and clinical heart failure (Huo et al., 2023; Tan et al., 2020; Tadic et al., 2025). At the cellular and tissue levels, chronic hyperglycaemia and insulin resistance alter myocardial substrate utilisation and promote a toxic milieu of glucotoxicity and lipotoxicity that drives mitochondrial dysfunction, oxidative stress, low-grade inflammation, abnormal calcium handling, endoplasmic-reticulum stress and cardiomyocyte death, thereby impairing myocardial energetics and contractile performance (Jia et al., 2018; Tan et al., 2020; Dillmann, 2019). These processes are further amplified by accumulation of advanced glycation end products, activation of the renin–angiotensin–aldosterone system, endothelial and microvascular dysfunction, cardiac autonomic neuropathy and maladaptive remodelling of the extracellular matrix, which together promote interstitial fibrosis, microvascular rarefaction and progressive ventricular stiffening (Jia et al., 2018; Tan et al., 2020; Huo et al., 2023). In keeping with this pathobiology, the earliest functional manifestation is usually impaired relaxation and reduced myocardial compliance, with diastolic dysfunction typically preceding any decline in conventional measures of systolic performance such as left ventricular ejection fraction, which explains why many patients remain asymptomatic until advanced stages of disease (Huo et al., 2023; Tadic et al., 2025). Modern imaging has therefore become central to early detection and phenotyping of DCM: echocardiographic speckle-tracking strain analysis can reveal subtle abnormalities in longitudinal, circumferential and radial deformation before ejection fraction falls, while multiparametric cardiac magnetic resonance including T1 mapping, late gadolinium enhancement and extracellular volume quantification provides sensitive assessment of diffuse and focal fibrosis, microvascular dysfunction and myocardial steatosis, thereby enabling identification of

at-risk individuals before the onset of overt heart failure (Huo et al., 2023; Tadic et al., 2025; Zimmermann et al., 2024). Therapeutic management of DCM accordingly extends beyond glucose lowering alone and now emphasises comprehensive cardiovascular risk reduction together with application of evidence-based heart-failure therapies that target the underlying pathophysiology (American Diabetes Association Professional Practice Committee, 2026; Huo et al., 2023). Sodium–glucose cotransporter-2 inhibitors have demonstrated clinically important benefits across the spectrum of heart-failure phenotypes, including heart failure with preserved ejection fraction, by reducing heart-failure hospitalisations, improving cardiac remodelling and exerting favourable metabolic and haemodynamic effects that are largely independent of glycaemic status (American Diabetes Association Professional Practice Committee, 2026; Huo et al., 2023; EMPEROR-Preserved and DELIVER trial investigators, 2025–2026). Glucagon-like peptide-1 receptor agonists and dual incretin therapies are increasingly relevant, particularly in patients with obesity and cardiometabolic heart failure with preserved ejection fraction, where they improve major adverse cardiovascular events, body weight, blood pressure and quality of life, and are now being considered in contemporary heart-failure guidelines for selected patients with elevated body mass index regardless of diabetes status (American Diabetes Association Professional Practice Committee, 2026; GLP-1 receptor agonist meta-analyses, 2025–2026; ESC Heart Failure Guidelines, 2026). This review summarises the biological basis, clinical evolution, diagnostic approach and current and emerging treatment strategies in diabetic cardiomyopathy, while highlighting the continuing gap between promising mechanistic findings derived from experimental models and the scarcity of disease-specific, rigorously phenotyped clinical evidence in humans (Dillmann, 2019; Huo et al., 2023; Jia et al., 2018; Tan et al., 2020; Tadic et al., 2025).

Clinical concept of diabetic cardiomyopathy

Diabetic cardiomyopathy was originally introduced to describe myocardial dysfunction occurring in diabetic patients in the absence of hypertension, significant coronary artery disease, or other recognized causes of cardiomyopathy. Contemporary literature continues to build on this idea, but it also acknowledges that in everyday clinical practice it is rarely possible to strictly exclude every cardiovascular comorbidity, since diabetes so often coexists with obesity, hypertension, chronic kidney disease, coronary microvascular dysfunction, and atherosclerosis (Jia et al., 2018; American Diabetes Association Professional Practice Committee, 2026). For

this reason, DCM is best understood as a predominantly metabolic myocardial phenotype rather than a condition that can be confirmed through any single diagnostic test. Interestingly, from a pathological standpoint, the diabetic heart may show cardiomyocyte hypertrophy, interstitial fibrosis, abnormal organelle structure, lipid accumulation, and increased apoptosis and these changes can develop well before clinical heart failure becomes apparent (Ren & Wold, 2008; Huo et al., 2023). In terms of functional progression, the disease commonly begins with impaired myocardial relaxation and increased stiffness of the ventricular wall, followed later by structural remodeling and, in more advanced stages, a decline in systolic function. This sequence, however, is not uniform across all patients, and some individuals present predominantly with a phenotype resembling heart failure with preserved ejection fraction (Dillmann, 2019; Tadic et al., 2025).

Epidemiological and Clinical Relevance

Diabetes substantially raises the risk of both cardiovascular disease and heart failure. According to current ADA guidance, heart failure occurs at least twice as often in people with diabetes compared with those without it, although the absolute level of risk varies depending on age, obesity, kidney disease, hypertension, and other contributing factors (American Diabetes Association Professional Practice Committee, 2026). The relationship between the two conditions runs in both directions: underlying metabolic disease contributes to myocardial injury, while established heart failure can, in turn, worsen insulin resistance, renal function, and overall metabolic balance. Diabetes also alters how acute coronary syndromes present and how they progress. Jain et al. (2023) found that patients with diabetes who were hospitalized with acute myocardial infarction were less likely to report classic acute chest pain and less likely to present with ST-segment elevation, while pulmonary edema, cardiogenic shock, and ventricular fibrillation or asystole occurred more frequently in this group. After adjusting for major confounding factors, diabetes remained associated with a 29% higher risk of death at 28 days and a 52% higher risk of death at one year. These findings relate mainly to diabetes-associated acute myocardial infarction rather than to diabetic cardiomyopathy in isolation, but they underscore the importance of distinguishing metabolic myocardial disease from ischemic injury, even as the two conditions frequently overlap in clinical practice.

Pathophysiology of Diabetic Cardiomyopathy:

- **Glucotoxicity and Altered Insulin Signaling:** Sustained hyperglycemia brings about substantial changes in cardiomyocyte metabolism and in the intracellular signaling pathways that govern cellular

function. In states of insulin resistance, the myocardium's ability to utilize glucose becomes impaired, while its reliance on fatty acids as an energy substrate remains disproportionately high. Excess glucose that cannot be properly metabolized is instead diverted into alternative pathways, including the polyol pathway, the hexosamine biosynthetic pathway, protein kinase C activation, and the formation of advanced glycation products, all of which contribute to heightened oxidative and inflammatory stress within the heart (Jia et al., 2018; Tan et al., 2020). Beyond its metabolic effects, insulin resistance also interferes with normal anabolic and regulatory signaling within cardiomyocytes, leading to reduced metabolic flexibility and setting the stage for maladaptive structural remodeling over time.

- **Lipotoxicity and Metabolic Inflexibility:** Under normal physiological conditions, the myocardium possesses a remarkable capacity to shift between different energy substrates, including fatty acids, glucose, lactate, and ketone bodies, depending on the body's metabolic demands. This flexibility becomes markedly disturbed in diabetes and obesity. Elevated circulating fatty acids, along with the accumulation of intracellular lipid intermediates, begin to build up within cardiomyocytes, where they interfere with mitochondrial oxidative capacity, disrupt cell membrane integrity, and disturb normal intracellular signaling. Rather than functioning as an independent process, lipotoxicity appears to act in conjunction with glucotoxicity, and together these two mechanisms amplify the production of reactive oxygen species while further promoting cardiomyocyte dysfunction and eventual cell death (Jia et al., 2018; Tan et al., 2020).
- **Mitochondrial Dysfunction:** Given the heart's continuous and substantial energy demands, mitochondria occupy a central position in the pathogenesis of the diabetic myocardial phenotype. Diabetes disrupts multiple aspects of mitochondrial physiology, including substrate selection, oxidative phosphorylation, membrane potential, organellar dynamics, and the quality-control mechanisms responsible for clearing damaged mitochondria. An excessive supply of metabolic substrates places additional strain on the electron transport chain and increases reactive oxygen species generation, while impaired mitophagy allows dysfunctional mitochondria to accumulate rather than be efficiently removed (Jia et al., 2018; Huo et al., 2023). The resulting decline in energetic efficiency compromises myocardial contractility and can further reinforce the oxidative and inflammatory signaling already present within the diabetic heart.
- **Oxidative Stress:** Oxidative stress serves as a critical intermediary linking the underlying metabolic abnormalities of diabetes to subsequent structural

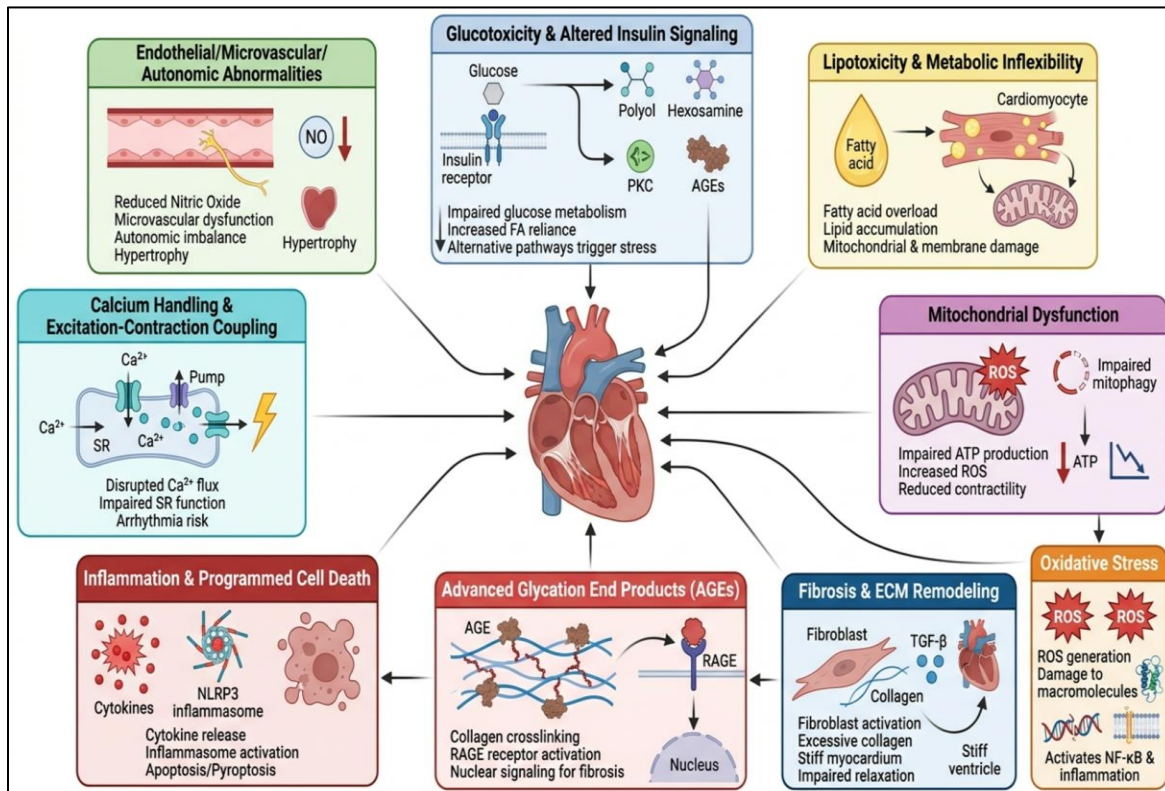
changes in the myocardium. A combination of hyperglycemia, disturbed fatty acid metabolism, mitochondrial dysfunction, and angiotensin II signaling contributes to an increased generation of reactive oxygen and nitrogen species. When present in excess, these reactive species cause damage to cellular proteins, lipids, and nucleic acids, while also activating redox-sensitive pathways that drive inflammation and fibrosis (Jia et al., 2018; Ren & Wold, 2008). More recent work has emphasized that oxidative stress should not be viewed as an isolated abnormality but rather as one component of a self-perpetuating network that also involves inflammatory signaling, mitochondrial injury, and progressive fibrotic remodeling (Hassan et al., 2026).

- **Advanced Glycation and its End Products:** Advanced glycation end products (AGEs) form through

nonenzymatic reactions between reducing sugars and proteins, lipids, or nucleic acids, and their accumulation increases progressively under conditions of chronic metabolic stress. Once formed, AGEs are capable of modifying extracellular matrix proteins, which increases tissue stiffness, and they can also alter intracellular signaling through engagement of the receptor for advanced glycation end products (RAGE). Activation of AGE-RAGE signaling has been shown to stimulate oxidative stress, promote nuclear factor- κ B-mediated inflammation, and activate profibrotic signaling cascades (Tan et al., 2020; Adem et al., 2024). This pathway offers a plausible mechanistic explanation for the increased myocardial stiffness and fibrotic change that are characteristically observed in the diabetic heart.

Figure 1: Pathophysiology of diabetes induced cardiomyopathies

Metabolic and vascular abnormalities promote lipotoxicity, mitochondrial dysfunction, oxidative stress, inflammation, impaired calcium handling, and extracellular matrix remodeling, ultimately contributing to myocardial fibrosis and cardiac dysfunction.



- **Inflammation and Programmed Cell Death:** There is growing recognition that low-grade, chronic inflammation represents an integral component of diabetic cardiomyopathy rather than a secondary or incidental finding. Hyperglycemia, lipotoxic injury, oxidative stress, and danger-associated molecular signals are all capable of activating inflammatory pathways, including nuclear factor- κ B signaling and the NLRP3 inflammasome. The cytokines and inflammasome-

related mediators generated through these pathways can, in turn, promote cardiomyocyte dysfunction, endothelial injury, and fibroblast activation (Tan et al., 2020; Huo et al., 2023). Cardiomyocyte apoptosis, along with other forms of regulated cell death, diminishes the heart's functional reserve and can facilitate ongoing pathological remodeling. Experimental research has also implicated pyroptosis, an inflammatory form of programmed cell death, in this process, although the

supporting evidence at present remains largely confined to preclinical models (Zhang et al., 2023).

- **Calcium Handling and Excitation Contraction Coupling:** Normal cardiac contraction is critically dependent on the precise regulation of intracellular calcium cycling. In diabetes, this regulation becomes disturbed at multiple levels, affecting calcium entry into the cell, calcium storage and release from the sarcoplasmic reticulum, and the subsequent reuptake of calcium following contraction. These disturbances in calcium handling are thought to contribute to impaired myocardial relaxation, reduced contractile reserve, and an increased susceptibility to arrhythmogenic electrical instability (Jia et al., 2018; Huo et al., 2023). Calcium dysregulation is also closely intertwined with mitochondrial dysfunction, given that mitochondria play a dual role in both buffering intracellular calcium and responding to fluctuations in cytosolic calcium load.
- **Endothelial, Microvascular, and Autonomic Abnormalities:** Diabetes gives rise to endothelial dysfunction and reduces the bioavailability of nitric oxide throughout the vasculature. Within the myocardium specifically, this microvascular dysfunction can impair oxygen delivery to cardiac tissue even in patients who's large epicardial coronary arteries remain free of significant obstruction. A reduction in nitric oxide-cyclic GMP signaling tends to favor a pro-inflammatory state and contributes to cardiomyocyte hypertrophy and increased cellular stiffness (Jia et al., 2018). In addition, autonomic neuropathy, a well-recognized complication of diabetes, can further disrupt normal heart rate regulation and blunt the perception of ischemic symptoms, a consideration of particular clinical relevance when diabetes coexists with underlying coronary artery disease (Jain et al., 2023).
- **Fibrosis and Extracellular Matrix Remodeling:** Fibrosis stands as one of the defining structural hallmarks of advanced diabetic cardiomyopathy. A combination of hyperglycemia, advanced glycation end products, oxidative stress, angiotensin II signaling, and

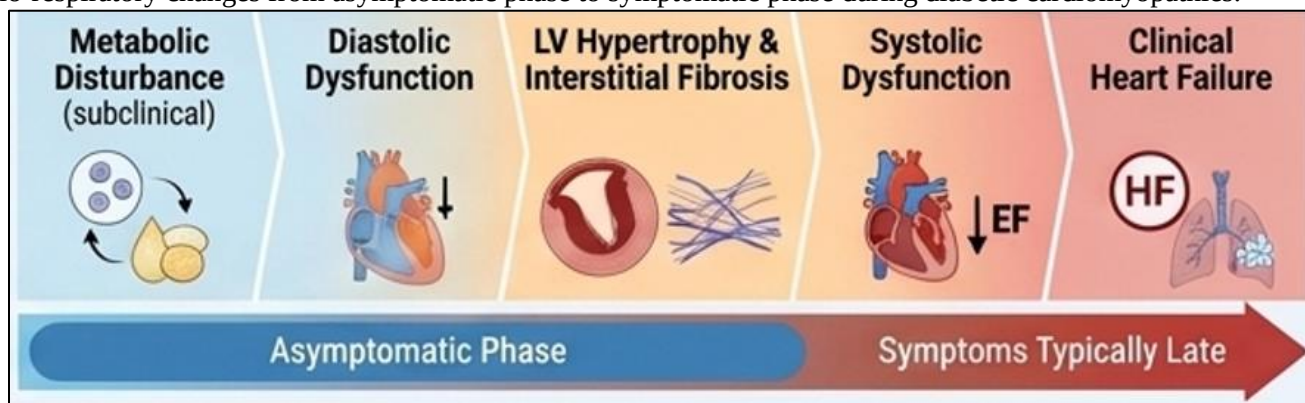
various inflammatory mediators converges to activate cardiac fibroblasts and to promote excessive deposition of extracellular matrix components. Transforming growth factor- β signaling, together with an imbalance between matrix metalloproteinases and their tissue inhibitors, has been implicated as a key driver of this fibrotic process (Huo et al., 2023; Tan et al., 2020). As interstitial fibrosis progresses, it leads to increased ventricular stiffness and disrupts the normal electrical and mechanical coupling that exists between individual cardiomyocytes, ultimately impairing both diastolic and, in more advanced disease, systolic myocardial function.

• The Structural and Functional Cardiac Phenotype

At the level of the whole organ, diabetic cardiomyopathy can present in a variety of ways, including left ventricular hypertrophy, increased myocardial stiffness, impaired ventricular relaxation, diastolic dysfunction, and, at a later stage, systolic impairment. It is important to recognize that a normal left ventricular ejection fraction does not rule out the presence of clinically significant myocardial disease. Conventional ejection fraction measurement reflects overall volumetric pump performance and can remain within the normal range even when underlying abnormalities in myocardial deformation are already present (Huo et al., 2023; Tadic et al., 2025). Diabetes-related heart failure with preserved ejection fraction (HFpEF) is of particular clinical relevance because it commonly occurs alongside obesity, hypertension, renal disease, systemic inflammation, and endothelial dysfunction. As a result, the diabetic HFpEF phenotype reflects not only direct metabolic injury to the myocardium but also the influence of a broader cardiometabolic environment (Dillmann, 2019). By contrast, some patients eventually go on to develop reduced ejection fraction, particularly in cases where myocardial fibrosis, apoptosis, ischemia, or other structural insults have become advanced (American Diabetes Association Professional Practice Committee, 2026).

Figure 2: Clinical course and structural changes

Cardio-respiratory changes from asymptomatic phase to symptomatic phase during diabetic cardiomyopathies.



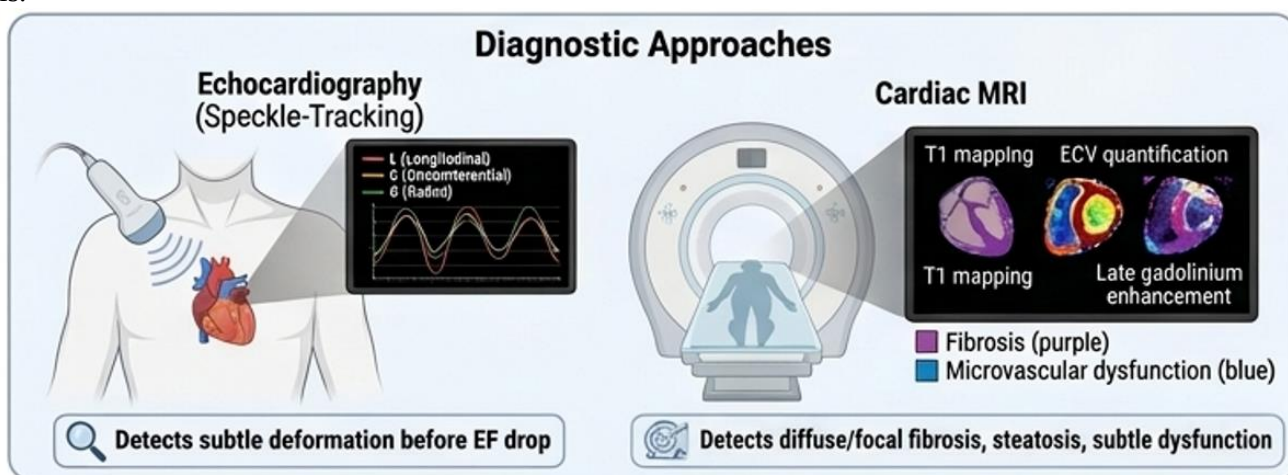
Diagnosis and Assessment

The diagnosis of diabetic cardiomyopathy continues to rely on a clinical and multimodal approach rather than a single defining test. A thorough clinical history should address the duration and degree of diabetes control, the presence of obesity, hypertension, and kidney disease, any coronary symptoms, relevant medication exposure, and the extent of functional limitation. Because diabetes frequently coexists with coronary artery disease, ischemic evaluation should be undertaken whenever clinically indicated, rather than assuming that all observed myocardial dysfunction is purely metabolic in origin (American Diabetes Association Professional Practice Committee, 2026). Echocardiography remains the most widely available and practical imaging modality for assessment. In addition to ejection fraction, evaluation of left ventricular mass, chamber geometry, diastolic function parameters, left atrial volume, and tissue Doppler indices can help identify abnormalities at an early stage. Speckle-tracking global longitudinal strain is particularly valuable in this setting, since impairment in myocardial deformation can be detected well before any measurable decline in ejection fraction becomes evident (Huo et al., 2023). Cardiac magnetic resonance imaging offers complementary diagnostic information, including detailed assessment of ventricular volumes, ventricular function, tissue characterization,

and the extent of myocardial fibrosis. Late gadolinium enhancement together with quantitative mapping techniques can assist in identifying specific patterns of myocardial injury and expansion of the extracellular volume, although these findings should always be interpreted within the broader clinical picture rather than in isolation (Tadic et al., 2025). Natriuretic peptides are useful for identifying patients who are at risk of developing heart failure or who already have established disease, although their concentrations can be influenced by coexisting obesity and kidney disease. The 2026 ADA Standards of Care recommend that screening with BNP or NT-proBNP be considered in selected asymptomatic adults with diabetes, with echocardiography advised whenever natriuretic peptide levels are found to be abnormal (American Diabetes Association Professional Practice Committee, 2026). Biomarkers such as high-sensitivity troponin can help identify ongoing myocardial injury, but at present no single circulating biomarker is sufficient to establish a diagnosis of diabetic cardiomyopathy on its own. Emerging research continues to explore the potential of microRNAs, long non-coding RNAs, extracellular vesicles, and specific metabolic signatures as candidate early biomarkers for this condition (Huo et al., 2023; Alshahrani et al., 2023).

Figure 3: Diagnostic approaches of diabetes induced cardiomyopathies

Echocardiographic and cardiac MRI induced diagnostic approaches for detecting microvascular dysfunction along with fibrosis.



Recent Therapeutic Strategies

- I. **Comprehensive Risk Factor Management:** Management of diabetic cardiomyopathy should begin with correction of the broader cardiometabolic environment rather than glucose control alone. Weight management, regular physical activity, attention to dietary quality, smoking cessation, adequate blood pressure control, lipid management,

and individualized glycemic targets all remain foundational components of care. The overarching goal is not simply to normalize blood glucose levels but to reduce the combined metabolic, vascular, and myocardial burden that drives disease progression over time (American Diabetes Association Professional Practice Committee, 2026).

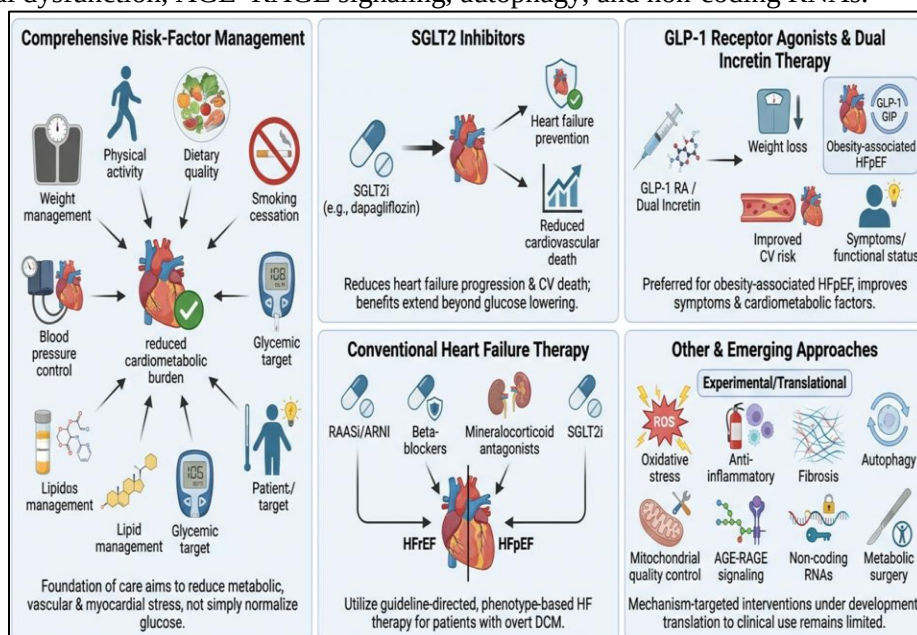
II. **The SGLT2 Inhibitors:** Sodium-glucose cotransporter-2 (SGLT2) inhibitors have become a central component of both the prevention and treatment of heart failure in people with type 2 diabetes. Their cardiovascular benefits extend well beyond their glucose-lowering effect. The 2026 ADA Standards of Care recommend the use of an SGLT2 inhibitor with demonstrated benefit in people with type 2 diabetes who have established heart failure with either preserved or reduced ejection fraction, in order to reduce the risk of worsening heart failure and cardiovascular death (American Diabetes Association Professional Practice Committee, 2026). In the DAPA-HF trial, dapagliflozin was shown to reduce the composite outcome of worsening heart failure or cardiovascular death in patients with heart failure with reduced ejection fraction, an effect that was observed in both patients with and without diabetes (McMurray et al., 2019). The consistency of this benefit regardless of diabetic status suggests that the underlying

mechanisms are not dependent solely on glycemic control.

III. **GLP-1 Receptor Agonists and Dual Incretin Therapy:** Glucagon-like peptide-1 (GLP-1) receptor agonists provide meaningful cardiovascular benefit in type 2 diabetes, particularly with respect to atherosclerotic outcomes, and they also promote weight loss while improving several cardiometabolic risk factors. Their role in established heart failure, however, appears to be more dependent on the specific heart failure phenotype than is the case with SGLT2 inhibitors. Recent evidence summarized in the 2026 ADA Standards supports the use of GLP-1 receptor agonists or dual GIP/GLP-1 receptor agonist therapy in patients with obesity and symptomatic HFpEF, with relevant clinical trials reporting improvements in both symptoms and functional status (American Diabetes Association Professional Practice Committee, 2026). These agents may therefore hold particular relevance for the obesity-associated diabetic HFpEF phenotype specifically.

Figure 4: Therapeutic Strategies of cardiac myopathies

Management combines cardiometabolic risk-factor control, SGLT2 inhibitors, GLP-1 receptor agonists/dual incretin therapy, and phenotype-guided heart-failure treatment. Emerging approaches target oxidative stress, inflammation, fibrosis, mitochondrial dysfunction, AGE–RAGE signaling, autophagy, and non-coding RNAs.



I. **Conventional Heart Failure Therapy:** When diabetic cardiomyopathy progresses to overt clinical heart failure, treatment should follow phenotype-specific heart failure guidelines rather than a separate or distinct DCM-specific regimen. For patients with diabetes who develop symptomatic heart failure with reduced ejection fraction, evidence-based therapy includes inhibition of the

renin-angiotensin system or angiotensin receptor-neprilysin inhibition where appropriate, along with beta-blockers, mineralocorticoid receptor antagonists, and SGLT2 inhibitors. The ADA emphasizes that guideline-directed heart failure therapy in people with diabetes is broadly comparable to that recommended for people without

diabetes (American Diabetes Association Professional Practice Committee, 2026).

- II. **Other and Emerging Approaches:** A number of mechanism-directed therapies remain under active investigation, including strategies that target oxidative stress, mitochondrial quality control, AGE-RAGE signaling, inflammatory pathways, fibrosis, autophagy, and non-coding RNAs. While experimental findings in this area are encouraging, translation into routine clinical practice remains limited, largely because many of these interventions have so far been evaluated predominantly in cell culture and animal models rather than in humans (Jia et al., 2018; Huo et al., 2023). Metabolic surgery may improve cardiometabolic physiology in carefully selected patients with severe obesity, and ongoing research continues to examine whether earlier intervention could prevent progression from subclinical myocardial abnormalities to overt, clinically apparent heart failure.

Future Research Directions

A number of important gaps remain in the current understanding of diabetic cardiomyopathy. First, there is still no universally accepted diagnostic biomarker or imaging criterion capable of reliably distinguishing diabetes-specific myocardial injury from the effects of coexisting hypertension, obesity, kidney disease, and coronary microvascular dysfunction. Second, a substantial proportion of the available mechanistic knowledge has been derived from animal and cell-based models, whereas human myocardial tissue remains difficult to obtain, and the heterogeneity of clinical phenotypes further complicates efforts to establish causal relationships (Sengupta et al., 2021). Third, many contemporary heart failure trials enroll broad and heterogeneous cardiometabolic populations, which makes it difficult to determine which specific interventions are responsible for reversing diabetic myocardial remodeling as opposed to addressing other coexisting conditions. Future research efforts should aim to combine longitudinal metabolic phenotyping with advanced echocardiographic strain imaging, cardiac magnetic resonance, circulating biomarkers, metabolomic analysis, and molecular profiling. Large, well-designed prospective cohort studies are needed to determine whether early changes detected through strain imaging or tissue characterization can reliably predict progression to clinical heart failure, and whether early treatment is able to modify this trajectory. Precision-based approaches that account for obesity status, renal function, glycemic phenotype, sex, duration of diabetes, and the degree of myocardial fibrosis may ultimately prove more informative than continuing to treat diabetic cardiomyopathy as a single, uniform disease entity.

Strengths of the Review

This review provides a comprehensive overview of diabetic cardiomyopathy, integrating its underlying pathophysiological mechanisms, clinical phenotypes, diagnostic approaches, and current and emerging therapeutic strategies. A major strength is the integration of metabolic, mitochondrial, inflammatory, vascular, fibrotic, and neurohormonal mechanisms to provide a multidimensional understanding of disease progression. The review also discusses contemporary diagnostic modalities, including echocardiographic strain imaging, cardiac magnetic resonance imaging, and circulating biomarkers, alongside established and emerging pharmacological approaches. In addition, the review highlights important gaps between mechanistic and experimental evidence and clinically validated evidence, thereby identifying areas requiring further investigation.

Limitations

This review has several limitations. As a narrative review, it does not follow a formal systematic review methodology and therefore may not include all available studies on diabetic cardiomyopathy. The interpretation of the available literature is also influenced by differences in study populations, disease definitions, diagnostic criteria, and clinical endpoints across published studies. Much of the mechanistic evidence discussed is derived from experimental and preclinical models, which may not be directly generalizable to human disease. Furthermore, the rapidly evolving evidence regarding newer pharmacological therapies and advanced diagnostic techniques means that some emerging findings may require further validation through large, prospective, and well-designed clinical studies.

CONCLUSION

Diabetic cardiomyopathy represents a clinically significant myocardial phenotype that arises from the complex interaction of chronic metabolic stress with oxidative, inflammatory, mitochondrial, vascular, and fibrotic pathways. Hyperglycemia and insulin resistance disturb normal substrate utilization within the myocardium, while lipotoxicity, advanced glycation end products, oxidative stress, abnormal calcium handling, endothelial dysfunction, and neurohormonal activation act together to progressively impair cardiomyocyte structure and function (Jia et al., 2018; Tan et al., 2020). The resulting disease process may remain clinically silent for many years before eventually manifesting as diastolic dysfunction, heart failure with preserved ejection fraction, or, in more advanced cases, systolic heart failure. Recognition of diabetic cardiomyopathy should therefore extend beyond reliance on ejection

fraction alone or the presence of overt symptoms. Echocardiographic strain imaging, natriuretic peptide measurement, and cardiac magnetic resonance imaging can each contribute to the earlier identification of myocardial abnormalities in appropriately selected patients. Clinical management should place emphasis on comprehensive cardiovascular risk reduction alongside contemporary, evidence-based heart failure therapy. Within the current pharmacological landscape, SGLT2 inhibitors possess the strongest disease-modifying clinical evidence, while GLP-1-based therapies continue to assume an expanding role in the management of obesity-associated cardiometabolic disease and heart failure with preserved ejection fraction (American Diabetes Association Professional Practice Committee, 2026). Ultimately, the central challenge that remains is translating an increasingly sophisticated mechanistic understanding of diabetic cardiomyopathy into earlier diagnosis and into interventions that can be demonstrated to prevent myocardial fibrosis and the eventual development of clinical heart failure. Further longitudinal studies conducted in human populations are needed to more precisely define the natural history of diabetic cardiomyopathy, to validate candidate biomarkers, and to establish whether emerging molecular therapies are truly capable of altering the underlying disease process rather than simply addressing its downstream clinical consequences.

Declarations

Ethics Approval and Consent to Participate

Not applicable. This article is a narrative review and does not involve human participants, patient data, or experimental animals.

Consent for Publication

Not applicable. No identifiable individual patient information or images are presented in this review.

Authors' Contributions

All authors contributed to the conception, literature review, interpretation of the available evidence, preparation, critical revision, and final approval of the manuscript.

Funding

The authors received no specific funding for the preparation or publication of this article.

Conflict of Interest

The authors declare that they have no conflict of interest.

Data Availability

No new datasets were generated or analyzed for this review. All information discussed is based on previously published literature cited in the manuscript.

Acknowledgements

The authors would like to acknowledge the contributions of the researchers whose work has informed the current understanding of diabetic cardiomyopathy.

AI Use Disclosure

The authors declare that no generative artificial intelligence tools were used to generate or substantially modify the scientific content of this manuscript.

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