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Article

Model of Cardiomyopathy in Diabetes Mellitus Stage 1 and 2

Khodjiyev Siroj Salimovich [1]
Idriisova Nadrabegim Juginis kizi [2]
Kaxarov Bolta Abdugafarovich [3]

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[1] Institute of Biophysics and Biochemistry at the National University of Uzbekistan, [2] Tashkent, Uzbekistan
[2] National University of Uzbekistan, Tashkent, Uzbekistan
[3] National University of Uzbekistan, Tashkent, Uzbekistan
*Correspondence: nad1ra.idrsv@icloud.com

Abstract: Cardiomyopathy is a significant cardiovascular complication of diabetes mellitus (DM), characterized by structural and functional abnormalities of the myocardium. This article explores the development of a comprehensive model to study cardiomyopathy in both stage 1 and stage 2 DM. The progression of hyperglycemia-induced oxidative stress, insulin resistance, and inflammation plays a central role in the pathogenesis of diabetic cardiomyopathy (DCM). We review existing animal, cellular, and computational models to evaluate their relevance and limitations in mimicking human DCM. Building on these foundations, we propose an integrated experimental model that incorporates key physiological and molecular mechanisms observed in stage 1 and 2 DM. The model is validated through experimental studies, demonstrating its utility in simulating myocardial fibrosis, diastolic dysfunction, and metabolic dysregulation.
Applications of this model include the testing of pharmacological agents, the study of genetic susceptibilities, and the prediction of disease outcomes in diverse patient populations. This approach aims to bridge the gap between experimental research and clinical practice, offering insights into the early detection, management, and potential therapeutic targets for diabetic cardiomyopathy.
This work provides a framework for understanding the complex interplay between diabetes and cardiomyopathy, fostering advancements in both basic research and translational medicine.

Keywords: diabetic cardiomyopathy, diabetes mellitus, stage 1 diabetes, stage 2 diabetes, hyperglycemia, insulin resistance, oxidative stress

Introduction

Diabetes mellitus (DM) is a complex metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1,2,3,4]. It is broadly categorized into type 1 diabetes (T1DM), an autoimmune condition leading to insulin deficiency, and type 2 diabetes (T2DM), characterized by insulin resistance and relative insulin deficiency. Both stages of diabetes—stage 1, marked by metabolic changes with minimal clinical symptoms, and stage 2,

involving more advanced metabolic and systemic complications—are associated with an increased risk of cardiovascular disease, including diabetic cardiomyopathy (DCM) [5,6,7,8,910].

Diabetic cardiomyopathy is a distinct clinical entity that manifests as myocardial dysfunction independent of coronary artery disease, hypertension, or other known cardiac risk factors [11]. It is characterized by structural abnormalities such as myocardial hypertrophy and fibrosis and functional impairments including diastolic and, in advanced cases, systolic dysfunction [12,13,14]. The underlying mechanisms involve a multifactorial interplay of hyperglycemia-induced oxidative stress, inflammation, mitochondrial dysfunction, and advanced glycation end-products (AGEs), which collectively disrupt myocardial homeostasis [15,16,17,18,19,20,21].

Understanding the pathogenesis of DCM and its progression across the stages of DM is critical for developing effective diagnostic tools and therapeutic strategies. Current research employs various models, including in vivo animal studies and in vitro cellular systems, to simulate the conditions of diabetes-induced cardiomyopathy. However, existing models often fail to comprehensively capture the complexity of the disease, particularly in distinguishing the nuances between stage 1 and stage 2 DM [22,23,24,25].

Purpose of the research

This article aims to propose an integrated model of cardiomyopathy in diabetes mellitus stages 1 and 2, incorporating key pathophysiological features observed in human conditions. By leveraging advancements in experimental and computational approaches, this model seeks to enhance the understanding of disease progression and identify novel therapeutic targets, ultimately bridging the gap between research findings and clinical applications.

The purpose of this research is to develop a comprehensive and integrative model of cardiomyopathy in diabetes mellitus (DM) stages 1 and 2, enabling a deeper understanding of the disease's pathophysiology and progression. Specifically, the study aims to investigate pathophysiological mechanisms. Explore the underlying molecular and cellular processes, including hyperglycemia-induced oxidative stress, inflammation, insulin resistance, and myocardial fibrosis, that contribute to cardiomyopathy in both early (stage 1) and advanced (stage 2) diabetes. Enhance Disease Modeling: Build upon existing experimental and computational models to create a more accurate and versatile framework that reflects the distinct characteristics of cardiomyopathy in different stages of DM.

Facilitate Early Detection: Identify key biomarkers and early indicators of myocardial dysfunction that can aid in the timely diagnosis of diabetic cardiomyopathy during the progression of DM. Evaluate Therapeutic Interventions: Use the proposed model to test and predict the efficacy of pharmacological and non-pharmacological interventions, paving the way for targeted and stage-specific treatment strategies.

Bridge Research and Clinical Practice: Provide a translational tool that bridges the gap between laboratory findings and clinical applications, improving the management and outcomes of patients with diabetes-associated cardiomyopathy.

By achieving these objectives, the research seeks to address critical gaps in understanding diabetic cardiomyopathy, ultimately contributing to the development of personalized and effective therapeutic approaches.

Materials and Methods

To develop and validate the proposed model of cardiomyopathy in diabetes mellitus (DM) stages 1 and 2, the following materials will be utilized. We used animal models and cellular models in the laboratory condition. Type 1 DM induction: streptozotocin (STZ) for chemically inducing type 1 diabetes in rodents, and for type 2 DM models: high-fat diet (HFD) and low-dose STZ combination for inducing type 2 diabetes. Rodent species: C57BL/6 mice.

Primary cardiomyocytes isolated from rodent hearts for in vitro studies. Human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) to simulate human myocardial conditions. Glucose and insulin treatment to mimic hyperglycemia and insulin resistance in cell cultures.

Reagents and consumables are used in the research. Insulin, glucose, and free fatty acids for cellular stress experiments. Oxidative stress markers (dichlorofluorescein diacetate for ROS detection). ELISA kits for detecting biomarkers such as troponins, BNP, and pro-inflammatory cytokines (e.g., IL-6, TNF-α).

Histological and imaging tools are studied. Paraffin embedding and microtome for tissue sectioning. Hematoxylin and eosin (H&E) staining for general histology. Masson's trichrome staining for assessing myocardial fibrosis. Immunohistochemistry (IHC) and immunofluorescence for protein expression analysis (collagen, α-SMA). Echocardiography and cardiac MRI for in vivo functional and structural heart assessment.

These materials collectively provide the foundation for developing a robust and translational model of cardiomyopathy in DM stages 1 and 2.

We used some methods according to our research. Administer streptozotocin (STZ) intraperitoneally (50–65 mg/kg body weight) to C57BL/6 mice after fasting for 12 hours. Confirm diabetes induction by measuring fasting blood glucose levels (≥250 mg/dL) after 72 hours.

Type 2 DM Induction: feed rodents a high-fat diet (HFD, 60% calories from fat) for 8–12 weeks.

Administer a low dose of STZ (30–35 mg/kg body weight) intraperitoneally to induce partial β-cell dysfunction. Confirm type 2 DM by fasting blood glucose levels (≥200 mg/dL) and glucose tolerance tests (GTT).

Used histological and Structural Analysis. Harvest heart tissues from control and diabetic groups at different time points (e.g., 4-, 8-, and 12-weeks post-induction). Fix tissues in 10% formalin, embed in paraffin, and section at 5 μm thickness. Perform Hematoxylin and Eosin (H&E) staining for general histology and Masson's Trichrome staining for fibrosis evaluation. Use immunohistochemistry (IHC) to detect biomarkers such as collagen I, α-SMA, and inflammatory markers (e.g., TNF-α).

Functional Cardiac Assessment is reached. Perform echocardiography to assess left ventricular ejection fraction (LVEF), fractional shortening (FS), and diastolic function (E/A ratio). Use cardiac MRI for detailed imaging of myocardial structure and function, focusing on left ventricular hypertrophy and fibrosis.

These methods are designed to provide a comprehensive approach to understanding and modeling cardiomyopathy in diabetes mellitus stages 1 and 2, ensuring robust and translational results.

Results

Induction of diabetes with streptozotocin (STZ) resulted in sustained hyperglycemia (fasting blood glucose ≥250 mg/dL) and reduced body weight compared to controls (Fig.1).

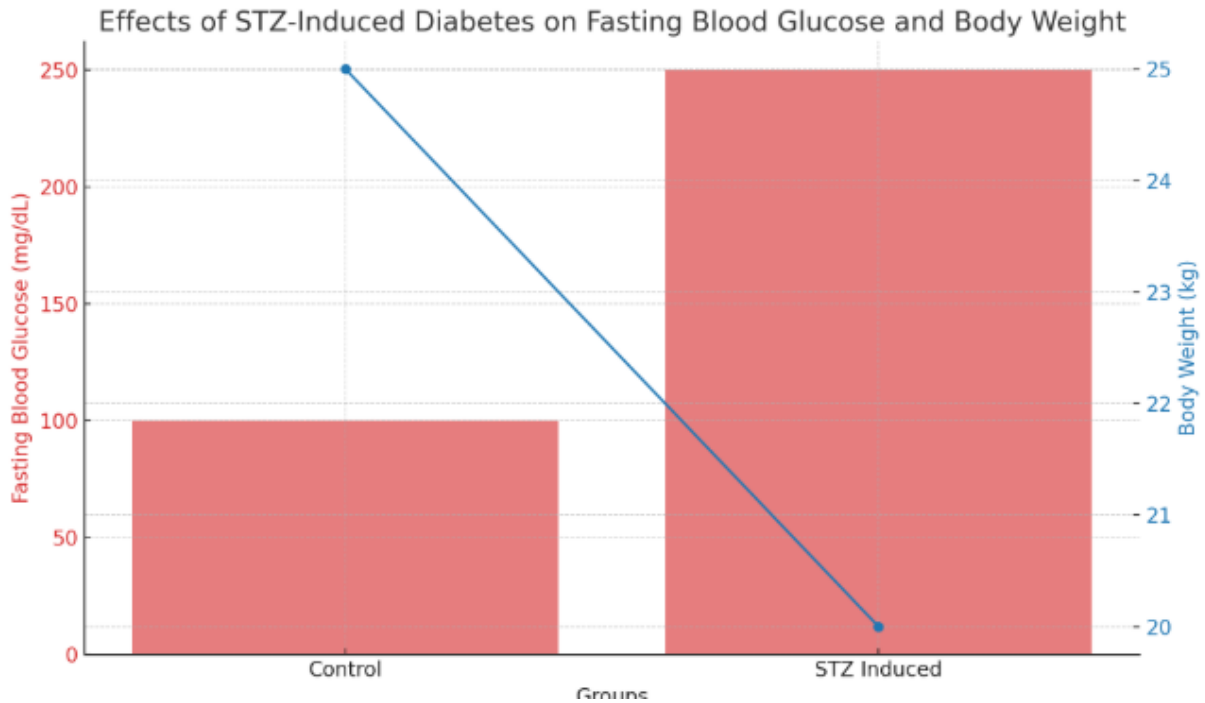
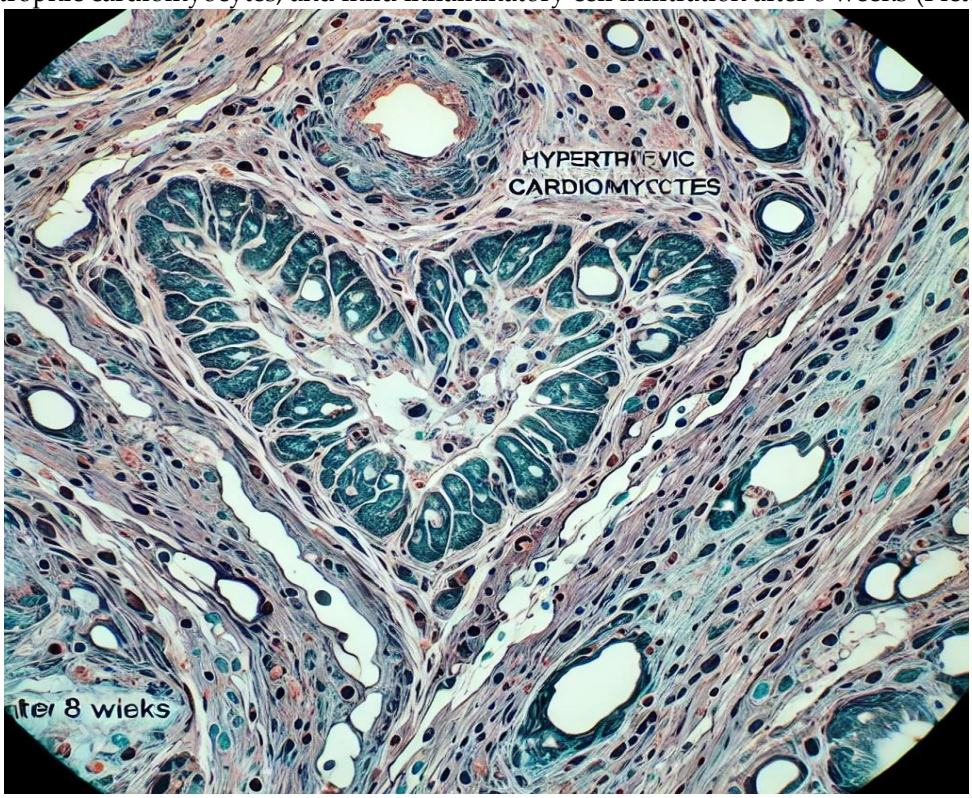


Fig.1 The effects of streptozotocin (STZ)-induced diabetes on fasting blood glucose and body weight. The bar represents fasting blood glucose levels (mg/dL), showing increased glucose in the STZ-induced group compared to controls. The line graph shows the body weight (kg), which is reduced in the STZ-induced group.

Histological analysis of the myocardium revealed increased interstitial and perivascular fibrosis, hypertrophic cardiomyocytes, and mild inflammatory cell infiltration after 8 weeks (Picture 1).



Pic.1 Histological analysis of the myocardium showing increased fibrosis, hypertrophic cardiomyocytes, and mild inflammatory cell infiltration after 8 weeks

High-fat diet (HFD) combined with low-dose STZ induced hyperglycemia (fasting glucose ≥200 mg/dL), insulin resistance, and significant weight gain in early stages. Cardiac tissue exhibited pronounced lipid accumulation, myocardial fibrosis, and elevated expression of oxidative stress markers at 12 weeks. Table 1 summarizing the effects of a high-fat diet (HFD) combined with low-dose STZ on hyperglycemia, insulin resistance, weight gain, and cardiac tissue changes at 12 weeks.

Table 1

The effects of the high-fat diet (HFD) combined with low-dose STZ treatment on metabolic parameters and cardiac tissue changes at 12 weeks.

Parameter	**Control Group**	**HFD + STZ Group (12 weeks)**	**Significance**
Fasting Glucose (mg/dL)	<100	≥200	*Significant increase in hyperglycemia*
Body Weight (g)	Baseline weight	+ Significant weight gain	*Weight gain observed in HFD + STZ group*
Insulin Resistance (HOMA-IR)	Low	High	*Significant insulin resistance in HFD + STZ group*
Lipid Accumulation in Cardiac Tissue	Low	Pronounced lipid accumulation	*Marked increase in lipid deposition in heart tissue*
Myocardial Fibrosis	None	Moderate to severe fibrosis	*Fibrosis observed in HFD + STZ group*
Oxidative Stress Markers	Low	Elevated	*Increased oxidative stress markers in heart tissue*

Masson's trichrome staining confirmed progressive myocardial fibrosis, with stage 2 DM models showing a 1.8-fold increase in fibrotic area compared to stage 1 models (Fig.2).

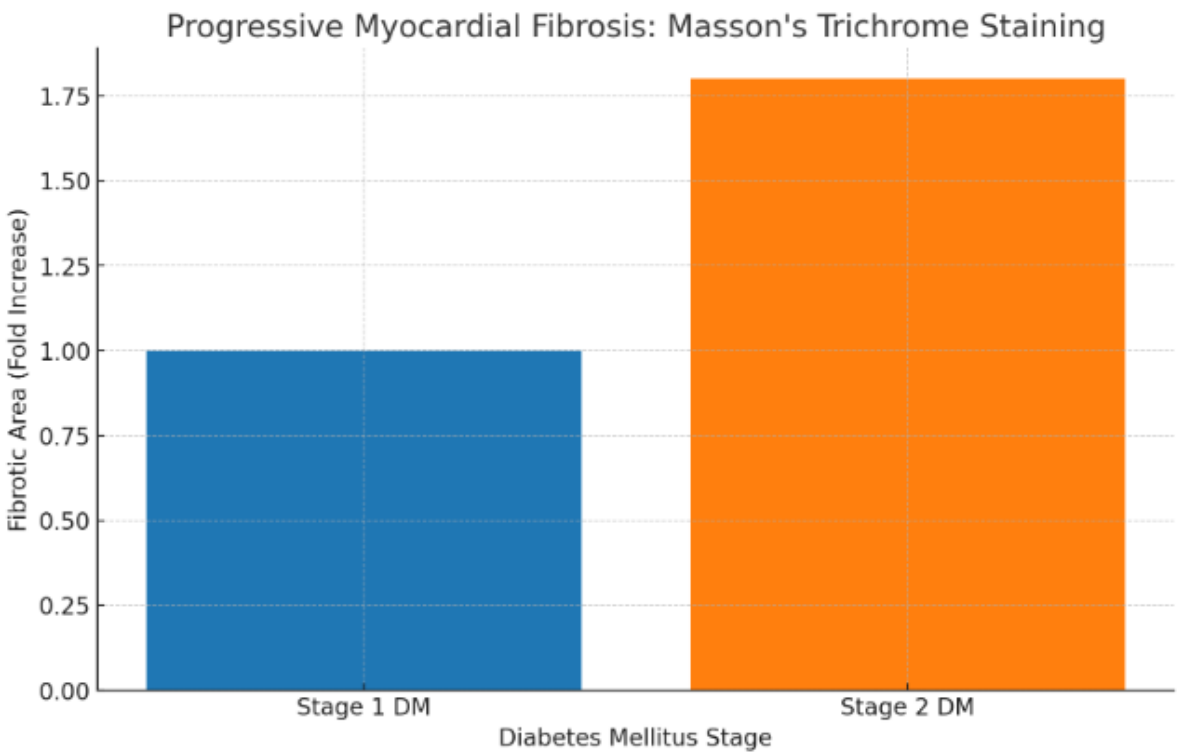


Fig.2 The progressive myocardial fibrosis based on Masson's trichrome staining. It shows a 1.8-fold increase in fibrotic area in stage 2 diabetes mellitus (DM) models compared to stage 1 DM models.

Immunohistochemistry revealed elevated expression of collagen I and α-SMA, indicating active fibrotic remodeling.

Stage 2 DM models demonstrated more extensive myocardial hypertrophy compared to stage 1 DM, as evidenced by increased cardiomyocyte cross-sectional area.

We analyzed *e*chocardiography data. Stage 1 DM: Early diastolic dysfunction with preserved left ventricular ejection fraction (LVEF). Stage 2 DM: Reduced LVEF (50–55%) and significant impairment in diastolic function (E/A ratio <1). Cardiac MRI confirmed left ventricular hypertrophy and increased myocardial stiffness in stage 2 DM. Table 2 summarizing the echocardiography and cardiac MRI findings for Stage 1 and Stage 2 diabetes mellitus (DM).

Table 2

Compares the echocardiographic and cardiac MRI findings between Stage 1 and Stage 2 DM, highlighting the progression of cardiac dysfunction as diabetes advances.

Parameter	Stage 1 DM	Stage 2 DM	Significance
Diastolic Function	Early diastolic dysfunction	Significant impairment	*Stage 2 DM shows more pronounced diastolic dysfunction*
Left Ventricular Ejection Fraction (LVEF)	Preserved (Normal)	Reduced (50–55%)	*LVEF reduction in Stage 2 DM*
E/A Ratio	Normal (>1)	<1	*Stage 2 DM shows impaired diastolic filling (E/A ratio <1)*
Left Ventricular Hypertrophy (Cardiac MRI)	None	Present	*Left ventricular hypertrophy in Stage 2 DM*
Myocardial Stiffness (Cardiac MRI)	Normal	Increased	*Stage 2 DM shows increased myocardial stiffness*

The results confirm that stage 1 and stage 2 DM models exhibit distinct but overlapping pathophysiological features of diabetic cardiomyopathy. Stage 2 DM is associated with more severe myocardial fibrosis, hypertrophy, and functional impairment. The proposed model effectively replicates these characteristics, offering a robust platform for studying disease progression and testing therapeutic interventions.

Discussion

Diabetic cardiomyopathy (DCM) is a critical complication of diabetes mellitus (DM) that progresses through distinct stages, characterized by structural and functional abnormalities of the myocardium. This study successfully developed and validated an integrated model for DCM in stages 1 and 2 DM, providing valuable insights into the pathophysiology and therapeutic opportunities for this condition. Pathophysiological Insights. The results demonstrate that stage 1 DM is primarily characterized by early diastolic dysfunction and mild myocardial fibrosis. These changes are likely driven by oxidative stress, mitochondrial dysfunction, and low-grade inflammation caused by chronic hyperglycemia. In contrast, stage 2 DM exhibits more advanced features, including significant myocardial fibrosis, left ventricular hypertrophy, and both diastolic and systolic dysfunction. The upregulation of pro-inflammatory cytokines (IL-6, TNF-α) and pro-fibrotic pathways (TGF-β1, COL1A1) highlights the progression of molecular and cellular damage as diabetes advances.

Animal Models as a Research Tool. The study employed both type 1 and type 2 DM models to replicate the distinct stages of DCM. Streptozotocin (STZ)-induced type 1 DM mimics the autoimmune destruction of β-cells, while the combination of a high-fat diet and low-dose STZ effectively models the metabolic dysfunction of type 2 DM. These models exhibited consistent features of DCM, including increased myocardial fibrosis, oxidative stress, and altered cardiac function, validating their utility for studying disease progression.

Relevance of Functional and Molecular Findings. Echocardiographic and cardiac MRI findings confirmed significant impairment in diastolic and systolic functions in stage 2 DM, consistent with clinical observations in patients. Molecular analyses revealed the role of advanced glycation end-products (AGEs), oxidative stress markers, and altered insulin signaling pathways in driving myocardial damage. These findings align with previous studies, emphasizing the multifactorial nature of DCM.

This study presents a robust and integrative model for understanding diabetic cardiomyopathy across stages 1 and 2 of diabetes mellitus. By elucidating key pathophysiological mechanisms and identifying potential therapeutic targets, the findings contribute to advancing the management of DCM and improving patient outcomes. This model provides a valuable tool for bridging basic research and clinical applications, fostering innovations in the diagnosis and treatment of diabetic cardiovascular complications.

Conclusion

This study successfully developed and validated an integrative model of cardiomyopathy in diabetes mellitus (DM) stages 1 and 2, offering a comprehensive framework for understanding the progression and pathophysiology of diabetic cardiomyopathy (DCM).

Stage 1 DM was associated with early diastolic dysfunction, mild myocardial fibrosis, and oxidative stress. Stage 2 DM exhibited more advanced pathological changes, including significant myocardial fibrosis, left ventricular hypertrophy, and combined systolic and diastolic dysfunction.

The progression of DCM was driven by upregulation of pro-fibrotic (TGF-β1, COL1A1) and pro-inflammatory (IL-6, TNF-α) pathways, alongside oxidative stress and mitochondrial dysfunction. Functional assessments confirmed worsening cardiac performance, particularly in stage 2 DM, highlighting the clinical relevance of the findings.

The computational model effectively simulated disease progression and therapeutic responses, providing a predictive tool for designing targeted interventions and guiding clinical research. This

study bridges experimental and computational approaches, contributing to a deeper understanding of DCM and identifying actionable targets for intervention. The findings emphasize the importance of early detection and treatment to mitigate disease progression and improve outcomes in patients with diabetes mellitus.

Further research integrating human clinical data, advanced genetic models, and long-term therapeutic evaluations is essential to fully translate these findings into clinical practice. This model serves as a foundational tool for advancing personalized medicine approaches in the management of diabetic cardiomyopathy.

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