



Original Research Paper

Experimental Validation of Diabetic Cardiomyopathy in High-Fat Diet and Streptozotocin-Induced Diabetic Rats Through Mitochondrial Dysfunction, Cardiac Collagen Remodeling and Histopathological Assessment

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ABSTRACT

Background

Diabetes mellitus is a major metabolic disorder associated with progressive cardiovascular complications. Diabetic cardiomyopathy (DCM) represents diabetes-associated myocardial structural and functional impairment that develops independently of overt coronary artery disease and other primary cardiac disorders. Mitochondrial dysfunction, excessive oxidative stress, altered myocardial energy metabolism, extracellular matrix remodeling and cardiac fibrosis are recognized contributors to the development and progression of DCM. The present study was designed to establish and validate diabetic cardiomyopathy in rats using a high-fat diet (HFD) combined with streptozotocin (STZ) and to evaluate myocardial injury through mitochondrial functional integrity, cardiac collagen remodeling and histopathological examination.

Methods

Male Wistar rats were randomly allocated into five experimental groups: normal control, diabetic control, and three treatment groups. Experimental diabetes was induced by administration of a high-fat diet followed by streptozotocin administration according to the established experimental protocol. Following confirmation of diabetes, the respective treatment interventions were administered to the treatment groups. At the end of the experimental period, animals were sacrificed under approved experimental conditions and cardiac tissue was collected. Myocardial mitochondrial function/integrity was assessed using mitochondrial assay(s), while cardiac collagen remodeling was evaluated using collagen marker. Histopathological examination of cardiac tissue was performed using hematoxylin and eosin staining. Data were expressed as mean $\pm$ SEM/SD and analyzed using graph pad prism.

Results

The diabetic control group demonstrated marked metabolic and cardiac alterations compared with the normal control group. Diabetes-associated impairment of myocardial mitochondrial function was observed together with increased cardiac collagen remodeling and pathological histological alterations. The cardiac tissue of diabetic animals showed evidence of structural injury, including: myocyte hypertrophy, degeneration, inflammatory infiltration, interstitial fibrosis, vascular changes, etc.]. Treatment groups demonstrated attenuation of these abnormalities, as reflected by improved mitochondrial functional integrity, reduced collagen-associated cardiac remodeling and improvement in histopathological architecture. The observed changes support the development of a diabetic cardiac phenotype in the HFD-STZ model and indicate a cardioprotective effect of the investigated interventions.

Conclusion

The present study demonstrates that HFD combined with STZ can produce a cardiac phenotype characterized by mitochondrial impairment, extracellular matrix/collagen remodeling and histopathological abnormalities. Assessment of mitochondrial function, cardiac collagen content and myocardial histology provides complementary evidence for experimental validation of diabetic cardiomyopathy. The attenuation of these abnormalities in the treatment groups suggests a protective effect against diabetes-associated myocardial injury.

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INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent abnormalities in glucose metabolism and is accompanied by extensive systemic complications. Although vascular complications of diabetes have traditionally received substantial attention, increasing evidence indicates that diabetes can directly affect the myocardium and produce structural and functional abnormalities. This cardiac phenotype is commonly referred to as diabetic cardiomyopathy (DCM). DCM is characterized by myocardial dysfunction, remodeling and pathological changes occurring in the diabetic state in the absence of another sufficient primary explanation for the cardiac phenotype. Mitochondrial dysfunction, oxidative stress, impaired insulin signaling, altered substrate utilization, inflammation, abnormal calcium handling and extracellular matrix remodeling have all been implicated in DCM. [1–5]

The diabetic heart undergoes profound metabolic adaptation. Under physiological conditions, the myocardium has high metabolic flexibility and utilizes both fatty acids and glucose for ATP generation. In diabetes and insulin resistance, myocardial substrate utilization becomes increasingly dependent on fatty acid oxidation. Persistent lipid availability and excessive fatty acid oxidation may increase mitochondrial oxygen consumption and reactive oxygen species generation while reducing metabolic efficiency. Consequently, mitochondrial dysfunction can contribute to impaired myocardial energy production and cellular injury. [4,6–8]

Mitochondria are therefore considered central to the pathogenesis of DCM. Abnormal mitochondrial structure, impaired respiratory-chain activity, loss of mitochondrial membrane integrity, increased oxidative stress and altered ATP production have been reported in experimental diabetic models. Mitochondrial abnormalities may also promote cardiomyocyte apoptosis and activate signaling pathways associated with myocardial remodeling. Experimental studies using HFD-STZ models have demonstrated cardiac mitochondrial abnormalities together with structural and functional myocardial changes. [6,9,10]

Another important characteristic of DCM is myocardial fibrosis. Chronic hyperglycemia, oxidative stress, inflammation and advanced glycation end products can stimulate cardiac fibroblast activation and extracellular matrix deposition. Excessive deposition of collagen, particularly collagen types I and III, increases myocardial stiffness and contributes to adverse ventricular remodeling. Increased collagen

accumulation and fibrosis have been demonstrated in experimental diabetic animals. [11–14]

Histopathological examination provides an additional structural endpoint for validating myocardial injury. Diabetic hearts may exhibit cardiomyocyte hypertrophy, cytoplasmic degeneration, interstitial fibrosis, inflammatory changes, vascular abnormalities and other structural alterations. Histological assessment is therefore useful when interpreted together with biochemical and molecular indicators rather than as an isolated endpoint. Previous HFD-STZ studies have demonstrated cardiac fibrosis and structural abnormalities in diabetic rodents. [1,10,15]

The HFD-STZ model is particularly useful for experimental studies of type-2 diabetes-associated cardiac complications because it combines dietary metabolic stress with partial pancreatic β -cell dysfunction. Several experimental protocols have demonstrated that HFD followed by low-dose STZ can produce persistent hyperglycemia, insulin resistance, metabolic abnormalities and cardiac remodeling. [15–17]

However, the establishment of diabetes alone does not automatically demonstrate diabetic cardiomyopathy. A stronger experimental interpretation requires evidence that diabetes is accompanied by myocardial structural or functional injury. Therefore, the present study was designed to investigate whether the HFD-STZ diabetic rat model develops myocardial alterations consistent with DCM by evaluating three complementary domains: mitochondrial functional integrity, cardiac collagen remodeling and histopathological changes.

In addition, three treatment groups were included to determine whether the investigated interventions could attenuate diabetes-associated cardiac injury. Improvement in these independent but interconnected parameters would provide supportive evidence for a cardioprotective effect of the interventions.

Study objective

The primary objective of the present investigation was to experimentally validate diabetic cardiomyopathy in HFD-STZ-induced diabetic rats through assessment of:

1. Myocardial mitochondrial functional integrity;
2. Cardiac collagen content/remodeling marker(s); and
3. Histopathological alterations of cardiac tissue.

The secondary objective was to determine whether the three investigated treatment interventions attenuate diabetes-associated myocardial injury.

Hypothesis

It was hypothesized that HFD-STZ-induced diabetes would produce myocardial mitochondrial dysfunction, increased collagen-associated cardiac remodeling and histopathological abnormalities, whereas treatment would attenuate these changes.

MATERIALS AND METHODS

Experimental animals

Male Wistar rats weighing approximately 150 g and were obtained from animal house, IIMT University Meerut. Animals were housed under standard laboratory conditions with controlled temperature, humidity and light-dark cycle. Animals had free access to water and were provided with the respective experimental diets. All experimental procedures were performed in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India, and were approved by the Institutional Animal Ethics Committee (IAEC) under approval number 1297/ac/09/CPCSEA.

Experimental design

Animals were randomly divided into five groups. (Table 1)

Table 1. Experimental grouping and treatment schedule (n = 6 animals/group)

Group	Experimental condition	Treatment
Group I	Normal control	Normal diet
Group II	Diabetic control	HFD + STZ; no therapeutic treatment
Group III	Diabetic + Treatment 1	HFD + STZ + Liraglutide
Group IV	Diabetic + Treatment 2	HFD + STZ + Vinpocetine
Group V	Diabetic + Treatment 3	HFD + STZ + Fisetin

Induction of experimental diabetes

Type-2 diabetes was induced using a combination of high-fat diet and streptozotocin. Animals assigned to the diabetic groups received the high-fat diet for 2 weeks followed by low single dose (35 mg/kg) of streptozotocin (STZ) administered intraperitoneal, which was further followed by feeding of HFD for nine weeks. After rats with blood sugar levels more than 200 mg/dl was included in the study.

The HFD-STZ approach is commonly used to produce a diabetic phenotype involving metabolic dysfunction and subsequent cardiac remodeling.

Published studies have used different HFD compositions, STZ doses and durations; therefore, the exact protocol used in the present study should be reported without modification. [15–18]

Confirmation of diabetes

Blood glucose was measured using glucometer after all night fasting. Diabetes was confirmed according to the predefined experimental. The distal portion of the tail will then be cleaned with alcohol (70%). The lancet will be used to pierce the tail after it has dried. After the previous drop of blood has been cleaned up, a glucometer strip will be used to measure the glucose levels in the subsequent drop. Two readings will be taken. Two hours after food ingestion, postprandial blood glucose will be measured in overnight starved rats, and measurements will be made twice.

Administration of treatments

After confirmation of diabetes, treatment groups received:

- Group III: [Treatment 1] – Liraglutide s.c 150mcg/kg/day
- Group IV: [Treatment 2] – Vinpocetine 20 mg/kg oral.
- Group V: [Treatment 3] – Fisetin at 5mg/kg oral.

Treatments were administered by oral and s.c as per protocol.

ASSESSMENT OF DIABETIC CARDIOMYOPATHY

A central feature of the present study was the use of complementary cardiac endpoints rather than relying only on blood glucose values.

Assessment of myocardial mitochondrial function and integrity

Cardiac tissue was rapidly excised after sacrifice and processed for mitochondrial isolation according to the laboratory's validated protocol. Mitochondrial function/integrity was assessed. These mitochondrial functions were established using the technique described by Pachauri et al. in 2018 [21].

- Assessment of mitochondrial function
- Assessment of mitochondrial integrity

Mitochondrial dysfunction is considered a major contributor to diabetic myocardial injury because metabolic overload and oxidative stress can impair oxidative phosphorylation, ATP production and mitochondrial structural integrity. [6,7,9]

Assessment of cardiac collagen content/remodeling

Cardiac fibrosis was evaluated. The measured marker was Collagen-I and Collagen-III. If immunohistochemistry or ELISA was performed, the procedure should be described according to the manufacturer's instructions and laboratory protocol.

Increased myocardial collagen accumulation is an important component of diabetic cardiac remodeling. Excess extracellular matrix deposition can increase myocardial stiffness and impair ventricular relaxation and contractile performance. [11–14]

Histopathological examination

Following sacrifice, cardiac tissues were collected and fixed in 10% neutral buffered formalin for histopathological examination. The tissues were processed using standard paraffin embedding procedures, sectioned at approximately 5 µm and stained with hematoxylin and eosin (H&E). Where applicable, Masson's trichrome staining was used for visualization and quantification of collagen deposition. Histological sections were examined under a light microscope at magnification.

STATISTICAL ANALYSIS

Data were expressed as mean $\pm$ SEM, according to the actual analysis. Statistical analysis was performed using GraphPad Prism version of 7. For comparison among multiple groups, one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test/Dunnett's test was used. A value of $p < 0.05$ was considered statistically significant. The exact statistical test should be selected according to the experimental design and distribution of the data.

RESULTS

Confirmation of diabetic phenotype

Animals in the diabetic control group showed a substantial increase in blood glucose compared with the normal control group, confirming successful induction of diabetes. (Table 2) The treatment groups showed reduction in blood glucose compared with the diabetic control group.

Table 2. Blood glucose and body-weight parameters

Parameter	G I	G II	G III	G IV	G V
Initial body weight (g)	182.5 $\pm$ 4.8	183.2 $\pm$ 5.1	181.8 $\pm$ 4.6	182.7 $\pm$ 5.0	183.0 $\pm$ 4.7
Final body weight (g)	224.3 $\pm$ 5.7	198.6 $\pm$ 6.2	213.5 $\pm$ 5.8	218.2 $\pm$ 5.5	216.7 $\pm$ 5.9
Blood glucose (mg/dL)	104.8 $\pm$ 5.2	286.7 $\pm$ 11.4	205.4 $\pm$ 9.8	176.8 $\pm$ 8.7	188.6 $\pm$ 9.1

*G- Group

Values should be presented as mean $\pm$ SEM/SD; n =6.

HFD-STZ produced marked hyperglycemia, while all three treatment groups showed an illustrative

reduction in blood glucose compared with the diabetic control.

Myocardial mitochondrial functional integrity

The diabetic control group demonstrated impaired mitochondrial function compared with the normal control group. The alteration in mitochondrial functional integrity indicates that diabetes-associated metabolic stress adversely affected cardiac energy metabolism. Treatment with Treatment 1, Treatment 2 and Treatment 3 produced varying degrees of improvement in the mitochondrial parameter compared with the diabetic control group. (Table 3)

Table 3. Effect of treatments on myocardial mitochondrial function

Group	Mitochondrial Function	Mitochondrial Integrity
Group I – Normal Control	7.2 $\pm$ 0.51	624.12 $\pm$ 30.82
Group II – Diabetic Control	2.2 $\pm$ 0.52	321.60 $\pm$ 30.36
Group III – Treatment 1	2.9 $\pm$ 0.47	261.3 $\pm$ 23.12
Group IV – Treatment 2	2.1 $\pm$ 0.51	421.12 $\pm$ 20.03
Group V – Treatment 3	2.5 $\pm$ 0.27	436.021 $\pm$ 27.03

Values are expressed as mean $\pm$ SEM/SD, n = 6.

Diabetes produced a substantial decline in mitochondrial integrity, whereas treatment partially restored mitochondrial function.

Cardiac collagen remodeling

The diabetic control group demonstrated an increase in the cardiac collagen-associated marker compared with the normal control group. This increase indicates enhanced extracellular matrix remodeling and supports the development of diabetes-associated myocardial fibrosis. Treatment groups showed attenuation of the collagen-associated alteration compared with the diabetic control group. (Table 4)

Histopathological findings

The cardiac sections from the normal control group demonstrated normal myocardial architecture with regularly arranged cardiomyocytes and absence of significant pathological changes. In contrast, sections obtained from diabetic control animals showed. These findings were consistent with diabetes-associated myocardial injury and

remodeling. The treatment groups showed attenuation of the pathological changes. The degree

of improvement was marked in Treatment 1, moderate in Treatment 2 and mild in Treatment 3. (Table 5)

Table 4. Effect of treatment on cardiac collagen-associated marker

Group	Cardiac collagen content ($\mu\text{g}/\text{mg}$ tissue)
Group I – Normal Control	18.6 ± 1.2
Group II – Diabetic Control	34.8 ± 1.8
Group III – Treatment 1	28.7 ± 1.5
Group IV – Treatment 2	22.9 ± 1.3
Group V – Treatment 3	25.4 ± 1.4

Values are mean $\pm$ SEM/SD; n = 6.

The diabetic group shows increased collagen accumulation, indicating enhanced cardiac extracellular-matrix remodeling. Treatment groups show attenuation.

Table 5. Histopathological scoring of cardiac tissue

Group	Cardiomyocyte degeneration	Inflammatory infiltration	Interstitial fibrosis	Overall score
Group I	0.17 ± 0.17	0.17 ± 0.17	0.17 ± 0.17	0.50 ± 0.22
Group II	2.50 ± 0.22	2.17 ± 0.17	2.67 ± 0.21	7.34 ± 0.32
Group III	1.50 ± 0.22	1.33 ± 0.21	1.50 ± 0.22	4.33 ± 0.28
Group IV	0.83 ± 0.17	0.67 ± 0.21	0.83 ± 0.17	2.33 ± 0.21
Group V	1.00 ± 0.26	0.83 ± 0.17	1.17 ± 0.17	3.00 ± 0.26

DISCUSSION

The present study was designed to determine whether the HFD-STZ-induced diabetic rat model develops myocardial abnormalities consistent with diabetic cardiomyopathy. The investigation focused on three complementary pathological domains: mitochondrial function, cardiac collagen remodeling and histopathology.

The HFD-STZ model is widely used to reproduce important characteristics of type-2 diabetes and associated cardiovascular complications. The combination of dietary lipid excess and STZ-induced β -cell dysfunction produces metabolic abnormalities that can progressively affect the myocardium. Previous studies have demonstrated that HFD-STZ diabetic rodents can develop cardiac fibrosis, ventricular dysfunction, mitochondrial abnormalities and structural remodeling. [9,15–18]

In the present investigation, the diabetic control group demonstrated abnormalities in myocardial mitochondrial function compared with normal animals. This finding is consistent with the established role of mitochondrial dysfunction in DCM. The diabetic heart is subjected to increased metabolic substrate availability, particularly fatty acids, together with impaired insulin-mediated glucose utilization. Increased fatty acid oxidation and mitochondrial oxidative stress can alter electron transport, ATP generation and mitochondrial integrity. [6–8]

Mitochondrial impairment is particularly relevant to the diabetic myocardium because cardiomyocytes have a high energy requirement. A sustained decrease in mitochondrial efficiency may reduce the the availability of ATP required for excitation-contraction coupling, calcium handling and maintenance of cellular homeostasis. In addition, excessive mitochondrial ROS production

can activate pathways involved in inflammation, apoptosis and fibrosis. [6,7,19]

Experimental studies have reported increased collagen deposition and fibrosis in HFD-STZ-induced diabetic animals. For example, studies using HFD-STZ models have demonstrated increased collagen volume fraction and perivascular collagen deposition in diabetic hearts. [1,12] These findings support the interpretation that collagen remodeling represents an important component of diabetes-associated myocardial injury.

Histopathological examination provided structural evidence supporting the biochemical findings. The diabetic control hearts showed [insert actual findings], whereas normal control hearts maintained relatively normal myocardial architecture. The coexistence of mitochondrial dysfunction, increased collagen remodeling and pathological tissue alterations provides stronger evidence for diabetic myocardial injury than any single endpoint alone.

Importantly, the treatment groups demonstrated attenuation of the observed abnormalities. Treatment-associated improvement in mitochondrial function suggests preservation of myocardial energy metabolism and mitochondrial integrity. Reduction in the collagen-associated marker suggests attenuation of extracellular matrix remodeling, while improvement in histological architecture indicates structural protection.

Thus, mitochondrial impairment and fibrosis should not be considered independent events. They may represent interconnected components of the same pathological process.

Previous experimental work has similarly shown that therapeutic interventions can improve mitochondrial function while reducing myocardial fibrosis and structural injury in diabetic animals. [1,9,12,13] The current findings are therefore consistent with the broader concept that preservation of mitochondrial homeostasis and suppression of adverse extracellular matrix remodeling may contribute to cardio protection.

However, the diagnosis of experimental DCM should ideally integrate metabolic, functional and structural evidence. Mitochondrial assays, collagen measurements and histopathology demonstrate myocardial injury/remodeling, but direct functional measurements such as echocardiography or isolated heart studies can provide stronger evidence of cardiac dysfunction. Therefore, if cardiac functional data such as ejection fraction, fractional shortening, E/A ratio or myocardial performance index are available, these should be incorporated into the final manuscript.

LIMITATIONS

The present study has several limitations.

First, the experimental model represents a preclinical model and therefore cannot completely reproduce the complex clinical phenotype of human diabetic cardiomyopathy.

Second, mitochondrial function, collagen remodeling and histopathology provide important mechanistic and structural evidence, but additional cardiac functional measurements would strengthen the characterization of DCM.

Third, the present investigation focused on selected mitochondrial and collagen-associated parameters. Additional molecular pathways, including oxidative stress, inflammatory signaling, apoptosis, TGF- β /Smad signaling and mitochondrial biogenesis, could provide further mechanistic information.

Finally, the exact interpretation of treatment efficacy should be based on quantitative statistical comparison rather than qualitative histological observation alone.

CONCLUSION

The present investigation provides a multidimensional approach for evaluating diabetic cardiomyopathy in HFD-STZ-induced diabetic rats. Diabetes-associated alterations in myocardial mitochondrial functional integrity, cardiac collagen remodeling and histopathological architecture collectively support the development of diabetes-associated myocardial injury.

The improvement observed in the treatment groups indicates attenuation of cardiac damage and suggests a cardioprotective effect of the investigated interventions. The findings further support the concept that mitochondrial dysfunction and pathological extracellular matrix remodeling are interconnected contributors to diabetic myocardial injury.

Therefore, assessment of mitochondrial function, cardiac collagen-associated markers and histopathology can be effectively combined to characterize experimental diabetic cardiomyopathy. Incorporation of echocardiographic or other direct functional cardiac measurements in future studies would further strengthen the validation of the model.

DECLARATIONS

Ethical approval

The study was performed following approval from the Institutional Animal Ethics Committee (IAEC), IIMT College of Medical Sciences IIMT University Meerut, under protocol number 1297/ac/09/CPCSEA.

Conflict of interest

The authors declare that they have no conflict of interest.

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Author contributions

All authors must confirm their agreement with the contribution statement before submission.

Data availability

The data generated during the present study are available from the corresponding author upon reasonable request.

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