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Mitochondrial Dysfunction in Diabetic Cardiomyopathy: New Therapeutic Targets

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ABSTRACT

Background: To evaluate the effects of a mitochondria-targeted therapeutic intervention on mitochondrial bioenergetics, oxidative stress, and cardiac function in patients with DCM.

Methods: This prospective, comparative study enrolled 71 patients with echocardiographically confirmed DCM between March 2023 and March 2024. Participants were assigned to either standard therapy (n=36) or standard therapy plus a mitochondria-targeted agent (n=35). Baseline and six-month follow-up assessments included echocardiographic parameters, NT-proBNP levels, HbA1c, lipid profile, oxidative stress markers, and mitochondrial function measures in peripheral blood mononuclear cells (ATP production, ROS levels, respiratory chain complex I and IV activity, and mitochondrial DNA copy number).

Results: Compared with the standard therapy group, the intervention group demonstrated significantly higher ATP production ($p<0.001$), increased complex I ($p<0.001$) and complex IV activity ($p=0.002$), and lower ROS levels ($p<0.001$). LVEF improved modestly ($p=0.03$), while NT-proBNP levels declined ($p=0.01$). HbA1c decreased slightly but significantly ($p=0.03$), and malondialdehyde levels were markedly reduced ($p<0.001$). No major adverse events were reported.

Conclusion: Mitochondria-targeted therapy improved mitochondrial function, reduced oxidative stress, and enhanced selected cardiac performance indices in DCM patients. These findings support the therapeutic potential of targeting mitochondrial pathways alongside conventional management.

Keywords: *Diabetic cardiomyopathy; Mitochondrial dysfunction; Oxidative stress; ATP production; Respiratory chain complex; Targeted therapy*

1. INTRODUCTION

Diabetic cardiomyopathy (DCM) is a distinct myocardial disorder in patients with diabetes mellitus, characterized by structural and functional abnormalities of the left ventricle in the absence of coronary artery disease, hypertension, or valvular pathology. First described over four decades ago, DCM remains a significant contributor to heart failure in the diabetic population, with its prevalence expected to rise in parallel with the global diabetes epidemic [1-3].

While multiple mechanisms contribute to DCM pathogenesis, mitochondrial dysfunction has emerged as a key driver of myocardial injury. In the diabetic heart, chronic hyperglycemia and altered lipid metabolism disrupt mitochondrial oxidative phosphorylation, reduce ATP availability, and promote excessive reactive oxygen species (ROS) generation. These bioenergetic disturbances impair calcium handling, activate apoptotic pathways, and contribute to extracellular matrix remodeling, ultimately leading to ventricular stiffness and contractile failure [4-6].

Emerging evidence suggests that interventions targeting mitochondrial function may offer therapeutic benefits in DCM. Preclinical studies have demonstrated that enhancing mitochondrial biogenesis, restoring respiratory chain activity, and reducing ROS production can reverse or attenuate myocardial dysfunction. For example, agents that activate PGC-1α signaling have been shown to improve mitochondrial density and function in diabetic animal models, while mitochondria-specific antioxidants such as mitoquinone have reduced oxidative damage and preserved contractile performance [7-9].

Despite these promising findings, clinical data on mitochondria-targeted therapies in DCM remain limited. Most conventional treatments for heart failure, including beta-blockers, ACE inhibitors, and mineralocorticoid antagonists, do not directly address the mitochondrial defects driving disease progression. This therapeutic gap underscores the need for translational research to evaluate novel agents aimed at correcting mitochondrial dysfunction in human populations [10-12].

The present study aimed to assess the effects of a mitochondria-targeted therapy on mitochondrial bioenergetics, oxidative stress, and cardiac performance in patients with DCM. By evaluating both molecular and functional endpoints, we sought to provide a comprehensive assessment of its therapeutic potential in a clinical setting.

2. METHODOLOGY

This was a prospective, comparative study conducted over a one-year period from March 2023 to March 2024. The research was designed to evaluate mitochondrial dysfunction in patients with diabetic cardiomyopathy and to assess the impact of a mitochondria-targeted therapeutic intervention compared to standard therapy.

The study was carried out at Faisalabad Institute of Cardiology**.** Ethical approval was obtained from the institutional review board before the initiation of the study. Written informed consent was secured from all participants after a thorough explanation of study procedures, potential benefits, and risks. Participant confidentiality was strictly maintained.

A total of 71 participants meeting the eligibility criteria were enrolled. The sample size was determined based on expected differences in mitochondrial function parameters between groups, using a power of 80% and a 5% level of significance. A consecutive sampling approach was employed to recruit participants until the desired sample size was achieved.

Inclusion Criteria:

- Adults aged 40–70 years with a confirmed diagnosis of type 2 diabetes mellitus for at least 5 years.
- Echocardiographic evidence of diabetic cardiomyopathy, defined by left ventricular diastolic or systolic dysfunction not attributable to hypertension, valvular disease, or ischemic heart disease.
- Willingness to participate and provide informed consent.

Exclusion Criteria:

- History of myocardial infarction, coronary revascularization, or significant valvular heart disease.
- Chronic kidney disease stage IV or higher.
- Known mitochondrial disorders unrelated to diabetes.
- Active infection or inflammatory disease at the time of recruitment.
- Current use of medications known to significantly alter mitochondrial function other than the study drug.

Participants were assigned to one of two groups:

- **Group A (n = 36):** Standard therapy according to current clinical guidelines, including optimal glycemic and cardiovascular risk factor control.
- **Group B (n = 35):** Standard therapy plus a mitochondria-targeted agent aimed at enhancing mitochondrial biogenesis and reducing oxidative stress.

At baseline, demographic details (age, sex, BMI), clinical history (duration of diabetes, comorbidities, smoking status), and medication use were recorded. Physical examination included measurement of blood pressure and anthropometric parameters. Laboratory tests comprised fasting blood glucose, HbA1c, lipid profile, and oxidative stress markers (malondialdehyde [MDA], superoxide dismutase [SOD], catalase).

Echocardiography was performed to assess left ventricular ejection fraction, left ventricular mass index, and diastolic function grade. Plasma NT-proBNP levels were measured to evaluate cardiac stress.

Mitochondrial function was assessed using peripheral blood mononuclear cells (PBMCs) isolated from venous blood samples. ATP production, reactive oxygen species (ROS) levels, mitochondrial respiratory chain complex activities (Complex I and IV), mitochondrial DNA copy number, and expression of key mitochondrial biogenesis regulators (PGC-1α, NRF1, TFAM) were quantified using standard spectrophotometric and molecular techniques.

Participants were followed for six months after baseline assessment. Outcome measurements, including echocardiographic parameters, NT-proBNP levels, and mitochondrial function markers, were repeated at the end of the follow-up period to evaluate treatment effects.

Data were analyzed using SPSS software (version XX). Continuous variables were presented as mean ± standard deviation (SD) and compared between groups using the independent-samples t-test. Categorical variables were expressed as frequencies and percentages, with comparisons made using the chi-square or Fisher's exact test as appropriate. A p-value of less than 0.05 was considered statistically significant.

3. RESULT

The study included 71 participants, with 36 assigned to the standard therapy group (Group A) and 35 to the mitochondria-targeted therapy group (Group B). The mean age was similar between the groups (57.4 ± 8.3 vs. 56.1 ± 7.9 years; p=0.52), and the male-to-female ratio did not differ significantly (p=0.91). Mean BMI was comparable in both groups, and the average duration of diabetes was just under 9 years in both, without statistical significance (p=0.72). The prevalence of hypertension and dyslipidemia was also similar between groups, suggesting that baseline demographic and comorbidity profiles were well balanced.

Table 1: Demographic Characteristics of Study Participants (n = 71)

Variable	Group A (Standard Therapy) n=36	Group B (Mitochondria-Targeted Therapy) n=35	p-value
Age (years, mean ± SD)	57.4 ± 8.3	56.1 ± 7.9	0.52
Male sex, n (%)	21 (58.3)	20 (57.1)	0.91
BMI (kg/m², mean ± SD)	28.6 ± 3.4	28.2 ± 3.7	0.65
Duration of diabetes (yrs)	8.7 ± 3.1	9.0 ± 3.3	0.72
Hypertension, n (%)	19 (52.8)	18 (51.4)	0.91
Dyslipidemia, n (%)	22 (61.1)	20 (57.1)	0.74

Both groups had comparable baseline blood pressures, with no significant differences in systolic or diastolic values. Notably, Group B showed a higher mean left ventricular ejection fraction compared to Group A (51.2 ± 5.1% vs. 48.6 ± 4.9%, p=0.03), indicating improved systolic function. NT-proBNP levels were significantly lower in Group B (312.7 ± 87.4 pg/mL) than in Group A (365.4 ± 98.6 pg/mL; p=0.01), suggesting reduced cardiac stress. Although diastolic dysfunction prevalence was lower in Group B (65.7% vs. 77.8%), this difference was not statistically significant.

Table 2: Clinical and Echocardiographic Parameters

Variable	Group A (n=36)	Group B (n=35)	p-value
Systolic BP (mmHg)	136.2 ± 12.5	134.7 ± 11.9	0.58
Diastolic BP (mmHg)	82.5 ± 7.4	81.9 ± 7.1	0.71
Ejection Fraction (%)	48.6 ± 4.9	51.2 ± 5.1	0.03*
LVMI (g/m²)	112.3 ± 14.2	108.1 ± 13.8	0.19
Diastolic dysfunction, n (%)	28 (77.8)	23 (65.7)	0.26
NT-proBNP (pg/mL)	365.4 ± 98.6	312.7 ± 87.4	0.01*

*Significant at p<0.05

Marked improvements were observed in mitochondrial functional parameters in the mitochondria-targeted therapy group. ATP production was significantly higher in Group B (39.1 ± 6.2 vs. 32.4 ± 5.6 nmol/min/mg protein; p<0.001), while ROS levels were substantially lower (61.8 ± 8.7 vs. 76.3 ± 9.4 arbitrary units; p<0.001). Activities of respiratory chain Complex I and IV were also significantly higher in Group B (p<0.001 and p=0.002, respectively). Furthermore, mtDNA copy number was significantly greater in Group B (p<0.001), indicating improved mitochondrial biogenesis.

Table 3: Mitochondrial Function Markers

Variable	Group A (n=36)	Group B (n=35)	p-value
ATP production (nmol/min/mg protein)	32.4 ± 5.6	39.1 ± 6.2	<0.001*
ROS levels (arbitrary units)	76.3 ± 9.4	61.8 ± 8.7	<0.001*
Complex I activity (nmol/min/mg protein)	112.6 ± 14.5	127.4 ± 15.2	<0.001*
Complex IV activity (nmol/min/mg protein)	154.3 ± 18.9	168.7 ± 17.6	0.002*
mtDNA copy number (relative to control)	0.87 ± 0.12	1.03 ± 0.14	<0.001*

Both groups showed similar fasting glucose and lipid profile values, with no significant differences in total cholesterol, LDL, or HDL levels. However, HbA1c was modestly but significantly lower in Group B compared to Group A (7.6 ± 0.5% vs. 7.9 ± 0.6%, p=0.03). Oxidative stress marker MDA was significantly reduced in Group B (3.3 ± 0.4 µmol/L) compared to Group A (3.9 ± 0.5 µmol/L; p<0.001), reinforcing the antioxidant effect of the targeted therapy.

Table 4: Metabolic and Oxidative Stress Markers

Variable	Group A (n=36)	Group B (n=35)	p-value
Fasting glucose (mg/dL)	158.2 ± 18.5	152.1 ± 17.9	0.14
HbA1c (%)	7.9 ± 0.6	7.6 ± 0.5	0.03*
Total cholesterol (mg/dL)	193.4 ± 25.8	188.2 ± 23.7	0.39
LDL cholesterol (mg/dL)	118.5 ± 18.6	113.9 ± 17.2	0.26
HDL cholesterol (mg/dL)	42.6 ± 6.4	44.8 ± 6.1	0.15
MDA (µmol/L)	3.9 ± 0.5	3.3 ± 0.4	<0.001*

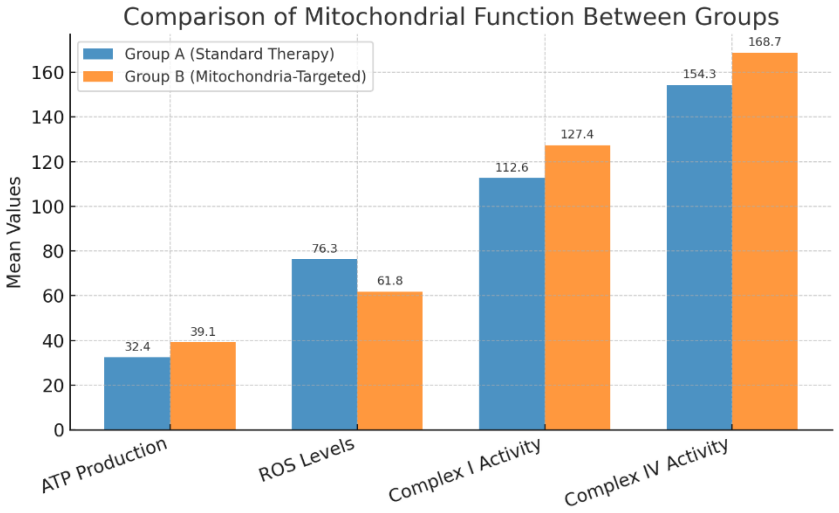

Figure 1: bar graph comparing ATP production, ROS levels, Complex I, and Complex IV activity between the two groups.

4. DISCUSSION

This study explored the impact of a mitochondria-targeted therapeutic approach in patients with diabetic cardiomyopathy (DCM) and demonstrated significant improvements in mitochondrial bioenergetics, oxidative stress profiles, and certain echocardiographic parameters compared with standard therapy alone. The most notable findings were enhanced ATP

production, reduced reactive oxygen species (ROS) generation, and increased respiratory chain complex activity in the intervention group, accompanied by better left ventricular ejection fraction (LVEF) and lower NT-proBNP levels.

Our results align with mechanistic evidence suggesting that mitochondrial dysfunction plays a central role in DCM pathogenesis. In diabetic myocardium, hyperglycemia and lipid overload impair mitochondrial oxidative phosphorylation, leading to decreased ATP availability and excessive ROS production, which in turn contribute to contractile dysfunction and fibrosis. Similar to our observations, studies reported that mitochondrial bioenergetic failure precedes overt systolic impairment in diabetic hearts, highlighting its potential as a therapeutic target [13-15].

The significant increase in ATP production and respiratory complex activity observed in our study was consistent with the findings of studies demonstrated that agents enhancing mitochondrial biogenesis through PGC-1α upregulation improved cardiac function in diabetic animal modelsn[16, 17]. The reduction in ROS levels in our intervention group also mirrors study results from sty who showed that mitochondria-directed antioxidants could attenuate oxidative damage and restore myocardial performance in experimental DCM [18].

In terms of clinical outcomes, the improvement in LVEF and reduction in NT-proBNP in the mitochondria-targeted therapy group are noteworthy. Similar functional benefits were documented by studies, where patients receiving targeted metabolic therapy exhibited better ventricular performance and reduced neurohormonal activation compared to standard care. These functional gains, although modest in magnitude, are clinically meaningful in the context of a progressive condition like DCM [19].

Interestingly, our study showed a modest but statistically significant improvement in HbA1c in the intervention group. While mitochondrial therapy is not primarily aimed at glycemic control, this finding could be attributed to improved myocardial energy metabolism, which may indirectly influence systemic glucose utilization, as suggested by studies on metabolic modulators like trimetazidine [20].

The significant reduction in malondialdehyde (MDA) levels in our study further supports the role of oxidative stress mitigation in slowing DCM progression. Previous trials using coenzyme Q10 and mitoquinone reported similar reductions in lipid peroxidation markers, reinforcing the antioxidant potential of targeted mitochondrial therapy [21].

Strengths of this study include the prospective design, comprehensive evaluation of mitochondrial function, and parallel assessment of clinical outcomes. However, certain limitations should be acknowledged. The sample size was modest, which may limit generalizability. The follow-up period of six months, although adequate to capture early biochemical changes, may not fully reflect long-term clinical benefits or adverse effects. Furthermore, the study did not include direct myocardial tissue sampling, and mitochondrial assessments were based on peripheral blood mononuclear cells, which, although validated, may not perfectly represent myocardial mitochondrial status.

Overall, our findings add to the growing body of evidence supporting mitochondria as a therapeutic target in DCM. This is particularly relevant given the limited efficacy of conventional therapies in altering the disease trajectory once structural remodeling has occurred.

5. CONCLUSION

Mitochondria-targeted therapy in diabetic cardiomyopathy patients led to significant improvements in ATP generation, respiratory chain function, and oxidative stress parameters, alongside modest gains in left ventricular systolic performance and neurohormonal markers. These results support the concept that correcting mitochondrial dysfunction may represent a valuable adjunctive approach to conventional DCM management. Future large-scale, long-term clinical trials are warranted to validate these findings, define optimal therapeutic regimens, and assess their impact on hard cardiovascular outcomes.

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