

Dapagliflozin-Induced Cardioprotection in Diabetic Cardiomyopathy Correlates with HMGB1-RAGE Axis Suppression

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ABSTRACT

Background: Diabetic Cardiomyopathy (DCM) is a clinically important cardiac complication of Type 2 Diabetes Mellitus (T2DM). Its progression is closely related not only to chronic hyperglycemia and metabolic overload, but also to sustained inflammatory activation. Among the candidate inflammatory pathways, the High Mobility Group Box 1 Protein (HMGB1)-Receptor for Advanced Glycation End products (RAGE) axis has attracted attention because it can connect tissue injury, innate immune signaling, and adverse myocardial remodeling. **Objectives:** To examine whether dapagliflozin can improve myocardial function in patients with T2DM complicated by DCM and to explore whether the benefits are associated with downregulation of circulating HMGB1 and RAGE. **Materials and Methods:** Eighty patients with T2DM-associated DCM who were admitted to the Department of Endocrinology of Zhuhai Hospital of Integrated Traditional Chinese and Western Medicine between July 2023 and July 2024 were randomly assigned to a control group or an observation group, with 40 cases in each arm. All participants received conventional management. The control group was treated with metformin sustained-release tablets, whereas the observation group received dapagliflozin in addition to metformin. The intervention period was 6 months. Fasting Blood Glucose (FBG), 2-hr Postprandial Blood Glucose (2hPBG), Glycated Hemoglobin (*HbA1C*), serum HMGB1, serum RAGE, and the myocardial performance index (Tei index) were assessed before treatment and again at 3 and 6 months. **Results:** Baseline characteristics were comparable between the two groups. After treatment, both regimens were associated with lower FBG, 2hPBG, *HbA1C*, HMGB1, RAGE, and Tei index compared with pretreatment levels. However, the decreases in glycemic variables and inflammatory markers were greater in the dapagliflozin group than in the metformin-alone group at both follow-up points (all $p < 0.05$). Tei index improved in both groups, and the between-group difference became significant by month 6, favoring combination therapy ($p < 0.05$). **Conclusion:** For patients with T2DM complicated by DCM, dapagliflozin added to standard glucose-lowering therapy may confer additional cardiac benefit. Its favorable effect appears to occur together with better metabolic control and lower circulating HMGB1 and RAGE levels, suggesting that the improvement of myocardial function is possibly related to the suppression of HMGB1-RAGE-mediated inflammation.

Keywords: Dapagliflozin, Diabetic Cardiomyopathy, HMGB1, *HbA1C*, RAGE.

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INTRODUCTION

Diabetes mellitus has become one of the most consequential chronic diseases worldwide, and the burden created by T2DM continues to rise in both developed and developing regions.¹ The clinical challenge of diabetes lies not only in disordered glucose metabolism itself but also in the cumulative vascular and

organ injury that develops over time. Among diabetes-related complications, cardiovascular disease remains a leading determinant of hospitalization, disability, and mortality.² Although coronary atherosclerosis and hypertension are widely recognized contributors to adverse cardiovascular outcomes in diabetes, there is increasing awareness that the diabetic heart may undergo direct structural and functional injury even in the absence of overt ischemic or valvular disease. This entity, often termed diabetic cardiomyopathy, represents a distinct myocardial phenotype associated with long-standing metabolic disturbance.³

The clinical course of DCM is often gradual and deceptive. In its early phase, left ventricular ejection fraction may remain preserved, symptoms can be absent or nonspecific, and



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conventional examinations may not fully capture the evolving myocardial injury.⁴ Nevertheless, the myocardium may already be experiencing impaired relaxation, reduced compliance, diffuse interstitial remodeling, and subtle abnormalities in global pump efficiency. If these early changes are not recognized, the disease can progress from subclinical diastolic dysfunction to combined systolic-diastolic impairment and, ultimately, symptomatic heart failure.⁵ This progression explains why early identification of biologically meaningful and functionally sensitive markers is important when evaluating patients with T2DM who are at risk for cardiac involvement.

From a pathophysiological standpoint, DCM should not be viewed as the consequence of a single insult. Rather, it is better understood as the cumulative result of persistent glucotoxicity, lipotoxicity, insulin resistance, oxidative stress, mitochondrial dysfunction, microvascular injury, altered calcium handling, autonomic imbalance, and maladaptive extracellular matrix deposition.⁶ These processes interact with one another. Metabolic overload can impair cellular energetics; mitochondrial dysfunction can amplify reactive oxygen species; oxidative stress can intensify inflammatory signaling; and chronic inflammation can in turn accelerate fibrosis and mechanical dysfunction. The result is a heart that gradually loses metabolic flexibility and becomes less able to adapt to hemodynamic demand.

Inflammation occupies a central position in this network. In the diabetic state, cardiomyocytes, endothelial cells, infiltrating immune cells, and fibroblasts are all exposed to a biochemical environment characterized by advanced glycation end products, free fatty acid excess, and repeated oxidative stress. Under such conditions, endogenous danger signals are more likely to be generated and released into the extracellular space. One of the best known of these signals is HMGB1, a non-histone nuclear protein that normally participates in chromatin organization and transcriptional regulation but acquires a proinflammatory role after extracellular release.⁷ Once outside the cell, HMGB1 can interact with pattern-recognition receptors, including RAGE, thereby promoting downstream inflammatory cascades that favor cytokine release, cell injury, and tissue remodeling.⁸

The HMGB1-RAGE pathway is of particular interest in DCM because it conceptually links the metabolic milieu of diabetes to persistent myocardial inflammation. RAGE is highly relevant in diabetes for two reasons. First, it is a receptor for advanced glycation end products, which accumulate during chronic hyperglycemia. Second, once activated by ligands such as HMGB1, it can amplify intracellular signaling through pathways related to nuclear factor-kappa B, mitogen-activated protein kinases, and oxidative stress.⁹ These downstream events are compatible with endothelial dysfunction, cardiomyocyte hypertrophy, extracellular matrix remodeling, and amplification of inflammatory tone in the diabetic heart.¹⁰ Accordingly, circulating HMGB1 and RAGE

are not only mechanistically interesting molecules but also potentially informative biomarkers reflecting the intensity of inflammation-associated myocardial stress.

Because DCM is often clinically silent in the early stage, echocardiographic tools that capture integrated ventricular performance are valuable. The Tei index, also known as the myocardial performance index, combines isovolumic contraction time, isovolumic relaxation time, and ejection time into a single parameter.¹¹ Rather than focusing on a single dimension of cardiac function, it offers a composite view of global ventricular performance and may reveal abnormality before overt reduction in ejection fraction appears. For studies of early diabetic myocardial injury, this index has practical appeal because it can reflect changes in both systolic and diastolic efficiency and can be repeatedly assessed during follow-up without major burden to the patient.^{4,12}

Dapagliflozin is a representative SGLT2 inhibitor and is widely used for the treatment of T2DM. Although it was first introduced as an antihyperglycemic agent that lowers blood glucose by reducing renal glucose reabsorption, subsequent work has shown that its benefit extends beyond glycemic control.^{8,13} Large clinical trials and mechanistic studies have suggested favorable effects on heart failure events, blood pressure, body weight, renal hemodynamics, oxidative stress, and inflammatory burden. This expanded therapeutic profile raises a clinically important question: in patients who already show evidence of DCM, could dapagliflozin improve myocardial performance through mechanisms that are not limited to glucose lowering alone?

At present, the anti-inflammatory dimension of dapagliflozin in human DCM remains insufficiently clarified. Many experimental reports emphasize pathways involving oxidative stress, NLRP3 inflammasome activity, mitochondrial preservation, and autophagy regulation, but fewer clinical observations directly relate dapagliflozin treatment to changes in HMGB1-RAGE signaling in patients with diabetic myocardial dysfunction.¹⁴⁻¹⁶ Clarifying this relationship has practical significance. If improvement in myocardial performance occurs together with a reduction in HMGB1 and RAGE, it would support the view that the cardioprotective effect of dapagliflozin is partly mediated through dampening of inflammation-related injury. On this basis, the present study compared metformin alone with metformin plus dapagliflozin in patients with T2DM complicated by DCM and examined changes in glycemic indices, circulating HMGB1 and RAGE, and Tei index over a 6-month treatment period.

OBJECTIVES

This study aimed to compare metformin alone with metformin plus dapagliflozin in patients with T2DM complicated by DCM and to determine whether improvement in cardiac status was accompanied by changes in circulating HMGB1 and RAGE.

MATERIALS AND METHODS

Study Design and Participants

This was a randomized comparative clinical study conducted in the Department of Endocrinology of Zhuhai Hospital of Integrated Traditional Chinese and Western Medicine. Eighty hospitalized patients with T2DM complicated by DCM were consecutively screened and enrolled from July 2023 to July 2024. The study protocol was reviewed and approved by the hospital ethics committee, and all participants provided written informed consent before study entry. Eligible participants were adults aged 18 years or older who fulfilled World Health Organization diagnostic criteria for T2DM and met the clinical definition of diabetic cardiomyopathy, which was defined as: patients with type 2 diabetes mellitus, Left Ventricular Ejection Fraction (LVEF) > 50% detected by echocardiography, combined with left ventricular diastolic dysfunction. Diastolic dysfunction was judged by echocardiographic indicators including E/e' ratio, tissue Doppler e' velocity and left atrial volume index. Patients with coronary artery disease were excluded by combining medical history, electrocardiogram, cardiac color Doppler ultrasound and coronary angiography when necessary; patients with primary cardiomyopathy and severe valvular heart disease were excluded according to echocardiographic results and clinical manifestations. *HbA1C* at enrollment ranged from 7% to 12%. Exclusion criteria were designed to avoid major confounders and included allergy to the study drugs, diabetic ketoacidosis or other serious acid-base disorders, established coronary artery disease, primary cardiomyopathy, significant valvular heart disease, severe dysfunction of the heart, liver, kidney, or lung, recent major surgery, severe infection or trauma, marked hypoxia, alcohol abuse, malnutrition, and poorly controlled blood pressure.

Grouping and Treatment

After enrollment, patients were allocated by a random number table in a 1:1 ratio to a control group and an observation group, with 40 cases in each group. Basic management was identical in both arms and included dietary instruction, exercise guidance, and routine health education. The control group received metformin hydrochloride sustained-release tablets at 1.0 g twice daily. The observation group received the same metformin regimen plus dapagliflozin 10 mg once daily in the morning. The planned treatment duration was 6 months.

The random sequence was generated independently by a research staff who did not participate in patient enrollment, treatment and outcome evaluation. The group allocation list was sealed in opaque envelopes to implement allocation concealment. Considering the characteristics of oral hypoglycemic drugs and clinical practicality, this study did not adopt single-blind or double-blind design, and the outcome assessors and laboratory technicians were aware of the grouping information of patients.

Observation Indices

Clinical evaluation was performed before treatment and repeated at 3 months and 6 months after treatment initiation. Indices of glucose metabolism included FBG, 2hPBG, and *HbA1C*. Serum HMGB1 and serum RAGE were measured as indicators of inflammation-associated signaling related to the HMGB1-RAGE axis. Cardiac functional status was assessed by echocardiography using the Tei index, which served as the main functional endpoint reflecting global ventricular performance.

Fasting venous blood samples were collected from all patients in the early morning after 8-12 hr of fasting. The blood samples were centrifuged within 30 min after collection, and the separated serum was stored in a -80°C refrigerator for unified detection. The laboratory staff were aware of the patients' grouping information during the detection process.

Statistical Analysis

SPSS 26.0 was used for statistical analysis. Continuous variables with approximately normal distribution are reported as mean $\pm$ standard deviation, whereas non-normally distributed continuous variables are presented as median with interquartile range. Between-group comparisons for continuous data were performed with the independent-samples *t*-test or the Mann-Whitney U test, as appropriate. Repeated measurements within the same group were analyzed by repeated-measures analysis followed by pairwise comparisons with correction for multiple testing. Categorical variables are summarized as number and percentage and were compared using the chi-square test. A two-sided *p* value below 0.05 was considered statistically significant.

RESULTS

Baseline information

Baseline comparison showed no statistically significant difference between the two groups with respect to sex composition or age. The control group included 25 men and 15 women, with a mean age of 50.67 years. The observation group included 23 men and 17 women, with a mean age of 53.17 years. These findings indicate that the two treatment arms were broadly comparable before intervention. The proportion of male patients was slightly higher in the control group, but the difference was not statistically significant ($p=0.073$), which indicated that this baseline characteristic would not confound the subsequent study results (Table 1).

Comparison of FBG, 2hPBG, and *HbA1C* Before and After Treatment in the Two Groups

With treatment, glucose control improved in both groups. Relative to pretreatment values, FBG, 2hPBG, and *HbA1C* all declined after 3 months and again after 6 months. The pattern of change was directionally similar in the two groups, indicating that both treatment strategies were effective in lowering blood

glucose. However, the magnitude of improvement was greater in the dapagliflozin group, which showed significantly lower glycemic indices than the control group at each follow-up assessment ($p<0.05$). Detailed results of the multiple comparisons are presented in Table 2.

Comparison of RAGE and HMGB1 Levels Before and After Treatment in the Two Groups

A similar trend was observed for the inflammatory markers. Serum HMGB1 and serum RAGE were comparable at baseline, decreased after treatment in both groups, and remained lower at 6 months than at baseline. Importantly, the decline was more marked in patients treated with dapagliflozin plus metformin than in those treated with metformin alone ($p<0.05$). This pattern suggests that the combination regimen was associated with a stronger attenuation of inflammation-related signaling

linked to the HMGB1-RAGE axis. Detailed results of the multiple comparisons are presented in Table 3.

Comparison of Myocardial Performance Index Before and After Treatment in the Two Groups

Analysis of the changes in the myocardial performance index (Tei Index) showed no significant difference between the two groups at baseline ($p>0.05$). At 3 months of treatment, the Tei index remained comparable between the two groups ($p>0.05$). However, at 6 months, the observation group demonstrated a significantly lower Tei index compared with the control group ($p<0.05$).

Within-group comparisons revealed significant reductions in the Tei index from baseline to 3 and 6 months in both groups ($p<0.05$). Detailed results of the multiple comparisons are presented in Table 4.

Table 1: Baseline information.

Groups	N	Gender		Age, years, ($\bar{x}\pm s$)
		Female, n (%)	Male, n (%)	
Control group	40	15(37.50)	25(62.50)	50.67 $\pm$ 12.35
Observation group	40	23(57.50)	17(42.50)	53.17 $\pm$ 11.57
χ^2/t		3.208		-0.935
p		0.073		0.353

Table 2: Comparison of indicators before and after treatment in the two groups of patients.

Groups	FBG (mmol/L, $\bar{x}\pm s$)			2hPBG (mmol/L, M (Q1, Q3))			HbA1C (% , $\bar{x}\pm s$)		
	Before treatment	3 months after treatment	6 months after treatment	Before treatment	3 months after treatment	6 months after treatment	Before treatment	3 months after treatment	6 months after treatment
Control group	9.45 $\pm$ 2.32	8.13 $\pm$ 1.71 ^a	7.27 $\pm$ 1.23 ^{ab}	13.24(10.65,15.03)	9.99(8.75,11.17) ^a	8.46(7.75,9.32) ^{ab}	10.02 $\pm$ 2.00	8.12 $\pm$ 1.54 ^a	7.15 $\pm$ 1.27 ^{ab}
Observation group	9.39 $\pm$ 1.97	9.01 $\pm$ 1.43	7.99 $\pm$ 1.23 ^{ab}	12.49(10.36,15.07)	10.56(9.84,12.61)	9.23(8.69,10.11) ^{ab}	9.79 $\pm$ 2.09	8.87 $\pm$ 1.54 ^a	7.91 $\pm$ 1.13 ^{ab}
t/Z	0.124	-2.504	-2.624	-0.443	-2.314	-3.017	0.497	-2.177	-2.821
P	0.902	0.014	0.010	0.658	0.021	0.003	0.620	0.032	0.006

Notes: FBG, fasting blood glucose; 2hPBG, 2-hr postprandial blood glucose; HbA1C, glycated hemoglobin. a $p<0.05$, vs. baseline within the same group; b $p<0.05$, vs. 3 months after treatment within the same group.

Table 3: Comparison of inflammatory indicators before and after Treatment in the Two Groups.

Groups	RAGE (pg/mL, $\bar{x}\pm s$)			HMGB1 (pg/mL, M (Q1, Q3))		
	Before treatment	3 months after treatment	6 months after treatment	Before treatment	3 months after treatment	6 months after treatment
Control group	1700.51 $\pm$ 1024.42	1269.58 $\pm$ 880.83a	1200.97 $\pm$ 850.15ab	2754.68(1981.64,3332.69)	2234.84(1438.59,2804.38)a	1730.01(1294.61,2600.49)ab
Observation group	1752.01 $\pm$ 979.16	1720.01 $\pm$ 970.80	1653.96 $\pm$ 952.71ab	2702.56(1842.58,3340.70)	2482.26(1812.20,3242.98)a	2339.53(1711.72,3034.38)ab
t/Z	-0.230	-2.173	-2.244	-0.289	-2.078	-2.848
p	0.819	0.033	0.028	0.773	0.038	0.004

Notes: RAGE, Receptor for Advanced Glycation End Products; HMGB1: High Mobility Group Box 1 Protein. a $p<0.05$, vs. baseline within the same group; b $p<0.05$, vs. 3 months after treatment within the same group.

Table 4: Comparison of Tei Index Before and After Treatment in the Two Groups.

Groups	Tei index, median (Q1, Q3)		
	Before treatment	3 months after treatment	6 months after treatment
Control group	0.38(0.37,0.39)	0.34(0.33,0.36)a	0.30(0.25,0.33)ab
Observation group	0.38(0.36,0.39)	0.35(0.33,0.36)a	0.32(0.31,0.34)ab
t/Z	-0.510	-0.341	-3.642
p	0.610	0.733	<0.001

Notes: Tei index, Myocardial Performance Index. a $p < 0.05$, vs. baseline within the same group; b $p < 0.05$, vs. 3 months after treatment within the same group.

DISCUSSION

The present study evaluated the influence of dapagliflozin on metabolic status, inflammatory signaling, and myocardial function in patients with T2DM complicated by DCM. The main findings can be summarized as follows. Both treatment strategies improved blood glucose and were associated with lower HMGB1, lower RAGE, and a reduced Tei index over time. Nevertheless, the group receiving dapagliflozin in addition to metformin achieved greater decreases in FBG, 2hPBG, and *HbA1C*, displayed a more obvious reduction in circulating HMGB1 and RAGE, and showed a clearer improvement in Tei index by month 6. These results support the idea that dapagliflozin exerts benefits in DCM that extend beyond routine glucose lowering.

The metabolic findings are consistent with the pharmacological properties of SGLT2 inhibition. By promoting urinary glucose excretion, dapagliflozin reduces glucose burden independently of insulin secretion and can therefore complement the insulin-sensitizing effect of metformin.⁸⁻¹⁰ Better glucose control itself is highly relevant in DCM because chronic hyperglycemia drives formation of advanced glycation end products, disturbs substrate utilization, impairs mitochondrial efficiency, and promotes oxidative stress within cardiomyocytes.⁵⁻⁷ In this sense, improved glycemia should not be interpreted merely as a biochemical achievement; it may reduce the intensity of the upstream stimuli that sustain myocardial injury.

At the same time, the present study suggests that the effect of dapagliflozin is not exhausted by glycemic improvement alone. The more pronounced reduction in HMGB1 and RAGE in the observation group points toward an anti-inflammatory contribution. HMGB1 is a prototypical danger-associated molecular pattern molecule. When released from damaged or stressed cells, it can transform a local stress signal into a broader inflammatory response. RAGE, in turn, can integrate signals from HMGB1 and other ligands that accumulate in diabetic tissues, thereby sustaining inflammatory amplification, endothelial dysfunction, and tissue remodeling.¹⁶ In a diabetic microenvironment characterized by repeated oxidative and metabolic insult, suppression of this axis may help break the cycle in which metabolic stress provokes inflammation and inflammation further aggravates myocardial dysfunction.¹⁷

The functional data lend additional support to this interpretation. Tei index fell in both groups after therapy, but the between-group advantage of dapagliflozin became evident mainly at the later time point. This temporal pattern is clinically plausible. Biochemical changes can occur relatively early, whereas measurable improvement in integrated ventricular performance may require more time because reversal of inflammatory injury, improvement in myocardial energetics, and partial relief of interstitial or microvascular abnormalities are not instantaneous processes.¹⁸ In other words, the delayed separation of Tei index between groups may reflect the fact that cardiac functional recovery lags behind the biochemical response.

Several mechanisms may underlie the observed association. Dapagliflozin has been linked in prior work to reductions in oxidative stress, attenuation of inflammasome activation, improvement in mitochondrial function, modulation of sodium-hydrogen exchange, enhancement of autophagic balance, and relief of renal and systemic hemodynamic burden.¹⁹ These mechanisms are not mutually exclusive. In patients with DCM, even modest improvement across several pathways may be sufficient to produce meaningful cumulative benefit.²⁰ The present results fit well with a multi-mechanistic model in which dapagliflozin lowers metabolic load, weakens inflammatory signaling, and gradually improves the conditions required for myocardial recovery.

The findings also have practical clinical implications. First, they reinforce the importance of viewing DCM as an active biological process rather than a static echocardiographic label. Monitoring only conventional blood glucose indices may miss relevant information about myocardial risk. The concomitant assessment of inflammatory markers such as HMGB1 and RAGE, together with a functional index like the Tei index, may provide a broader picture of treatment response.²¹ Second, the results suggest that patients with preserved ejection fraction but evidence of diabetic myocardial dysfunction may still benefit from timely pharmacological intervention before advanced structural damage develops. Early treatment is especially important in DCM because symptoms may remain mild even while myocardial remodeling progresses.²²

Another point worth emphasizing is the potential interpretive value of the HMGB1-RAGE axis in human studies of diabetic heart

disease. Experimental literature has repeatedly implicated this pathway in ischemia-reperfusion injury, endothelial activation, hypertrophic signaling, and inflammatory remodeling.²³⁻²⁵ Yet direct clinical observation in patients with DCM is relatively limited. Although the present study cannot establish causality at the molecular level, the parallel decline in HMGB1, RAGE, and Tei index after dapagliflozin treatment is biologically coherent. It suggests that peripheral blood markers related to inflammatory signaling may reflect, at least in part, changes in the pathological environment affecting the myocardium.

The study should also be interpreted with appropriate caution. It was a single-center investigation with a relatively small sample size and a follow-up period of 6 months. Serum HMGB1 and RAGE were measured in peripheral blood rather than directly in myocardial tissue, and no imaging markers of fibrosis or microvascular dysfunction were included. In addition, the present study design does not allow firm separation of the anti-inflammatory effect attributable to better glycemic control from the anti-inflammatory effect attributable to direct pleiotropic actions of dapagliflozin.²⁶ Larger multicenter studies with longer follow-up, richer echocardiographic or magnetic resonance assessment, and more detailed mechanistic evaluation will be important for clarifying the degree to which HMGB1-RAGE suppression mediates cardiac benefit. In addition, this study did not implement blinding design for researchers, outcome assessors and laboratory personnel, which may bring potential bias to the research results. Due to the limitation of sample size and research design, we did not conduct correlation analysis between the changes of HMGB1, RAGE and Tei index in this study. Relevant statistical verification will be carried out in subsequent large-sample clinical studies.

Despite these limitations, the overall signal observed in this study is meaningful. The direction of change was internally consistent across metabolic, inflammatory, and functional domains, and the superiority of dapagliflozin over metformin alone became progressively apparent during follow-up. Such coherence strengthens the plausibility of the central conclusion. In a population prone to insidious myocardial injury, an intervention that simultaneously improves glucose control, dampens inflammation-related signaling, and improves integrated cardiac performance is of clear clinical interest.

CONCLUSION

In summary, dapagliflozin used in combination with metformin was associated with superior improvement in glycemic control, greater reduction in circulating HMGB1 and RAGE, and better recovery of myocardial performance than metformin alone in patients with T2DM complicated by DCM. These findings indicate that the improved myocardial performance after dapagliflozin treatment is closely associated with the suppression of HMGB1-RAGE-related inflammatory activity. Further studies

with larger samples and longer observation are warranted to confirm this relationship and to define its clinical implications more precisely.

ABBREVIATIONS

DCM: Diabetic Cardiomyopathy; **T2DM:** Type 2 Diabetes Mellitus; **HMGB1:** High Mobility Group Box 1; **RAGE:** Receptor for Advanced Glycation End Products; **FBG:** Fasting Blood Glucose; **2hPBG:** 2-hr Postprandial Blood Glucose; **HbA1C:** Glycated Hemoglobin; **Tei Index:** Myocardial Performance Index; **LVEF:** Left Ventricular Ejection Fraction; **SGLT2:** Sodium-Glucose Cotransporter 2; **WHO:** World Health Organization; **SPSS:** Statistical Package for the Social Sciences; **NLRP3:** NOD-, LRR-, and Pyrin Domain-Containing Protein 3; **AMPK:** AMP-Activated Protein Kinase; **mTOR:** Mechanistic Target of Rapamycin; **ERK1/2:** Extracellular Signal-Regulated Kinase 1/2; **Nrf2:** Nuclear Factor Erythroid 2-Related Factor 2; **HO-1:** Heme Oxygenase-1.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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