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Ranolazine as a therapeutic agent for diabetic cardiomyopathy: reducing endoplasmic reticulum stress and inflammation in type 2 diabetic rat model

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Abstract

Background Diabetic cardiomyopathy (DCM) is a significant cardiovascular complication of diabetes, characterized by structural and functional heart muscle dysfunction. Oxidative stress, endoplasmic reticulum (ER) stress, and inflammation are pivotal in the pathogenesis of DCM. Ranolazine, primarily used for angina, has demonstrated potential cardioprotective effects. This study investigates the effects of ranolazine on oxidative stress, ER stress, and inflammation in the heart tissue of type 2 diabetic rats.

Methods Diabetes was induced in male Wistar rats using Nicotinamide (110 mg/kg) and Streptozotocin (60 mg/kg). The rats were then divided into control and diabetic groups, with further subdivision into ranolazine-treated and untreated subgroups. Ranolazine was administered via gavage for eight weeks. Various parameters, including body weight, heart weight, serum glucose, troponin-I levels, oxidative stress markers, ER stress markers, and inflammatory markers, were assessed.

Results Diabetic rats showed increased heart weight and decreased body weight over eight weeks. Ranolazine treatment improved body weight but didn't affect serum glucose levels. The treatment significantly lowered serum troponin-I and oxidative stress markers, increased superoxide dismutase (SOD) and glutathione (GSH) levels, and decreased malondialdehyde (MDA) concentrations. Additionally, ranolazine reduced the expression of stress-related genes (GRP78, XBP1, and NLRP3) and lowered serum IL1β levels.

Conclusions The results indicate that ranolazine protects against DCM by attenuating oxidative stress, ER stress, and inflammation. Its potential as a therapeutic agent for DCM warrants further investigation.

Keywords Diabetes, Cardiomyopathy, Ranolazine, Inflammation, ER stress

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Introduction

Diabetes mellitus (DM) is becoming far more common, especially in developing nations. About 382 million individuals worldwide were estimated to have diabetes in 2013. Of them, type 2 diabetes accounts for approximately 90% of the occurrences. Besides, the related morbidity and mortality due to complications increases steadily, making diabetes the eighth most common cause of death globally in 2012–2021 [1].

Diabetic cardiomyopathy (DCM) is a significant cardiovascular complication of diabetes that causes the death of many people in the world every year [2, 3]. DCM is a form of persistent heart muscle dysfunction [4], characterized by structural and functional changes in the myocardium that occur independently of coronary artery disease or hypertension [5]. The prevalence of DCM is increasing due to the rising incidence of T2DM, highlighting the need for effective therapeutic interventions. The pathophysiology of DCM is complex and multifactorial, with metabolic, hemodynamic, and neurohormonal changes interrelated. While the mechanisms underlying the pathogenesis of DCM remain poorly understood, increasing evidence points to some mechanisms such as oxidative stress, ER stress, and inflammation which appear to play a crucial role in its pathogenesis [6, 7].

Excessive generation of Reactive Oxygen Species (ROS) within the diabetic heart will result in oxidative damage to lipids, proteins, and DNA, thus promoting cardiomyocyte injury with apoptosis and fibrosis [8]. Additionally, oxidative stress might perturb ER homeostasis, activating ER stress, a condition in which unfolded or misfolded proteins accumulate in the lumen of ER [9]. The unfolded protein response (UPR) occurs to restore ER function, increasing protein-folding capacity and reducing protein translation while enhancing protein degradation [10]. However, chronic ER stress may activate apoptosis and inflammation, thus driving cardiac myocyte loss and cardiac remodeling [11, 12].

One of the main regulators for DCM-induced inflammation is the multiprotein complex of the NLRP3 inflammasome. Activated NLRP3 inflammasome cleaves and activates caspase-1, releasing active IL-1β and IL-18. Then, these pro-inflammatory cytokines induce an inflammatory response, enhancing tissue damage [13]. Ranolazine is primarily used to treat chronic stable angina, and evidence exists that it decreases myocardial oxygen consumption and ischemic burden. Ranolazine demonstrates significant cardioprotective effects extending beyond its primary use as an anti-anginal medication. It inhibits the late sodium current, preventing intracellular calcium overload and diastolic dysfunction, which is beneficial in conditions with disturbed myocardial ion homeostasis. Studies also suggest ranolazine improves mitochondrial function during ischemia-reperfusion and enhances glycemic control while reducing oxidative damage in diabetic models [14–16]. Previous studies also suggest that ranolazine may exert cardioprotective effects beyond its anti-anginal activity, encompassing anti-inflammatory and antioxidant properties. Ranolazine was shown to inhibit NADPH oxidase and increase the activity of antioxidant enzymes, which could reduce oxidative stress. Moreover, ranolazine has anti-inflammatory effects, inhibiting the activation of NF-κB, which leads to a decreased production of pro-inflammatory cytokines. These findings highlight its potential in managing cardiovascular complications, particularly in diabetes, and underscore the need for further research into its broader cardioprotective mechanisms [17–19].

The present study investigated the therapeutic potential of ranolazine in attenuating DCM in a type 2 diabetic rat model. The model has been extensively used to elucidate diabetes complications and their mechanisms. Our findings will increase insight into the DCM pathophysiology and could provide information about the potential therapeutic utility of ranolazine for this complex disease.

Material and methods

Experimental design

Forty male Wistar rats (180 ± 20 g) at ten weeks old were obtained from the Animal House of the Pasteur Institute of Iran (Tehran, Iran). Animals were maintained on a 12 h-12 h light-dark cycle in a climate-controlled room with a 24–26 °C temperature and 20–60% relative humidity. These animals were housed under controlled conditions and fed a standard diet with unrestricted access to water for two weeks after purchase. Then, the rats were divided into two main groups; control and experimental, 20 animals in each. Rats were randomly allocated to the treatment groups using a computer based random order generator (https://www.random.org/sequences/). In the experimental group, a single intraperitoneal injection was administered, consisting of Nicotinamide (110 mg/kg body weight dissolved in 1 ml of normal saline) followed by Streptozotocin (60 mg/kg body weight dissolved in 1 ml of sodium citrate buffer, pH 4.5). Control animals received 2 ml of normal saline [20, 21]. After seven days, the experimental rats were subjected to blood glucose measurement using a glucometer (Accu-Chek, Swiss), and the rat with a blood sugar of more than 200 mg/dl were entered into diabetic groups. The diabetic and control rats were further divided into two subgroups, to receive either the treatment with ranolazine (40 mg/Kg body weight through daily gavage) or normal saline. Cages of different groups of rats were given a numerical designation and a cage was selected randomly from the pool of all cages to receive its treatment with different orders on treatment days. Animals were monitored daily check for any adverse effects and sufferings.

The investigators who performed the experiments and statistical analysis were unaware of the treatment group allocation.

After 8 weeks, animals were euthanized using an intraperitoneal injection of Ketamine hydrochloride (BERMER) at a dosage of 80 mg/kg body weight and Xylazine hydrochloride (VET-AGRO) at a dosage of 12 mg/kg body weight. Heart tissue, whole blood, and serum samples were collected and stored at – 80 °C for analysis. The study protocol was approved by the Ethics Committee of Tarbiat Modares University (IR.MODARES.AEC.1401, 022). The experiment was conducted in accordance with ARRIVE guidelines.

Body weight, heart weight, and biochemical analysis

The weights of rats' bodies (before sacrificing) and hearts (after sacrificing) were measured by a digital scale. The serum glucose of each rat was measured by the Pars Azmun kit (Tehran, Iran) using a Hitachi Autoanalyzer (Roche) at a wavelength of 546 nm. Troponin-I and IL1β concentrations were also measured in serum samples by rat Troponin and IL1β ELISA kits (CUSABIO, Cat. No: CSB-E08594r and CSB-E08055r) according to the instruction kits at a wavelength of 450 nm.

Oxidative stress parameters

Superoxide dismutase (SOD), Malondialdehyde (MDA), and Glutathione (GSH) were measured and analyzed in the heart tissue of rats following the instructions provided by the Navand Salamat kits, employing colorimetric methods. The heart tissue was lysed using liquid nitrogen and a laboratory mortar to measure MDA levels, which indicate lipid peroxidation. Thiobarbituric acid was used to produce a pink color which was quantified at 550 nm using an ELISA reader, with results expressed as nmol/mg protein. Also, SOD activity was measured through the autoxidation of pyrogallol (C6H3(OH)3). Pyrogallol, an organic compound that reacts with oxygen, was mixed and allowed to incubate for 5 minutes before measurement at 405 nm with an ELISA reader. The results were reported as IU/g protein. To measure glutathione levels, 20 µl of tissue sample was mixed with DTNB [5,5′-dithiobis (2-nitrobenzoic acid)] and glutathione reductase, followed by a 30-second incubation. After adding a cofactor solution, reduced glutathione was converted to glutathione oxide, which then transformed hydrogen peroxide into water. Glutathione reductase subsequently converted glutathione oxide back to reduced glutathione, and detection was performed at 412 nm. The results were expressed as µg/mg protein according to an earlier study [22].

Evaluation of mRNA expression

The Pars Tous nucleic acid extraction kit (Tehran, Iran) was used for RNA extraction. RNA content of 20 mg of heart tissue was extracted using TRIzol reagent following the protocol provided by the kit. In the final step, RNA was eluted using DEPC water. The purity and concentration of the extracted RNA were assessed by measuring UV absorption at 260/280 nm with a NanoDrop spectrophotometer. Additionally, the quality of the purified RNA was evaluated using 2% agarose gel electrophoresis. The extracted RNA was converted into cDNA by the H-minus MMLV reverse transcriptase enzyme for cDNA synthesis, using a Pars Tous cDNA synthesis kit [23].

Real-time PCR was performed on a Stratagene mx3000p Real-Time PCR system (CA, USA) using RealQ Plus 2x Master Mix Green (Ampliqon, Odense, Denmark). The PCR reaction mixture contained approximately 50 ng cDNA templates, forward and reverse primers (10 µM each), and a master mix reaching a final volume of 20 µl. The RT-qPCR cycling conditions were set as follows: Denaturation for 40 cycles at 95 °C for 45 seconds, annealing at 61 °C for 45 seconds, and extension at 72 °C for 45 seconds, with all measurements performed in duplicate. The expression of the target genes was quantified relative to the expression of the β-Actin as the housekeeping gene based on the ΔΔCt method [24]. The sequences of the primers are depicted in Table 1.

Table 1 Specifications of primers used in real-time PCR

Gene		Primer Sequence	Tm (°C)	Annealing Temp. (°C)
β-Actin	Forward	CTATCGGCAATGAGCGGTTCC	63	61
	Reverse	GCACTGTGTTGGCATAGAGGTC	64	
XBP1	Forward	GAGTCCGCAGCAGGTG	56	58
	Reverse	GCGTCAGAATCCATGGGA	56	
GRP78	Forward	TCCTGCGTCGGTGTATTC	56	57
	Reverse	CGTGAGTTGGTTCTTGGC	56	
NLRP3	Forward	GCTGCTCAGCTCTGACCTCT	63	61
	Reverse	AGGTGAGGCTGCAGTTGTCT	60	
CHOP	Forward	CCAGCAGAGGTCACAAGCAC	63	61
	Reverse	CGCACTGACCACTCTGTTTC	60	

Statistical analysis

Statistical analyses were performed using SPSS Ver. 25.0 (SPSS Inc., Chicago, IL, USA). All data were expressed as the mean ± SD. The statistical significance was analyzed using one-way ANOVA followed by Tukey's test for multiple comparisons. For all of the statistical tests, the significance level was considered as $p < 0.05$. The Levene test was used for homogeneity of variances. The sample size calculation was based on serum IL1β level as a main outcome after administration of ranolazine (standard deviation = 12) as the main treatment using Statulator tools (https://www.statulator.com/SampleSize/ss1P.html). Considering that the analysis has 80% power, a total of 8 rats were assigned to each group.

Results

Clinical presentation and premature death

No mortality or significant behavioral changes were observed in any of the groups during the study period. The success rate of diabetes induction was 80%, so 16 animals were considered diabetic and included in the study. The diabetic rats were further randomly assigned into untreated and treated diabetic groups, 8 animals each.

Body weight, heart weight, serum glucose, and troponin-I levels

As shown in Fig. 1A and B, the induction of diabetes significantly increased heart weight and heart weight-to-body weight ratio compared to the control rats. However, the body weight of diabetic rats decreased continuously during 8 weeks. In addition, the obtained results indicate a significant difference between the body weight of the diabetic group treated with ranolazine and the diabetic group without treatment after 8 weeks (Fig. 1C). Moreover, ranolazine treatment had no significant effect on serum glucose in diabetic rats (Fig. 2A). As shown in Fig. 2B, the troponin-I level in the diabetic group treated with ranolazine was significantly lower compared to the untreated diabetic group ($p < 0.05$).

Levels of oxidative stress parameters

Superoxide dismutase (SOD) activity and glutathione (GSH) concentration were significantly decreased in the diabetic group (Fig. 3, A and B). Ranolazine

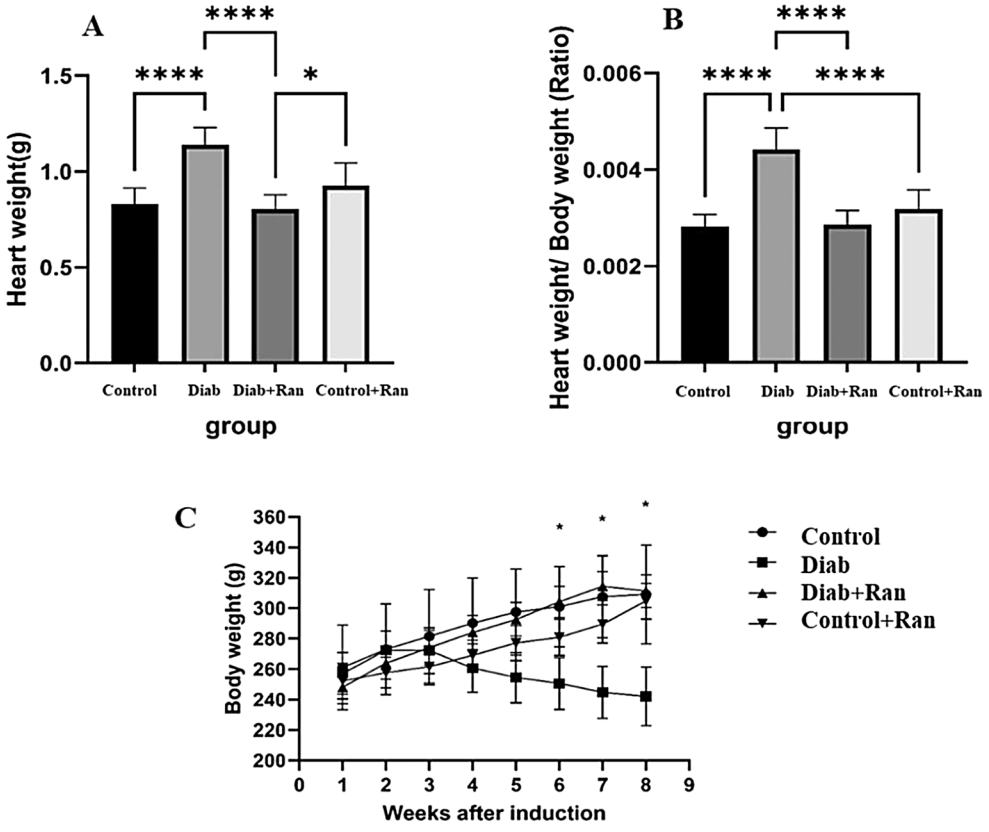

Fig. 1 Changes of heart weight (**A**), heart-to-body weight ratio (**B**), and body weight (**C**) in different groups. Data are represented as mean ± S.D (n = 8). Control: control group without treatment; Diab: diabetic group without treatment; Diab + Ran: the diabetic group received ranolazine; Control + Ran: the control group received ranolazine. * $p < 0.05$, and **** $p < 0.0001$

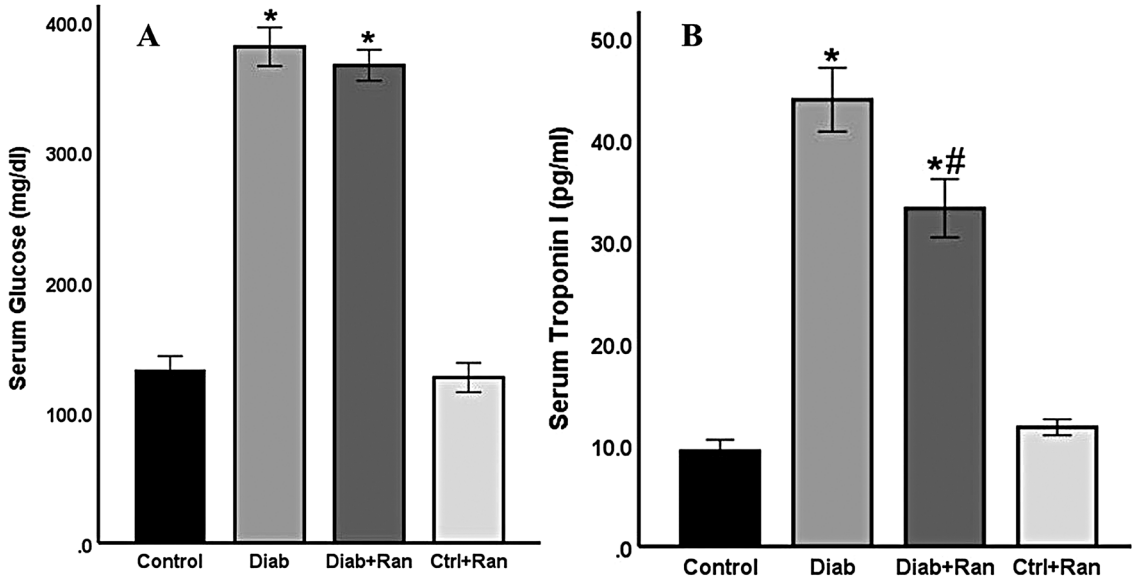

Fig. 2 Changes of serum glucose (**A**), and serum troponin-I (**B**) in different groups. Data are represented as mean ± S.D (n = 8). Control: control group without treatment; Diab: diabetic group without treatment; Diab + Ran: the diabetic group received ranolazine; Control + Ran: the control group received ranolazine. * $p < 0.05$, Diab. vs Control group and # $p < 0.05$, Diab + Ran vs Diab

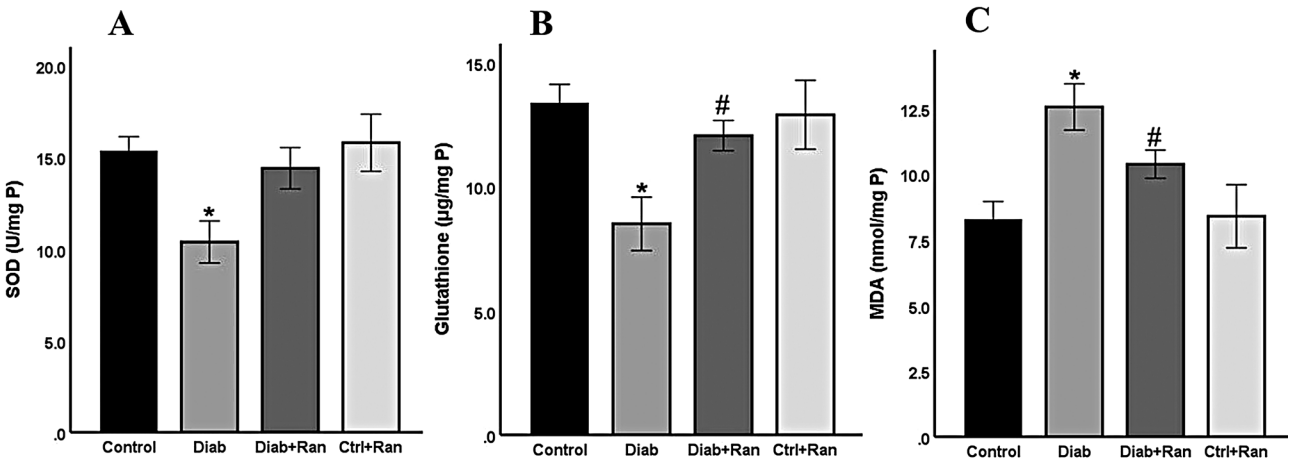

Fig. 3 Changes of specific activity of Superoxide dismutase (**A**), Glutathione concentration (**B**), and Malondialdehyde concentration (**C**) in different groups. Data are represented as mean ± S.D (n = 8). Control: control group without treatment; Diab: diabetic group without treatment; Diab + Ran: the diabetic group received ranolazine; Control + Ran: the control group received ranolazine. * $p < 0.05$, Diab. vs Control group and # $p < 0.05$, Diab + Ran vs Diab

treatment increased the mean SOD and GSH levels in the diabetic rats. However, unlike GSH, the increase in SOD activity was not statistically significant. Moreover, a significant increase was observed in malondialdehyde (MDA) concentration in the heart tissue of diabetic rats. Eight weeks of treatment with ranolazine significantly alleviated MDA levels in diabetic rats (Fig. 3C).

Gene expression results

Induction of diabetes in rats resulted in a rise in the expression of the GRP78 gene in the heart tissue of rats ($p < 0.001$). Ranolazine treatment decreased the GRP78 gene expression level in the diabetic group, but the decrease was not statistically significant. Moreover, there was no significant difference between the control groups (Fig. 4A). Figure 4B also indicates a significant increase in the XBP1 gene expression in the heart of diabetic rats that was significantly attenuated by ranolazine treatment ($p < 0.05$). Accordingly, the CHOP expression gene was induced in the heart tissue of diabetic rats ($p < 0.01$) (Fig. 4C). Ranolazine could not significantly correct the induced CHOP gene expression following 8 weeks of treatment.

A significant increase in NLRP3 gene expression in the myocardial tissue of diabetic rats was observed. This

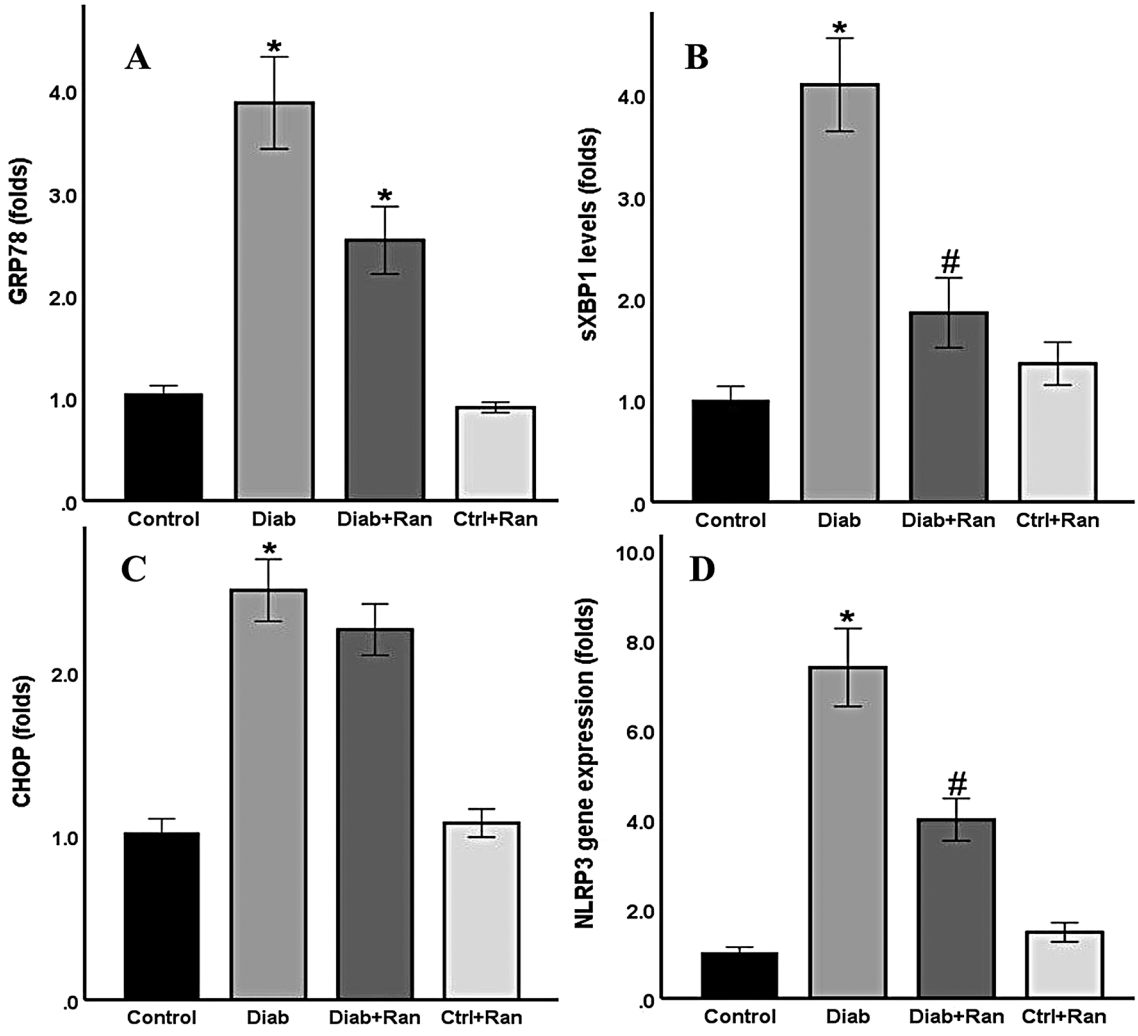

Fig. 4 Changes of GRP78 gene expression (**A**), XBP1 gene expression (**B**), CHOP gene expression (**C**), and NLRP3 expression gene (**D**) in different groups. Data are represented as mean ± S.D (n = 8). Control: control group without treatment; Diab: diabetic group without treatment; Diab + Ran: the diabetic group received ranolazine; Control + Ran: the control group received ranolazine. * $p < 0.01$, Diab. vs Control group and # $p < 0.05$, Diab + Ran vs Diab

induction was relieved by ranolazine treatment to a significant extent as can be seen in Fig. 4D. Ranolazine treatments did not show a significant effect on the expression of our genes in the heart tissues of control rats (Fig. 4D).

Serum IL1β level

Figure 5 indicates the serum IL1β concentration after 8 weeks of treatments. Serum IL1β level was markedly increased in diabetic rats compared to the control group. Whereas, ranolazine treatment could significantly diminish the elevated IL1β level in the diabetic group. There was no significant difference in Serum IL1β levels between the control groups.

Discussion

The present study investigated the effects of ranolazine on oxidative stress, endoplasmic reticulum (ER) stress, unfolded protein response (UPR), and inflammatory markers in diabetic rats. Our results demonstrate that ranolazine treatment exerts a protective effect against diabetes-induced cardiac changes by mitigating these interrelated pathways.

Diabetes-induced hyperglycemia can lead to oxidative stress, characterized by an imbalance between the productions of reactive oxygen species (ROS) and antioxidant defenses [25]. In our study, diabetic rats exhibited increased oxidative stress, evidenced by elevated MDA levels and decreased SOD activity and GSH concentration in the heart tissue of diabetic rats, which is consistent with previous studies [19, 26]. Ranolazine treatment effectively attenuated oxidative stress, suggesting its potential to reduce ROS production or enhance antioxidant capacity. NADPH oxidase (NOX), an important enzyme responsible for generating reactive oxygen species, such as superoxide radicals (O2•-) and hydrogen peroxide could be involved. Inhibiting NOX may alleviate

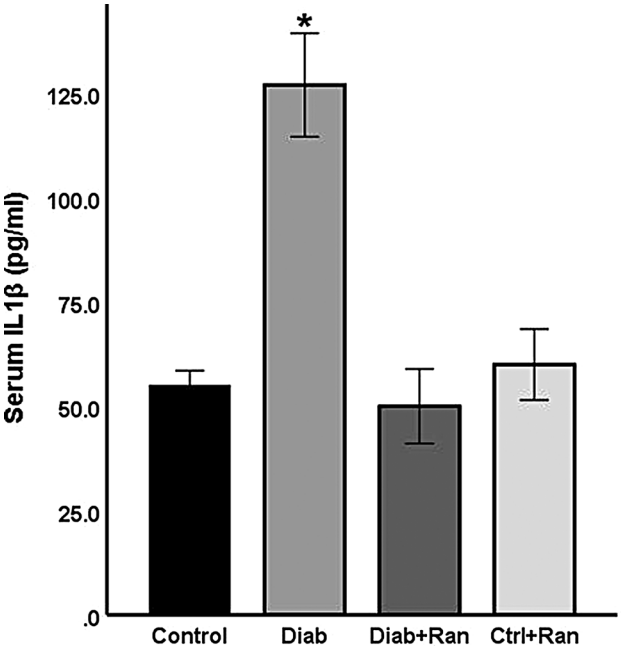

Fig. 5 Changes of IL1β concentration in different groups. Data are represented as mean ± S.D (n = 8). Control: control group without treatment; Diab: diabetic group without treatment; Diab + Ran: the diabetic group received ranolazine; Control + Ran: the control group received ranolazine. * $p < 0.01$, Diab. vs Control group

oxidative stress in tissues affected by various disease conditions [27]. It has been reported that ranolazine reduces the expression and activity of NOX and mitigates oxidative stress in the cardiac myocytes of diabetic rats [28].

ER stress, a cellular response to misfolded proteins in the ER lumen, is another critical factor in diabetic cardiomyopathy. The UPR is activated in response to ER stress and involves signaling pathways that attempt to restore ER homeostasis in cardiomyocytes [12]. However, chronic ER stress can lead to apoptosis and tissue damage. In our study, diabetic rats exhibited increased expression of XBP1 in myocardial tissue, indicating activation of the UPR. Ranolazine treatment reduced the expression of these UPR markers, suggesting its ability to mitigate ER stress which is consistent with a previous study [29]. Because of high reactivity, ROS react with ER proteins and disrupt their natural folding. The enhanced burden of oxidative stress in diabetes, gives rise to the accumulation of misfolded proteins inside the myocytes. The development of ER stress induces the UPR pathways which can trigger the downstream inflammatory mediators such as NLRP3 inflammasome activation [30]. We suggest that ranolazine can ameliorate the accumulation of misfolded ER proteins through its favorable cardiometabolic effects, relieving mitochondrial dysfunction and mitigating oxidative stress in diabetic hearts.

Inflammation plays a crucial role in the pathogenesis of diabetic cardiomyopathy. Activation of inflammatory pathways such as the NLRP3 inflammasome results from the ER stress and oxidative stress in diabetic conditions marked by increased inflammatory cytokines such as IL-1β and TNFα. Chronic oxidative stress and inflammation in myocytes eventually cause a decrease in the function of the heart myocardium, myocardial fibrosis, dysfunctional remodeling, and apoptosis. Our study demonstrated that diabetic rats exhibited increased levels of IL-1β and NLRP3, key inflammatory markers that are consistent with previous studies [31]. Ranolazine treatment effectively reduced these inflammatory markers, suggesting its anti-inflammatory properties. In more recent studies, the anti-inflammatory role of ranolazine in neurodegenerative disease has also been observed [32, 33]. The observed results of ranolazine in our study were independent of any change in glucose levels in our diabetic rats.

Studying diabetic cardiomyopathy using animal models, especially rats, has some limitations. Human diabetic cardiomyopathy is a complex disease influenced by many factors, which aren't fully replicated in rat models [34]. Moreover, the shorter duration of diabetes in rats and the fact that these animals are usually younger do not accurately capture the long-term effects and disease progression seen in older humans, who often receive various treatments.

Conclusion

In conclusion, our findings confirm that ranolazine has beneficial effects on the parameters of diabetic cardiomyopathy in diabetic rats as evidenced by the decrease in heart weight and troponin-I levels. These findings suggest that ranolazine could be a promising therapeutic option for improving diabetic cardiomyopathy in patients who also experience chronic angina. Further studies are needed to elucidate the precise mechanisms underlying ranolazine's protective effects and to evaluate its efficacy in clinical trials in combination with antidiabetic agents.

Supplementary information

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Supplementary Material 1

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Author contributions

HY and SZB supervised the project, conceived and designed the analysis, interpreted the results, and worked on the manuscript. AF and MM performed the experiments, collected the data, and wrote the original draft. All authors have approved the final version of the manuscript.

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Data availability
Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate
All experimental procedures adhered to the ethical guidelines of animal studies and were approved by the Ethical Committee of Tarbiat Modares University (IR.MODARES.AEC.1401, 022).

Competing interests
The authors declare no competing interests.

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