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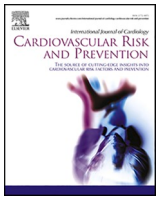

High glucose affects the cardiac function of diabetic Akita mice by inhibiting cardiac ATP synthase beta subunit☆

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ABSTRACT

Object: To explore the mechanism of diabetic cardiomyopathy that hyperglycemia may affect the cardiac function by inhibiting the expression of ATPase β subunit.
Method: Cardiac function, fibrosis levels, and the expression of the ATPase β subunit were observed in Akita mice-a diabetes mice model without lipid metabolism disorders-—using morphological, molecular biology, and echocardiographic analyses compared to wild-type mice. The study revealed a connection between the decreased ATPase β subunit and the development of diabetic myocardial injury. Furthermore, study on primary culture of cardiomyocytes hints that the effect of high glucose on myocardium and ATP are related to the decrease of the expression of ATP synthase β subunit.
Result: With the increase of hyperglycemia time, the heart function of akita mice decreased, AV peak and estimated weight of left ventricle were statistically less than that of wild-type mice, the left ventricular ejection fraction was not statistically different from that of the control group; the E/A ratio of akita mice decreased significantly with age, but did shows significant cardiac dysfunction at the end of the experiment; collagen deposition increased in the heart of akita mice. In the cell level, the protein level of ATPase β subunit in primary cultured cardiomyocytes decreased significantly after high glucose treatment.
Conclusion: Hyperglycemia may affect the cardiac function by affecting the expression of ATPase β subunit in cardiomyocytes, which may be one of the mechanisms of diabetic cardiomyopathy.

1. Introduction

Cardiovascular disease is a major cause of heart failure and death in patients with diabetes. In addition to coronary artery disease, structural and functional damage to the heart caused by diabetic cardiomyopathy (DCM) is also an important factor contributing to diabetic heart injury [1]. DCM was first proposed by Rubler et al., in 1972, referring to a cardiomyopathy that occurs in diabetic patients without significant clinical coronary artery disease, valvular disease, or other conventional cardiovascular risk factors such as hypertension and dyslipidemia. It is characterized by early myocardial fibrosis, functional remodeling, and associated diastolic dysfunction, ultimately manifesting as clinical heart failure [2]. The incidence of DCM is related to the dysregulation of glucose metabolism in diabetes itself, impaired cardiac insulin signaling, mitochondrial dysfunction, increased oxidative stress, and reduced bioavailability of nitric oxide [3]. The development of DCM is associated with increased levels of advanced glycation end products and collagen-based myocardial cell and extracellular matrix stiffness, impaired mitochondrial and cardiac calcium handling, inflammation, activation of the renin-angiotensin-aldosterone system, cardiac autonomic neuropathy, endoplasmic reticulum stress, microvascular dysfunction, and cardiac metabolic abnormalities [4]. Studies have suggested that in DCM, there is low ATP content and reduced ATP production capacity in cardiac mitochondria. Further research indicates that impaired ATP synthesis and mitochondrial uncoupling lead to abnormal myocardial energy metabolism and increased mitochondrial oxidative stress. Increased mitochondrial reactive oxygen species, impaired mitochondrial calcium uptake, and other factors contribute to the impaired myocardial energy in DCM [5,6]. Early studies have found that ATP synthase is a key molecular complex involved in ATP synthesis in mitochondria. Among its components, the function of the ATP synthase beta subunit is particularly crucial, as it plays a significant role in

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the electron transport chain of mitochondrial oxidative phosphorylation and ATP production [7]. This study aims to use a type 1 diabetes mouse model, the heterozygous Akita mouse, to investigate the effects of glucose metabolism disorder on cardiac function and to explore whether the ATP synthase beta subunit is involved in the cardiac energy metabolism dysfunction in diabetic cardiomyopathy (DCM).

2. Methods and materials

2.1. Experimental animals and grouping

Male Akita mice and age-matched wild-type control mice (C57BL/6) weighing 20–25g were purchased from Vital River Company and used in this study (N = 7, Each group) and were fed with normal diet (ND) for 10 months. To observe the body weight and blood glucose levels of the experimental animals, the Akita mice and the C57BL/6 mice were weighed every 4 weeks during the 10-month period of breeding and observation. Fasting tail vein blood glucose levels were measured. Ultrasound echocardiography was performed on the mice at 5 months and 10 months of age. The mice were housed under a 12-h light-dark cycle with access to adequate water, food, and enrichment, ensuring compliance with animal welfare regulations.

2.1.1. Reagents

Blood glucose meter for glucose measurement (Roche); Two-step reverse transcription reagent kit, real-time quantitative polymerase chain reaction (PCR) reagent kit (Takara, Japan); BCA protein concentration determination reagent kit (Bio-Rad, USA); Rabbit anti-mouse/rat ATP synthase beta subunit monoclonal antibody (Cell Signaling, USA), rabbit anti-mouse/rat/human eIF5 monoclonal antibody (Santa Cruz, USA); ECL chemiluminescence reagent kit (Beijing Trans-gene Biotechnology Co., Ltd.), horseradish peroxidase-conjugated goat anti-rabbit polyclonal secondary antibody (Beijing Trans-gene Biotechnology Co., Ltd.).

2.2. Echocardiography

The animals were weighed and had their blood glucose levels measured monthly, and their general condition was recorded. Echocardiography was performed on the anesthetized animals using isoflurane anesthesia in the 5th and 10th months to observe their cardiac function. Anesthetic injections were administered intraperitoneally with a dose of 0.30–0.32 mL/10g of Afudine (1.2 %) and a dose of 0.10 mL/10g of Chloral Hydrate (4 %). Maintain anesthesia for a moderate duration (40 m–77 m). VisualSonics Vevo 2100 color ultrasound diagnostic instrument, with a probe frequency of 30 MHz, scans the left and right sternal edges, apex, and suprasternal fossa of mice to collect cardiac ultrasound images and measure cardiac structural parameters.

2.3. Sampling

After the completion of echocardiography, the animals were weighed, and tissue samples were collected after anesthesia. The heart tissue was perfused with physiological saline, fixed in 4 % paraformaldehyde, dehydrated in graded alcohol, cleared in xylene, embedded in paraffin, and sectioned for routine histology. Some sections were used for Masson's trichrome staining, while others were stored in liquid nitrogen for further analysis.

2.4. Primary cardiomyocytes

After disinfecting the hearts of SD rats with 75 % alcohol, they were placed in pre-cooled culture medium. After washing the blood vessels and fibrous tissues, the hearts were transferred to another cooled culture medium. The hearts were minced, and then washed with a 0.25 % pancreatin solution containing 0.02 % EDTA. The supernatant was discarded, and the tissue blocks were digested with pancreatin at 37 °C for twice the volume of the tissue blocks. After digestion was terminated, the mixture was filtered through a triple-layered 200-mesh sieve and centrifuged at 1500 rpm for 5 min. The cell suspension was then seeded into culture dishes, and after 90 min, the supernatant was transferred to a new dish. The cells remaining in the original culture dish were cardiac fibroblasts, while those transferred out were cardiomyocytes. After overnight incubation, the cardiomyocytes were observed to contract spontaneously. The culture medium consisted of DMEM supplemented with 10 % fetal bovine serum (FBS) and 1 % antibiotics. Before experimentation, the cells were serum-starved for 8 h and then switched to different glucose concentration DMEM culture media. The high-glucose medium contained 4500 mg/L of glucose, and the low-glucose medium contained 1000 mg/L of glucose.

2.5. Masson's trichrome staining

After the paraffin-embedded sections of mouse heart tissue were sliced, they were routinely dewaxed in xylene and dehydrated in a graded alcohol series. Subsequently, they were stained with acid fuchsin solution, 5 % phosphotungstic acid solution, and light green staining solution, followed by washing with 2 % acetic acid. Dehydration was performed with absolute alcohol, and after clearing in xylene, the sections were embedded in neutral gum for observation of collagen fiber deposition (appearing bright blue-green) under a light microscope.

2.6. RT-PCR and real-time PCR

After Trizol lysis of tissues/cells and phenol-chloroform extraction to isolate total RNA, the purity of RNA is confirmed by measuring the A260/A280 ratio using a spectrophotometer. Subsequently, an RT-PCR kit is used to reverse transcribe cDNA.

For Real-time PCR, the amplification conditions are as follows: predenaturation at 93 °C for 2 min, followed by 40 cycles of denaturation at 93 °C for 1 min, annealing at 55 °C for 1 min, extension at 72 °C for 1 min, and a final extension at 72 °C for 7 min. The reference gene selected is β-actin.。

2.7. Western Blotting (WB)

Western Blotting (WB) is used to detect the expression of ATP synthase protein in mouse heart tissue: Total protein is extracted using complete RIPA lysis buffer and the protein concentration is determined by the BCA method. Each sample is mixed with 30ug and 5 × loading buffer, boiled for denaturation, then subjected to 12 % polyacrylamide gel electrophoresis (SDS-PAGE) for separation. The separated proteins are transferred to nitrocellulose membrane, blocked with 5 % non-fat milk at room temperature for 1 h. Primary antibodies (1:1000) and the internal control eIF5 antibody (1:5000) are added and incubated overnight. The membrane is washed with TBST 3 times, followed by the addition of secondary antibodies conjugated with horseradish peroxidase (1:5000 goat anti-rabbit secondary antibodies), and incubated at room temperature for 1 h. After standard membrane washing 3 times, chemiluminescence is used for imaging, and images are captured using the SYNGENE automated gel imaging analysis system. Quantification is performed using the expression levels of the internal control eIF5 protein, with the experiment repeated independently 3 times.

2.7.1. Statistic

Experimental data were expressed as mean ± standard deviation. Statistical analysis was performed using Prism 5.0 software. For comparison among multiple groups, One-Way ANOVA test was used, and for comparison between two groups, *t*-test was used. A P-value <0.05 was considered statistically significant.

3. Result

3.1. General information of mice

There was no statistically significant difference in body weight and weight gain between the Akita mice and the control group (Fig. 1A). However, fasting blood glucose levels were significantly higher than the control group at each observation time point, and the difference was statistically significant (*P < 0.05,**P < 0.01) (Fig. 1B).

3.2. Akita mice exhibit a cardiac functional status characteristic of DCM

To clarify the effect of high glucose on mouse cardiac function, echocardiography was performed in the 5th and 10th months. The main parameters included left ventricular weight, peak aortic ejection flow velocity, left ventricular ejection fraction, and E/A ratio. Compared to the wild type, echocardiography estimated a significantly lower peak AV velocity in the left ventricle of the Akita mice (Fig. 2A). The estimated left ventricular weight was decreased, but there was no statistically significant difference in left ventricular ejection fraction compared to the wild type (Fig. 2B). Echocardiography suggested that with increasing age, cardiac function in mice with high blood glucose deteriorated, primarily showing a decline in diastolic function. Compared to the wild type, the E/A ratio in Akita mice decreased significantly with age, but the ratio still remained greater than 1, indicating that mice did not yet show apparent signs of heart failure (Fig. 2C)

3.3. Akita mice exhibit a cardiomyocyte phenotype with decreased ATP synthase β subunit expression

Morphological examination indicated that, upon observation at 10 months, the Akita mice showed increased interstitial collagen deposition in the heart that usually indicates exacerbation of myocardial fibrosis and decreased expression of the ATP synthase β subunit (Fig. 3A and B). This suggests the presence of energy metabolism abnormalities in myocardial cells during diabetic cardiomyopathy (DCM), which may be related to the decreased expression of the ATP synthase β subunit.

Through Western blotting (WB) and real-time quantitative PCR experiments, it can be observed that compared to the control group, the expression level of ATP synthase subunit beta in the hearts of diabetic Akita mice is decreased (Fig. 4A), but there is no statistical difference at the mRNA level (Fig. 4B).

3.4. High glucose culture induces a time-dependent decrease in ATP synthase β subunit expression in primary cultured cardiomyocytes

To further investigate the effect of high glucose on the expression of the ATP synthase β subunit in primary cultured cardiomyocytes, we conducted observations after high glucose treatment. The results indicated that after 24–48 h of pure high glucose treatment, there was no significant change in the mRNA levels of the ATP synthase β subunit (Fig. 5A). However, when high glucose treatment was continued for 72 h, the mRNA levels of the ATP synthase β subunit were significantly reduced compared to the low glucose group (Fig. 5A). At the protein level, at the three time points of 24 h, 48 h, and 72 h, the expression of the ATP synthase β subunit protein in primary cultured cardiomyocytes treated with high glucose was decreased compared to the low glucose group (Fig. 5B and D).

Furthermore, by adding insulin, we simulated the effects of different insulin levels on the expression of the ATP synthase β subunit in cardiomyocytes at different glucose concentrations (Fig. 5C). The experiment indicated that there was no statistical difference in the effect of different insulin concentrations on the expression of the ATP synthase β subunit in cardiomyocytes at different glucose concentrations.

4. Discussion

Currently, it is believed that DCM is heart damage related to metabolic disorders of myocardial cells, independent of dyslipidemia, coronary atherosclerosis, and myocardial injury caused by hypertension [8]. The pathogenesis of DCM is related to decreased cardiac compliance caused by glycosylation mediated by protein kinase C (PKC) and nitric oxide (NO) as second messengers, as well as myocardial cell calcium transport defects. It is also associated with diffuse intramyocardial microvascular disease caused by long-term hyperglycemia [9–11]. DCM is often characterized by histological myocardial interstitial fibrosis and diastolic dysfunction in cardiac function, accompanied by or without cardiac autonomic neuropathy [12]. Due to the continuous occurrence and development of DCM accompanied by energy metabolism disorders, the production of ATP in myocardial cells is particularly important as they serve as the providers of cardiac pumping function.

Traditional diabetes animal models induced by high-fat diet, obesity (ob/ob or db/db mice) often combine dyslipidemia, which does not well reflect the direct impact of hyperglycemia on the myocardium. Streptozotocin (STZ)-induced animal models have limitations as long-term observation models due to unstable hyperglycemic phenotypes, gradual normalization of blood glucose in some animals with disease progression, and low modeling rates. In this study, a heterozygous Akita mouse model was used, where glucose metabolism disorder is caused by a mutation in the $Ins2^{Akita}$ allele gene located on chromosome 7. With aging, misfolded insulin proteins accumulate in the endoplasmic reticulum, leading to sustained dysfunction of the endoplasmic reticulum in beta cells and initiation of apoptosis, simulating the natural course of diabetes. This model does not involve lipid metabolism disorders, obesity, or pancreatic inflammation, allowing for a better observation of the progressive effects of hyperglycemia on the organism [13,14].

Previous studies have confirmed that mitochondria are the sites for cellular respiration, and glucose and lipid metabolism largely depend on

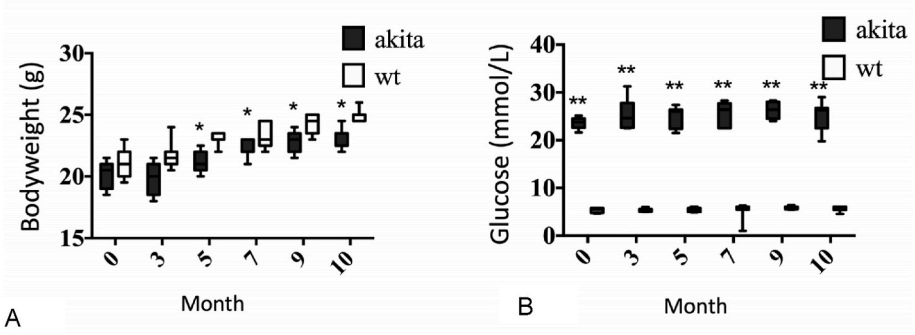


Fig. 1. Changes in mouse body weight and blood glucose levels.
A:The bodyweight of wild-type mice and Akita mice after 10 months of breeding.(N = 7);
B:The blood glucose of wild-type mice and Akita mice after 10 months of breeding.(N = 7).

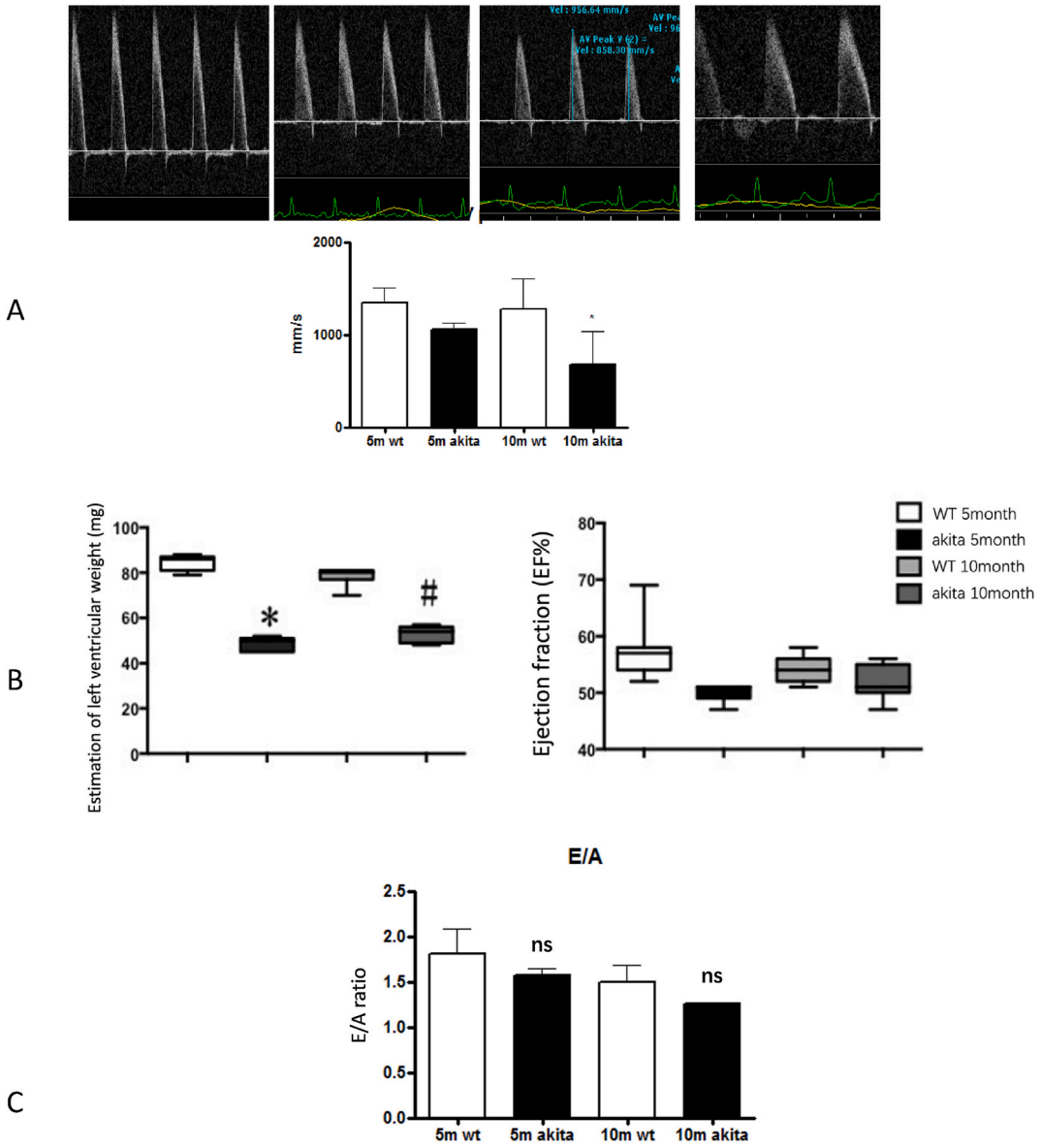


Fig. 2. Echocardiography of mice.
A. Peak aortic flow velocity; B. Estimation of left ventricular weight and ejection fraction; C. E/A peak ratio
(N = 7 each group, *: comparison between Akita and wild-type at 5 months, #: comparison between Akita and wild-type at 10 months, $P < 0.05$, ns: no statistically significant difference compared to age-matched wild-type mice.).

ATP produced by mitochondria. Research indicates that the hepatic ATP synthesis rate is lower in diabetic patients compared to healthy individuals. Hepatic ATP content is negatively correlated with insulin resistance, fatty degeneration, and hyperglycemia in obese diabetic patients and animals [15–18]. In diabetic kidney disease, a decrease in ATP content in the renal cortex has also been observed [19]. These results suggest that ATP plays an important role in the body's glucose and lipid metabolism processes. Cellular ATP is mainly produced by mitochondrial ATP synthase, which is composed of the F0 and F1 portions and other auxiliary factors. The F0 portion is mainly embedded in the inner mitochondrial membrane, forming a proton backflow channel [20]. The F1 portion is composed of α, β, γ, δ, and ε subunits, located in the mitochondrial matrix, responsible for ATP synthesis. The ATP synthase β subunit is the catalytic subunit of ATP synthase, and almost all ATP synthesis sites are located on the ATP synthase β subunit [21]. In the liver of diabetic animals, it has been found that the expression of the ATP synthase β subunit and the levels of the ATP synthase complex are decreased, which may be a key factor leading to the metabolic disorders of glucose and lipids in humans and animals. Previously, in the liver of diabetic mice, we found that the mRNA and protein expression levels of the ATP synthase β subunit were reduced. Further mechanistic studies suggest that the ATP synthase β subunit can promote the synthesis and secretion of ATP in liver cells and improve insulin resistance and alleviate diabetes in an insulin-independent manner through the P2 receptor-Ca^{2+}/CaM-PI3K-Akt pathway [22]. However, there is currently no systematic report on the expression and function of the ATP synthase β subunit in DCM.

In our study, we found that ATP synthase β is primarily regulated at the translational level rather than through transcription, and its expression does not respond to insulin treatments at the mRNA level. This translational regulation may enable cells to rapidly respond to changes in metabolic demands without relying on the slower transcription process [23]. Such a mechanism allows cells to adjust the synthesis rate of ATP synthase in response to specific metabolic conditions by modulating translation efficiency without altering mRNA expression levels. Research indicates that ATP synthase β is sensitive to

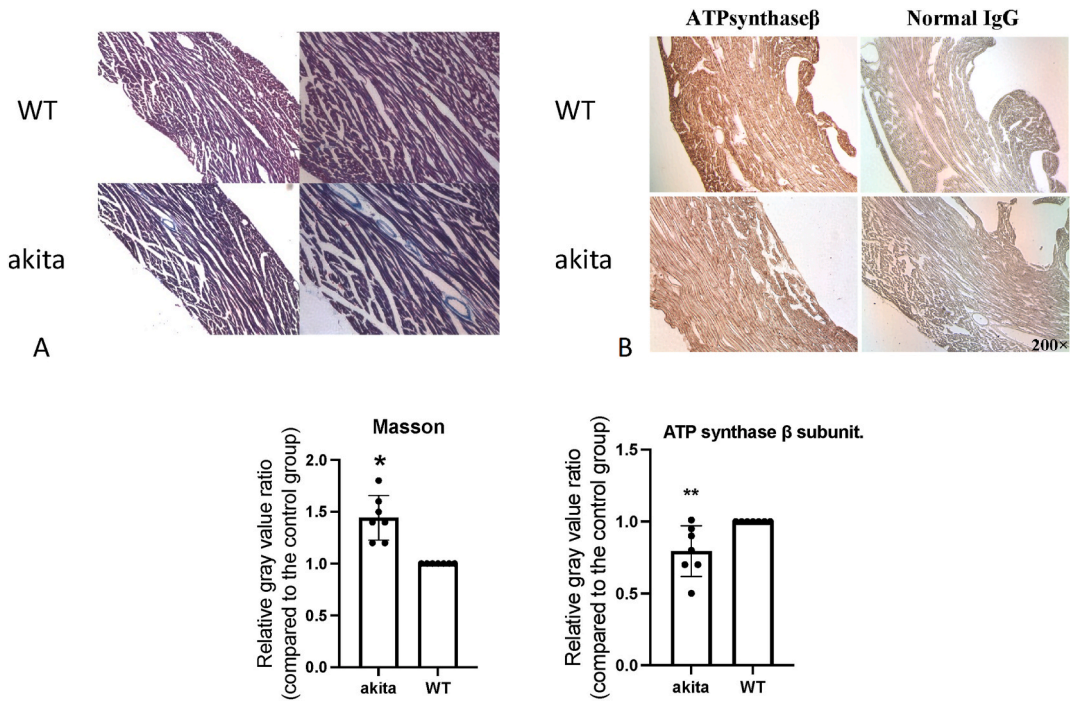


Fig. 3. Cardiac morphology of mice.
A. Masson's trichrome staining, with the blue-green part indicating collagen deposition; B. Immunohistochemical staining for ATP synthase β subunit, with the brown-yellow color showing ATP synthase β subunit expression, and the control with normal IgG from the same species (200x).
The bar charts represent the statistical analysis of the relative gray values for Masson's staining and immunohistochemistry.

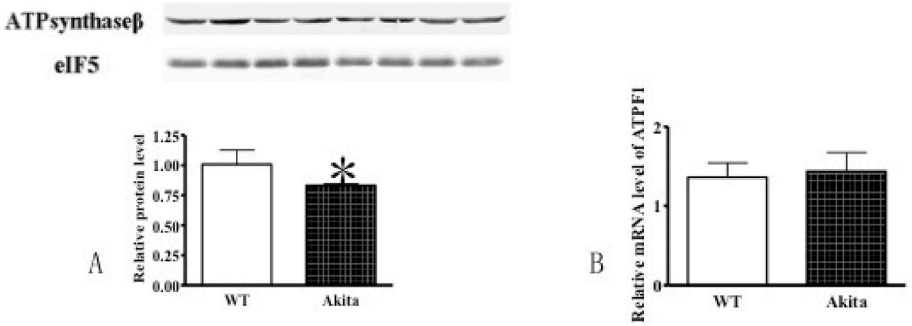
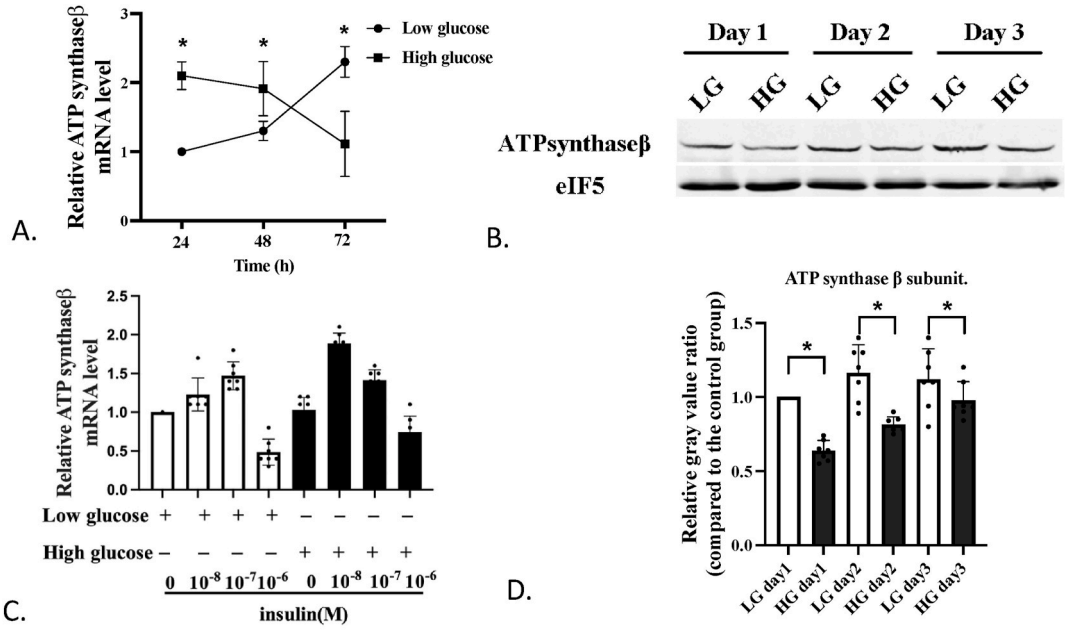


Fig. 4. Expression of ATP synthase β subunit in mouse hearts.
A. Western blot analysis of ATP synthase β subunit protein expression;
B. Quantitative PCR analysis of ATP synthase β subunit mRNA expression (N = 7, *: P < 0.05).

the cellular energy state and metabolic signals, such as the AMP /ATP ratio, further supporting the possibility of its translational regulation [24]. Future studies should focus on how post-translational modifications (e.g., phosphorylation and acetylation) affect the function and stability of ATP synthase β, as well as the interactions between translation factors and ATP synthase β mRNA. These findings provide new insights into how cells regulate energy metabolism and suggest potential directions for further research.

In our current study, we found that as hyperglycemia progressed, the experimental animals exhibited cardiac interstitial fibrosis, consistent with the pathological phenotype of DCM. Using echocardiography, we observed changes in cardiac function similar to those seen in human DCM during a prolonged course of diabetes. Histological studies indicated that the expression of the ATP synthase β subunit was indeed reduced in the hearts of akita mice, suggesting that the decreased expression of the ATP synthase β subunit may be involved in the occurrence and development of DCM. At the cellular level, through culturing with media of different glucose concentrations, we found that with prolonged incubation in high glucose conditions, the expression of the ATP synthase β subunit in cardiac myocytes decreased. This corroborated the observations in animal experiments and confirmed that the decreased expression of the ATP synthase β subunit is involved in the development of DCM.

This study also has certain limitations. The sample size in this study is relatively small, and the conclusions drawn require validation through larger sample sizes and more in-depth exploration of the underlying mechanisms. Clinical signs of heart dysfunction were not observed in the animal experiments, indicating that future research should consider extending the observation period. We only observed the expression of the ATP synthase β subunit and did not directly measure cellular ATP levels. Further exploration of the underlying reasons for the reduction in the ATP synthase β subunit and the mechanisms leading to mitochondrial dysfunction is lacking in-depth molecular mechanistic exploration. However, this study provides a strong exploration of the metabolic dysfunction mechanisms in DCM and supplements the existing mechanisms. It suggests that future drug development targeting the



the expression of ATP synthase β subunit in primary cardiac myocytes.

Fig. 5. Impact of high glucose on the expression of ATP synthase β subunit in primary cardiac myocytes.
A. Quantitative PCR of ATP synthase subunit beta mRNA expression (N = 7, *: P < 0.05, compared to the low-glucose culture group);
B. Western blot analysis of ATP synthase subunit beta protein expression;
C. Quantitative PCR analysis of ATP synthase subunit beta mRNA expression (N = 7, compared to the low-glucose culture group under the same treatment conditions).
D. The image is a quantitative representation of the relative grayscale values of Fig. 5B (N = 7, *: P < 0.05, compared to the low-glucose culture group under the same treatment conditions).

enhancement or increase in the function of the ATP synthase β subunit may be a potential target for DCM treatment drug development.

CRediT authorship contribution statement

Yuanfang Ma: Writing – original draft, Formal analysis, Data curation. **Guang Wang:** Writing – review & editing, Supervision, Project administration. **Jing Li:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Funding acquisition.

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