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Influence of sodium-glucose co-transporter type 2 inhibitor on cardiomyocytes after acute myocardial infarction

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Abstract

Objective: To determine the influence of sodium-glucose co-transporter type 2 (SGLT2) inhibitor on cardiomyocytes after acute myocardial infarction (AMI).

Methods: Altogether 36 clean C57B/L6 mice (8-10 weeks old) were chosen and assigned to a control group (con group; Sham operation group), research group (res group; AMI+SGLT2 group), and model group (mod group; AMI group) (each n=12) via the sortition randomization means. AMI models were established by ligating the left coronary artery of each mice in the research and model groups, and each mice in the res group was given 30 mg/kg SGLT2 each day for 2 weeks. Afterwards, the cardiac function indexes, myocardial injury markers, inflammatory factors, oxidative stress, cardiomyocyte apoptosis and associated proteins of mice in the three groups were evaluated and recorded.

Results: Compared with the mod group, the res group showed notable smaller myocardial infarction area. In contrast to the con group, the mod group presented a notable increase in left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic dimension (LVEDD), and myocardial injury markers and a notable decrease in left ventricular ejection fraction (LVEF) and short axis shortening rate (FS). The cardiac function and myocardial injury of the res group were greatly ameliorated after administration with SGLT2. Additionally, in contrast to the con group, the mod group showed a notable increase in the levels of serum TNF-α, IL-1β, and IL-6, and SGLT2 relieved the inflammatory state in the res group. In contrast to the con group, the mod group presented an increase in serum MDA and a decrease in serum SOD, and SGLT2 alleviated the oxidative stress in the res group. Moreover, in contrast to the con group, the mod group presented notably increased apoptosis rate of cardiomyocytes, and SGLT2 reduced the apoptosis rate and improved apoptosis-related proteins in the res group.

Conclusion: For mice with AMI, SGLT2 inhibitor can relieve their myocardial injury and reduce their inflammatory level and oxidative stress *in vivo* and cardiomyocyte apoptosis.

Keywords: SGLT2 inhibitor, acute myocardial infarction, cardiomyocytes, influence

Introduction

Cardiovascular disease is a material cause of death, and acute myocardial infarction (AMI) shows an increasing morbidity and mortality as people live longs and have changed diet (Choi et.al,2019 ; Sumarjaya, Nadha and Lestari,2020). AMI is an acute myocardial necrosis caused by the serious imbalance of coronary blood supply and myocardial demand, which gives rise to myocardial ischemia and hypoxia, myocardial structure damage, and decline of cardiomyocyte contractility and cardiac pump function (Larsen et.al,2018; Swain, et.al,2020). Myocardial ischemia is caused by many factors. For instance, inflammation, oxidative stress and cardiomyocyte apoptosis are all bound up with myocardial ischemic injury. With terribly unfavorable prognosis, AMI is more common in patients as they grow older (Anand, et.al,2020). Therefore, it is of great value to develop vascular protective agents to improve myocardial function and reduce cardiovascular events in patients with AMI in view of factors such as cardiomyocyte apoptosis (CA) and inflammation.

SGLT2, a novel hypoglycemic drug, boasts of unique property of lowering blood glucose by increasing glycosuria but not involving insulin (Flores, et.al,2018). One study has pointed out that SGLT2 can lower the mortality related to

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cardiovascular diseases among patients with type 2 diabetes mellitus (TM) facing a high cardiovascular risk (Muller, et.al,2018). Moreover, for patients with TM, SGLT2 inhibitor can low the hospitalization rate due to heart failure (HF) and the risk of cardiovascular composite end points (death, myocardial infarction, hospitalization due to HF, and stroke) (Derosa and Maffioli,2018). According to one other study, SGLT2 inhibitor possesses many functions, such as reducing glycosylated hemoglobin, blood pressure, body weight, reabsorption of filtered sodium and glucose in proximal tubules, workload of oxygen-consuming transportation, and pro-inflammatory factors and improving the integrity of tubular cells (Dekkers, et.al,2018). In one study by Lahnwong S and others (Lahnwong, et.al,2020), SGLT2 is favorable in reducing the severity of hyperglycemia and HF, and SGLT2 inhibitor can exert positive effect in myocardial infarction area, left ventricular function, arrhythmia and cardiac rhythm during heart ischemia/reperfusion injury. In one study by Papademetriou V and others (Papademetriou and Geladari,2018), SGLT2 inhibitor can improve the outcomes of patients with cardiovascular diseases. For instance, for patients with HF, the inhibitor can lower their blood pressure, alleviate their arterial stiffness, and greatly ameliorate their left ventricular and diastolic dysfunction.

This study established AMI mice models to evaluate the influence of SGLT2 inhibitor on cardiac function, myocardial injury, inflammatory stress response and cardiomyocyte apoptosis of mice and explore its protective mechanism on myocardium of AMI mice.

Materials and methods

Source of experimental animals

Altogether 36 clean C57B/L6 (8-10 weeks old; Veterinary Research Institute, Lanzhou, CN, J006) were raised in a clean environment with well ventilation at (22±2) ℃ and relative humidity of 50-65% under alternative day and night during 24 hours for one week, and provided with water and food under standard animal care procedures. This experiment was performed with permission from the Ethics Committee of our hospital and in conformity to *Guidelines for the protection and use of experimental animals* (Sikes,2016).

Modeling of AMI

The 36 mice were randomly assigned to a control group (con group), model group (mod group) and research group (res group) (each n=12). AMI models were established by ligation of the left anterior descending coronary artery of mice (Gao, et.al,2010). Each mice was given 2% isoflurane by continuous inhalation for anesthesia. The chest cavity between the 3rd and 4th ribs on the left side of the mice was opened, and squeezing the heart out gently. It was ligated at 2 mm below the front of the left atrial appendage with a 6-0 suture needle. After operation, the mice was given 40,000 U penicillin to prevent postoperative infection. Moreover, effective measures were taken to keep the mice warm after operation. On the 2nd day after operation, pathological Q waves in more than 6 of ECG I, AVL and V1-16 leads marked modeling success of myocardial infarction. After operation, mice in the res group were given 30 mg/kg SGLT2 for 2 weeks. For those in the con group, threads were not knotted after threading, and the rest steps were the same with those for modeling of myocardial infarction.

Outcome measures

1. Measurement of AMI area: At 2 weeks after operation, each mice was anesthetized, and religated the anterior descending branch, then the aortic arch was quickly separated, the aorta was cut and bled, and the aorta was retrogradely injected with 1% Evans blue; the heart was quickly cut and placed in ice 0.9% nanohydrogen oxide, the ligated anterior descending branch was untied, and the aorta was retrogradely cannulated and fixed with a flat-tipped syringe needle with a groove of No. 7; the heart was slowly injected with 1% TTC solution in a 37℃ The heart was slowly injected with 1% TTC solution in a warm bath and incubated at 37℃ for 3~4min; after that, the ear was cut off and 15% alginate paste was injected into the heart cavity to solidify the shape, and after drying, it was placed in 4% paraformaldehyde and fixed for 12~24h; the heart was placed in a sectioning mold, poured with 10% agarose, and after cooling, it was evenly cut into 5~6 slices (about 1mm) with a thin blade; The infarcted area was not stained, while the uninfected area was dyed dark purple. They were photographed, and the areas were measured on image analysis system and the ischemic and infarcted areas were calculated according to the formula: Ischemic or infarcted area = (length of epicardium + endocardium in the unstained area) / (circumference of epicardium + endocardium of the left ventricle) ×100%.
2. Cardiac function indexes: On the 2nd day after the last administration, 3% pentobarbital sodium was injected intraperitoneally to

anesthetize mice in each group, and an ultrasonic imaging system was adopted for ultrasonic cardiograms of the mice for determining their left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular ejection fraction

3. (LVEF), and short axis shortening rate (FS). Each index was measured three times, and the results were averaged.
4. Myocardial injury markers: Blood (2-3mL) was sampled from the femoral artery of each mice, and subjected to 10-min centrifugation (1500Xg, 4℃), followed by storing in a refrigerator at -70℃. An automatic biochemical analyzer was adopted for detecting the myocardial injury markers and blood lipid including creatine kinase (CK), creatine kinase isoenzyme (CK-MB), and lactate dehydrogenase (LDH).
5. Inflammatory and oxidative stress factors: An ELISA assay was performed for quantifying inflammatory and oxidative stress factors, including TNF-α, IL-1β, IL-6, malondialdehyde (MDA), and superoxide dismutase (SOD) (Singh, et.al,2020).
6. Cardiomyocyte apoptosis: The heart of each mice in the three groups was taken out via thoracotomy after anesthesia, and cultured cardiomyocytes were isolated, followed by apoptosis detection by a flow cytometer under instructions of an Annexin V-FITC/PI double staining apoptosis kit (Jingke Chemical Technology Co., Ltd., Shanghai, CN, AD10-2). Additionally, the cells were trypsinized, followed by twice of washing via PBS, and then transferred to centrifuge tubes. Annexin-V-FITC labeling solution (20 μl) and PI reagent (20 μl) were successively put into 1 ml buffer, followed by 5-min incubation at indoor temperature with dark surroundings, and then detected via flow cytometry. The results of three times of detection were averaged.
7. WB assay: Extracted myocardial tissues (50 mg) were placed in 500 μL lysate (HaiGene Biotech Co., Ltd., Harbin, China, C1901) for lyse and subjected to 20-min centrifugation (12000×g, 4°C) after homogenization in ice bath, so as to obtain the supernatant. Its protein concentration was quantified via a BCA kit (Amyjest Scientific Co., Ltd., Wuhan, CN, 701780-480). The protein was isolated via 12% SDS-PAGE (Yiji Industry Co., Ltd., Shanghai, CN, YJ0014B), and then placed on a PVDF membrane (Acmec Biochemical Technology Co., Ltd., Shanghai, CN, ISEQ00010). Subsequently, the membrane was immersed in 5% defatted milk for later immune response. It was incubated with primary antibody (1: 1000) at 4℃ all night long, and the primary antibody was washed off. Then it was subjected to 1-h incubation with horseradish peroxidase labeled goat anti-rabbit secondary antibody (1: 1000; Abbkine Biology Technology Co., Ltd., Wuhan, CN, A21010) at 37℃ for 1h, followed by three times of rinsing via PBS (5 min/time). After incubation, the protein was developed and immobilized with ECL agent. The image was taken by the Quantity One infrared imaging system. The relative expression of protein under determination = Gray value of the band under determination / that of internal reference protein band.

Statistical analyses

SPSS25.0 (EASYBIO Technology Co., Ltd., Beijing, CN) was adopted for statistical analyses and GraphPad 6 for data analysis and figure drawing. All data, presented by the (mean ± SD), were compared between groups via the independent-samples T test and among multiple groups via the one-way anova (expressed by F), and their post hoc pairwise comparison was conducted via the LSD-t. $P < 0.05$ suggests a remarkable difference.

Results

Comparison of myocardial ischemia and infarcted areas

According to the comparison of myocardial ischemia and infarcted areas between the res and mod groups, the two groups were not greatly different in the former ($P > 0.05$), but the infarcted area in the res group decreased greatly and was notably lower than that of the mod group (both $P < 0.05$) (Table 1).

Table 1. **Comparison of myocardial ischemia and infarcted area between the research group and model group (mean±SD, %)**

Group	n	Myocardial ischemia area	Myocardial infarcted area
The research group	12	33.54±3.68	29.87±2.82
The model group	12	35.16±3.69	33.54±3.17
t	-	1.077	2.996
P-value	-	0.293	0.007

Comparison of cardiac function indexes

According to the results of cardiac function

indexes of the three groups, in contrast to the con group, the mod group showed a notable increase in LVESD and LVEDD and a notable decrease in LVEF and FS (all $P < 0.05$), and in the res group, SGLT2 greatly suppressed the increase of LVESD and LVEDD, and LVEF and FS increased notably (all $P < 0.05$) (Table 2).

Table 2. **Comparison of cardiac function indexes among the three groups (mean±SD)**

Group	n	LVESD (mm)	LVEDD (mm)	LVEF (%)	FS (%)
The control group	12	1.99±0.19	3.28±0.28	70.23±2.48	44.55±1.21
The model group	12	4.61±0.31	3.71±0.16	49.72±5.54	27.28±5.39
The research group	12	3.42±0.35	3.46±0.22	54.26±2.15	31.79±1.67
t	-	161.7120	7.206	63.477	57.769
P-value	-	< 0.001	< 0.005	< 0.001	< 0.001

Comparison of myocardial injury markers

According to the results of myocardial injury markers of the three groups, in contrast to the con group, the mod group presented a notable increase in CK, CK-MB, and LDH, and SGLT2 greatly decreased the concentrations of them in the res group (all $P < 0.05$) (Table 3).

Table 3. **Comparison of myocardial injury markers of the three groups (mean±SD)**

Group	n	CK (UI)	CK-MB (U/mg)	LDH (U/mg)
The control group	12	108.68±10.47	84.19±8.04	186.37±18.03
The model group	12	356.16±31.15	146.37±14.18	321.36±30.48
The research group	12	153.79±15.19	104.29±10.03	205.38±20.03
t	-	477.200	98.950	116.100
P-value	-	< 0.001	< 0.001	< 0.001

Comparison of inflammatory factors

According to the inflammatory factors of the three groups, in contrast to the con group, the mod group presented a notable increase in the expression of serum TNF-α, IL-1β, and IL-6 (all $P < 0.05$), and intervention with SGLT2 greatly decreased the expression of them in the res group (all $P < 0.05$) (Table 4).

Table 4. **Comparison of expression of inflammatory factors among the three groups (mean±SD)**

Group	n	TNF-α(ng/mL)	IL-1β(ng/L)	IL-6(ng/mL)
The control group	12	14.62±1.46	3.17±0.25	78.26±7.09
The model group	12	32.97±2.42	9.58±0.91	109.37±10.78
The research group	12	30.49±2.08	6.02±0.58	89.73±8.92
t	-	192.45	302.600	36.220
P-value	-	< 0.001	< 0.001	< 0.001

Comparison of oxidative stress parameters

According to the results of oxidative stress parameters of the three groups, in contrast to the con group, the mod group presented a notable increase in serum MDA and a notable decrease in serum SOD (both $P < 0.05$), and intervention with SGLT2 greatly decreased serum MDA and increased SOD in the res group, (both $P < 0.05$) (Figure 1).

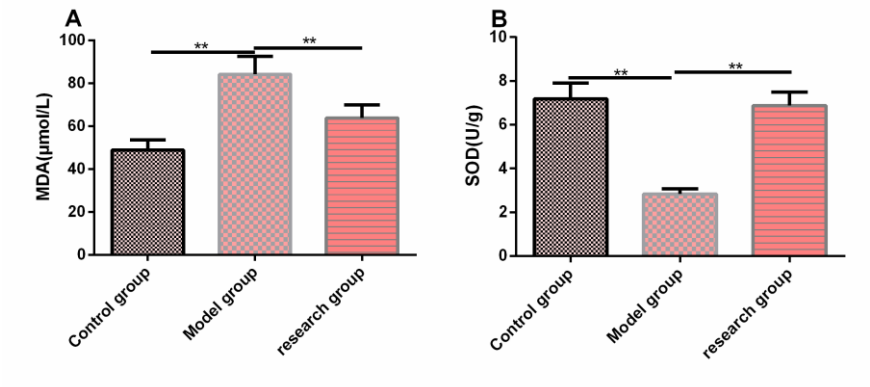

Figure 1 **Comparison of oxidative stress parameters among the three groups**

A, Influence of metoprolol on MDA in mice with coronary heart disease.

B, Influence of metoprolol on SOD in mice with coronary heart disease.

Notes: In comparison with the control group or in inter-group comparison, *P<0.05 and **P<0.001.

Comparison of cardiomyocyte apoptosis and expression of related factors

We adopted the flow cytometry for evaluation of the cardiomyocyte apoptosis of the three groups, finding that in contrast to the con group, the mod group presented notably increased cardiomyocyte apoptosis (P < 0.05), while intervention with SGLT2 slowed down the apoptosis in the res group (P < 0.05). We also determined apoptosis-associated proteins, finding that in contrast to the con group, the mod group presented increased Bax and Bcl-xl and apoptosis and decreased Bcl-2 and cell viability, while in the res group, intervention with SGLT2 strongly reversed the above situation (Figure 2).

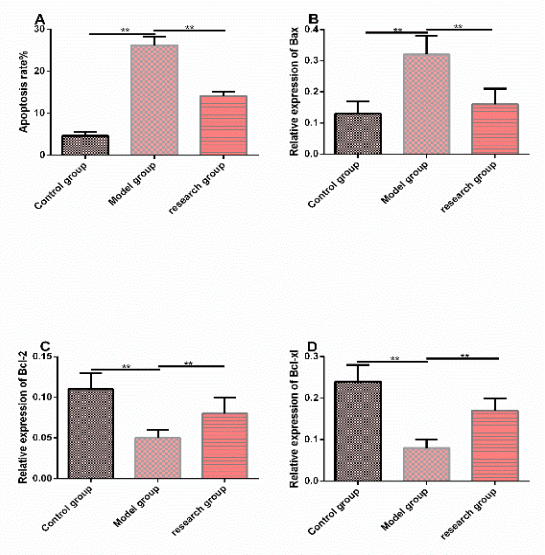

Figure 2 **Comparison of cardiomyocyte apoptosis and expression of related factors among the three groups**

A, Influence of SGLT2 on cardiomyocyte apoptosis in AMI group

B-D, Influence of SGLT2 on Bax, Bcl-xl and Bcl-2 in cardiomyocytes of AMI group.

Notes: In comparison with the control group or in inter-group comparison, *P<0.05 and **P<0.001.

Discussion

Cardiomyocytes in patients suffering from AMI will die massively, so effective cells will be less, which will result in ventricular remodeling and HF (Chen, et.al,2020). After myocardial infarction, cardiomyocytes will die by apoptosis or necrosis (Gong, et.al,2020), Apoptosis is an active and orderly process of cell self-extinction regulated by genetic genes (Ucker,2016). Many studies have revealed that after myocardial infarction, cardiomyocytes die by apoptosis mostly (Yoshimura, et.al,2020). Thus, researchers focus their efforts on alleviating myocardial injury and cardiomyocytes in patients with myocardial infarction.

As one earlier study shows, intervention with SGLT2 inhibitor can reduce vascular events, mortality and myocardial infarction in patients (Monami, Dicembrini and Mannucci,2017). However, the

influence of SGLT2 inhibitor on myocardial protection and cardiomyocyte apoptosis in mice with AMI is rarely studied. Therefore, to understand the myocardial protection of SGLT2 inhibitor in such rats, this experiment was designed. The results verified that SGLT2 inhibitor can strongly reduce inflammatory cells in mice, alleviate their myocardial injury and accelerate cardiomyocyte apoptosis. According to one study (Stieger, et.al,2017), after myocardial infarction, the formed myocardial edema around the infarction area will further damage the cardiac function, so narrowing the infarct area and improving the myocardial function are of great importance. In our study, after modeling of AMI, the mod group presented larger MYOCARDIAL INFARCTION AREA, and after intervention with SGLT2 inhibitor, the MYOCARDIAL INFARCTION AREA of the res group decreased greatly and was smaller than that of the mod group. The results imply that SGLT2 inhibitor can narrow myocardial infarction in mice, and thus protect the cardiac function. One study has concluded that SGLT2 inhibitor is beneficial to ventricular remodeling of patients, because of its ability of reducing body mass and blood pressure without increasing the heart rate of the patients (Karg, et.al,2018). According to our obtained results, in contrast to the con group, the mod group showed a notable increase in LVESD and LVEDD and a notable decrease in LVEF and FS, and in the res group, SGLT2 greatly suppressed the increase of LVESD and LVEDD, and LVEF and FS increased notably. The results suggest that SGLT2 inhibitor can improve myocardial energy production in mice, thus improving the cardiac function of AMI rats. Moreover, one study has revealed that myocardial injury markers including serum CK-MB, LDH and troponin in patients will increase notable after they suffer from AMI (Chen, et.al,2015). The results are similar to those of our study that the concentrations of CK, CK-MB, and LDH in the mod group increased

notably, and intervention with SGLT2 greatly decreased the concentrations of them in the res group. Our results denote that intervention with SGLT2 inhibitor can effectively improve the myocardial function of AMI group, thus alleviating the damage to the function.

Many factors such as inflammation and apoptosis after AMI are implicated in myocardial ischemic injury, and myocardial inflammation takes a crucial part in the physiological and pathological mechanism of cardiac dysfunction (Li et al, 2019). Excessive myocardial inflammation can seriously damage myocardium, and give rise to diseases such as myocardial infarction (Teixeira et al, 2019). According to the results in our study, in contrast to the con group, the mod group presented a notable increase in the expression of serum TNF-α, IL-1β, and IL-6, and intervention of SGLT2 greatly decreased the expression of them in the res group. Additionally, in one study by Lee SG and others (Lee et al, 2020), in atherosclerosis models, intervention with SGLT2 inhibitor can strongly reduce aneurysm load and lipid accumulation, and weaken inflammatory factors in cases without TM. The results are in consistent to those of our study, indicating that SGLT2 inhibitor can alleviate the inflammatory state in AMI group and reduce the release of inflammatory factors in the heart, thus protecting the myocardium of mice. The damage of ischemic tissues in cases with myocardial infarction is bound up with excessive reactive oxygen species, and cases with myocardial infarction face a risk of oxidative damage aggravation and antioxidant capacity decrease (Shahzad et al.,2018). In our study, in contrast to the con group, the mod group presented a notable increase in serum MDA and a notable decrease in serum SOD, and intervention with SGLT2 greatly decreased serum MDA and increased SOD in the res group. Moreover, one study by Li W and others showed that SGLT2 inhibitor can reduce major adverse cardiovascular events, mainly because it can lower blood pressure, improve heart function and reduce inflammation and oxidative stress (Li et al.,2020). This is similar to the findings of our study, which suggests that SGLT2 inhibitor can alleviate myocardial oxidative stress injury in AMI group model, thus alleviating cardiomyocyte damage. One study has pointed out that cardiomyocyte apoptosis occupies a crucial position in ventricular remodeling and other complications after AMI (Li et al.,2019). In our study, the mod group presented notably increased cardiomyocyte apoptosis, while intervention with SGLT2 slowed down the apoptosis in the res group. We determined apoptosis-associated proteins, finding that in contrast to the con group, the mod group presented increased Bax and Bcl-xl and apoptosis and decreased Bcl-2 and cell viability, while in the res group, intervention with SGLT2 strongly reversed the above situation. Moreover, one study by Lahnwong S and others has indicated that the direct effect of SGLT2 against diabetic cardiomyopathy may be mediated by its ability to relieve heart inflammation, oxidative stress, and apoptosis (Lahnwong et al.,2018), which is also similar to the results of our study. Those data indicate that SGLT2 inhibitor can alleviate the apoptosis-associated injury of cardiomyocytes in AMI group, inhibit pro-apoptotic genes and up regulate anti-apoptotic genes.

To sum up, for mice with AMI, SGLT2 inhibitor can relieve their myocardial injury and reduce their inflammatory level and oxidative stress in vivo and the cardiomyocyte apoptosis.

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