ChinaRxiv

AI translation · View original & related papers at
chinarxiv.org/items/chinaxiv-202212.00100

Regulation of miR-423-5p and Effect on Cardiac Function by Dapagliflozin in Patients with Type 2 Diabetes Mellitus Complicated by Chronic Heart Failure: Postprint

Authors: Chen Ruimin, Liu Fang, On Red, Han Shufang, Chen Yingjian, Su Congcong, On Red

Date: 2022-12-20T08:38:08+00:00

Abstract

Background: The number of patients with diabetes mellitus complicated by heart failure is substantial. Dapagliflozin, as a novel hypoglycemic agent, is currently recommended by guidelines for the treatment of heart failure; however, its mechanism for improving cardiac function remains incompletely understood.

Objective: To investigate the effect of dapagliflozin on plasma miR-423-5p expression in patients with type 2 diabetes mellitus (T2DM) complicated by chronic heart failure and its correlation with cardiac function.

Methods: Fifty patients with T2DM complicated by chronic heart failure who presented to the 960th Hospital of the People's Liberation Army between April 1, 2021 and November 30, 2021 were enrolled as study subjects. The subjects were randomly divided into two groups: a control group (conventional drug therapy) and a dapagliflozin group (conventional drugs plus dapagliflozin), with 25 cases in each group. Additionally, 25 healthy individuals with normal cardiac function from the physical examination center during the same period were selected as the healthy population group. After 4 weeks of drug treatment, changes in N-terminal pro-B-type natriuretic peptide (NT-proBNP), plasma miR-423-5p expression levels, left ventricular ejection fraction (LVEF), stroke volume (SV), left ventricular fractional shortening (LVFS), and left ventricular end-diastolic diameter (LVEDD) were observed. After 6 months of drug treatment, cardiac function indicators were reassessed.

Results: At baseline, NT-proBNP, LVEDD, and plasma miR-423-5p expression levels in both the control and dapagliflozin groups were significantly higher than those in the healthy population group ($P<0.05$), while LVEF, SV, and LVFS

levels were significantly lower (P<0.05). After 4 weeks of drug treatment, NT-proBNP and plasma miR-423-5p expression levels decreased significantly in both the control and dapagliflozin groups (P<0.05). Moreover, compared with the control group, the dapagliflozin group exhibited a more pronounced decrease in NT-proBNP and plasma miR-423-5p expression levels (P<0.05). After 4 weeks of treatment, LVEF, SV, and LVFS increased while LVEDD decreased in both groups compared with baseline (P<0.05); however, no significant statistical differences were observed between the dapagliflozin and control groups (P>0.05). After 6 months of drug treatment, LVEDD levels decreased significantly while LVEF, SV, and LVFS levels increased significantly in both groups compared with baseline (P<0.05). Furthermore, compared with the control group, the dapagliflozin group demonstrated more significant changes in LVEDD, LVEF, SV, and LVFS (P<0.05).

Conclusion: Dapagliflozin improves cardiac function in patients with type 2 diabetes complicated by chronic heart failure, reduces NT-proBNP and LVEDD levels, and increases LVEF, SV, and LVFS levels. Its mechanism of action may be associated with the regulation of plasma miR-423-5p expression.

Full Text

Effects of Dapagliflozin on the Expression of miR-423-5p and Cardiac Function in Patients with Type 2 Diabetes Mellitus and Chronic Heart Failure

CHEN Ruimin[1], LIU Fang[2], TAN Hong[1]*, HAN Shufang[1], CHEN Yingjian[1], SU Congcong[2]

[1]Department of Cardiology, 960th Hospital of PLA, Jinan 250031, China
[2]Graduate Training Base of Jinzhou Medical University, 960th Hospital of PLA, Jinan 250031, China

Corresponding author: TAN Hong, MD, PhD, Chief Physician; E-mail: tanhong3769@163.com

Funding: This study was supported by the Shandong Provincial Medical and Health Science and Technology Development Plan Project (Project Title: Study on the Functional Regulation of FAS Gene in Vascular Endothelial Cells by Circulating Exosome-Derived microRNA hsa-let-7b-5p under High Glucose Conditions; Grant No.: 202103011061).

Abstract

Background: The prevalence of diabetes mellitus complicated with heart failure is substantial. Dapagliflozin, as a novel hypoglycemic agent, has been recommended by clinical guidelines for heart failure treatment, though its mechanism for improving cardiac function remains incompletely elucidated.

Objective: To investigate the effect of dapagliflozin on plasma miR-423-5p expression in patients with type 2 diabetes mellitus (T2DM) and chronic heart failure, and to examine its correlation with cardiac function.

Methods: Fifty patients with T2DM and chronic heart failure admitted to the 960th Hospital of PLA between April 1, 2021 and November 30, 2021 were enrolled and randomly divided into two groups: a control group (conventional drug therapy) and a dapagliflozin group (conventional therapy plus dapagliflozin), with 25 patients in each group. Additionally, 25 healthy individuals with normal cardiac function from the physical examination center during the same period were selected as the healthy control group. After four weeks of treatment, changes in N-terminal pro-brain natriuretic peptide (NT-proBNP), plasma miR-423-5p expression, left ventricular ejection fraction (LVEF), stroke volume (SV), left ventricular fractional shortening (LVFS), and left ventricular end-diastolic diameter (LVEDD) were assessed. Cardiac function indices were re-evaluated after six months of treatment.

Results: At baseline, NT-proBNP, LVEDD, and plasma miR-423-5p expression levels were significantly higher in both the control and dapagliflozin groups compared to the healthy group ($P<0.05$), while LVEF, SV, and LVFS levels were significantly lower ($P<0.05$). After four weeks of treatment, NT-proBNP and plasma miR-423-5p expression decreased significantly in both groups ($P<0.05$), with more pronounced reductions in the dapagliflozin group compared to the control group ($P<0.05$). LVEF, SV, and LVFS increased while LVEDD decreased in both groups after four weeks ($P<0.05$), though no significant differences were observed between the dapagliflozin and control groups ($P>0.05$). After six months of treatment, both groups showed significant decreases in LVEDD and increases in LVEF, SV, and LVFS compared to baseline ($P<0.05$), with the dapagliflozin group demonstrating more significant improvements in all these parameters compared to the control group ($P<0.05$).

Conclusion: Dapagliflozin improves cardiac function in patients with T2DM and chronic heart failure by reducing NT-proBNP and LVEDD levels while increasing LVEF, SV, and LVFS. The underlying mechanism may involve the regulation of plasma miR-423-5p expression.

Keywords: Dapagliflozin; Chronic heart failure; Diabetes mellitus; Cardiac function; miRNA-423-5p

Introduction

Heart failure (HF) represents a clinical syndrome characterized by ventricular systolic and diastolic dysfunction resulting from various cardiovascular diseases. The prevalence of diabetes among HF patients ranges from 10% to 47%, exceeding 40% in hospitalized HF patients. Diabetes constitutes an independent risk factor for HF, with HF prevalence among diabetic patients reaching 9%-22%—

approximately four times higher than in the general population and even more pronounced in diabetic patients aged 60 and above [2,3]. The coexistence of diabetes and HF significantly increases the risk of adverse cardiorenal outcomes [4,5], with a Spanish retrospective study demonstrating substantially elevated in-hospital mortality and cardiorenal event risks in patients with T2DM and HF [6].

Current clinical management relies primarily on the "golden triangle" of ACEI/ARB/ARNI, aldosterone receptor antagonists, and β-blockers. However, rehospitalization and mortality rates among HF patients remain unacceptably high. The landmark DAPA-HF study published in 2019 prompted updates to international HF guidelines, establishing dapagliflozin as a standard HF therapy and shifting the treatment paradigm from the "golden triangle" to the "new quadruple therapy," thereby expanding therapeutic options for HF management.

Dapagliflozin, a representative sodium-glucose cotransporter 2 inhibitor (SGLT2i), has been increasingly recognized through numerous studies for its cardiovascular protective effects independent of its glucose-lowering action. The 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure explicitly recommend SGLT2i (dapagliflozin, empagliflozin) for HF treatment. Curtain et al. demonstrated that adding dapagliflozin to standard therapy in patients with heart failure with reduced ejection fraction (HFrEF) reduces the risk of severe ventricular arrhythmias, resuscitated cardiac arrest, and sudden death. Lin et al. reported that dapagliflozin inhibits myocardial fibrosis and endoplasmic reticulum stress while improving hemodynamics. A meta-analysis by Wang et al. on the efficacy and safety of SGLT2i in HF treatment indicated that SGLT2 inhibitors, particularly dapagliflozin, improve survival in HFrEF patients with favorable safety profiles. While these findings collectively support the cardiovascular benefits of dapagliflozin, the precise mechanisms underlying its improvement of HF outcomes remain incompletely understood.

Emerging evidence demonstrates that microRNAs (miRNAs) regulate gene expression and play crucial roles in cardiomyocyte injury, apoptosis, and myocardial fibrosis. Our previous studies revealed elevated plasma miR-423-5p expression in chronic HF patients, with levels decreasing as cardiac function improved. However, whether dapagliflozin exerts its cardioprotective effects through modulation of miR-423-5p expression has not been previously reported. This study therefore enrolled patients with T2DM and chronic HF to investigate the relationship between dapagliflozin's cardiac function improvement and miR-423-5p levels, aiming to further elucidate the mechanistic basis for dapagliflozin's beneficial effects on HF prognosis.

1.1 Study Subjects

Following approval by the hospital ethics committee and obtaining informed consent, 50 patients with T2DM and chronic heart failure admitted to the 960th Hospital of PLA between April 1, 2021 and November 30, 2021 were enrolled (25 in the control group and 25 in the dapagliflozin group). Additionally, 25 healthy individuals with normal cardiac function from the physical examination center during the same period were selected as the healthy control group.

Inclusion criteria: (1) Age 18-80 years; (2) CHF diagnosis according to the Chinese Guidelines for the Diagnosis and Treatment of Heart Failure (2018), with HF duration $ $3 months, NYHA class II-IV, and left ventricular ejection fraction (LVEF) <40%; (3) T2DM diagnosis according to the Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes Mellitus (2020) [14], defined as typical diabetes symptoms with random glucose $ $11.1 mmol/L, or fasting glucose $ $7.0 mmol/L, or 2-hour oral glucose tolerance test (OGTT) $ $11.1 mmol/L, or HbA1c $ $6.5%, with T2DM duration $ $3 months; (4) No prior SGLT2 inhibitor use; (5) Signed informed consent.

Exclusion criteria: (1) Acute decompensated HF; (2) Type 1 diabetes; (3) Severe arrhythmias, acute myocardial infarction, valvular disease, severe cor pulmonale, or hypertrophic cardiomyopathy; (4) Hypotension or recurrent hypoglycemia; (5) Severe hepatic or renal insufficiency; (6) Severe infectious diseases, hemodialysis, or malignant disease; (7) Pregnancy or lactation.

1.2 Reagents and Instruments

Dapagliflozin tablets (Forxiga, AstraZeneca, 10 mg/tablet); miRNA extraction and isolation kits, miRNA reverse transcription and fluorescence quantitative PCR kits were purchased from Beijing Tiangen Biotech Co., Ltd.; PCR-specific upstream primers were synthesized by GeneCopoeia (USA). NanoDrop 2000 micro-spectrophotometer was purchased from Thermo Scientific (USA), and LightCycler 480II PCR amplifier from Roche (Switzerland).

1.3 Plasma Sample Collection, Separation, and Storage

Fasting elbow venous blood (4 mL) was collected on the morning of the second day after admission from patients and during physical examination from healthy controls, placed in EDTA anticoagulant tubes, and centrifuged at 3000 rpm for 10 minutes at 4°C to collect the supernatant. The supernatant was aliquoted and stored at -80°C for future use. For enrolled T2DM patients with chronic HF, fasting elbow venous blood (4 mL) was collected again after four weeks of treatment and processed using the same method.

1.4 Plasma Total RNA Extraction

Frozen plasma samples were thawed at room temperature and centrifuged at 15,000 rpm for 5 minutes at 4°C. Then, 200 L of supernatant was transferred

to a new RNase-free EP tube. Total RNA was extracted according to the kit instructions. RNase-free water served as the blank control for calibration, with $1.9 < \text{OD260/OD280} < 2.1$ indicating good RNA purity. High-quality specimens were selected for reverse transcription.

1.5 Reverse Transcription and Fluorescence Quantitative PCR Detection of Plasma miR-423-5p Expression

Plasma miR-423-5p expression was detected using reverse transcription and fluorescence quantitative PCR. Following the kit instructions, poly(A) tailing and reverse transcription were performed at 42°C for 60 minutes, followed by enzyme inactivation at 95°C for 3 minutes. The resulting cDNA served as the template for quantitative PCR using U6 as the internal reference. PCR conditions were: 95°C for 15 minutes (initial denaturation, 1 cycle); 94°C for 20 seconds, 64°C for 30 seconds, 72°C for 34 seconds (5 cycles); and 94°C for 20 seconds, 60°C for 34 seconds (40 cycles). Relative miR-423-5p expression was calculated using the $2^{\wedge}(-\Delta\Delta Ct)$ method.

1.6 Statistical Analysis

Statistical analysis was performed using SPSS 25.0 software. Normally distributed continuous data were expressed as mean ± standard deviation ($\bar{x} \pm s$). Normality was assessed using the Shapiro-Wilk test, and homogeneity of variance using Levene's test. For normally distributed data with equal variance, independent samples t-test and one-way ANOVA were used for inter-group comparisons, while paired t-test was used for intra-group comparisons before and after treatment. Non-normally distributed data were expressed as median (P25, P75) and analyzed using the rank-sum test for inter-group comparisons and paired rank-sum test for intra-group comparisons. Categorical data were expressed as counts and percentages and compared using chi-square test or Fisher's exact test. Pearson correlation was used for bivariate normal distribution data, and Spearman correlation for non-normal distribution data. $P<0.05$ was considered statistically significant.

2.1 Comparison of General Clinical Data Among Groups

No significant differences were observed among groups in personal history, past medical history, blood pressure, body mass index, lipid profile, creatinine, NYHA functional class, or concomitant use of diuretics, β-blockers, RAAS inhibitors, nitrates, ARNI, antiplatelet agents, or trimetazidine ($P>0.05$). See
.

2.2 Comparison of Glycemic Indices, Cardiac Function Parameters, and miR-423-5p Levels Before Treatment

Before treatment, FBG, HbA1c, NT-proBNP, LVEDD, and miR-423-5p expression levels were significantly higher in both the dapagliflozin and control groups compared to the healthy group, while LVEF, SV, and LVFS levels were significantly lower ($P<0.05$). No significant differences were observed between the dapagliflozin and control groups in FBG, HbA1c, LVEF, LVEDD, SV, LVFS, NT-proBNP, or miR-423-5p expression ($P>0.05$). See .

2.3 Comparison of Cardiac Function Indices and miR-423-5p Levels After 4 Weeks of Treatment

After four weeks of treatment, NT-proBNP and plasma miR-423-5p expression levels decreased significantly in both the control and dapagliflozin groups compared to baseline ($P<0.05$). Moreover, the dapagliflozin group exhibited more pronounced reductions in NT-proBNP and miR-423-5p compared to the control group ($P<0.05$). LVEF, SV, and LVFS increased while LVEDD decreased in both groups after four weeks ($P<0.05$), though no significant differences were observed between the dapagliflozin and control groups ($P>0.05$). See .

2.4 Comparison of Cardiac Function Indices After 6 Months of Treatment

After six months of treatment, both groups showed significant decreases in LVEDD and increases in LVEF, SV, and LVFS compared to baseline ($P<0.05$). The dapagliflozin group demonstrated more significant improvements in LVEDD, LVEF, SV, and LVFS compared to the control group ($P<0.05$). See .

2.5 Comparison of Blood Pressure and Hepatic/Renal Function Indices in the Dapagliflozin Group Before and After 6 Months of Treatment

After six months of dapagliflozin treatment, both systolic and diastolic blood pressure decreased compared to baseline ($P<0.05$). However, no significant differences were observed in ALT, AST, or Cr levels compared to baseline ($P>0.05$). See .

2.6 Correlation Analysis Between miR-423-5p Expression and NT-proBNP Levels

Spearman correlation analysis revealed a significant positive correlation between plasma miR-423-5p expression and NT-proBNP levels ($r=0.609$, $P<0.05$). See [Figure 1: see original paper].

[Figure 1: see original paper]

2.7 Correlation Analysis Between miR-423-5p Expression and LVEF Levels

Pearson correlation analysis demonstrated a significant negative correlation between plasma miR-423-5p expression and LVEF levels ($r=-0.406$, $P<0.05$). See [Figure 2: see original paper].

[Figure 2: see original paper]

Discussion

The pathogenesis of heart failure is highly complex. Initially, enhanced sympathetic nerve activity and activation of the renin-angiotensin-aldosterone system (RAAS) exert compensatory effects to maintain normal cardiac output. However, as the disease progresses, these compensatory mechanisms become insufficient, leading to irreversible cardiac structural changes including cardiomyocyte injury, myocardial fibrosis, and ventricular remodeling. With societal development, the diabetic population continues to expand, and the clinical coexistence of diabetes mellitus (DM) and HF has become increasingly common, with each condition exacerbating the risk and progression of the other [2,3]. The prevalence, rehospitalization, and mortality rates of HF remain persistently high, driving continuous evolution in therapeutic strategies. From the 1950s to 1980s, conventional HF management focused on "cardiac strengthening, diuresis, and vasodilation," which effectively alleviated symptoms but failed to prevent disease progression or significantly reduce mortality. Since the late 1980s, neuroendocrine blockade emerged as a novel therapeutic concept, establishing the "golden triangle" paradigm. The 2014 PARADIGM-HF trial marked a significant advancement, demonstrating that ARNI could replace ACEI as a new component of the "golden triangle." The groundbreaking DAPA-HF study in 2019 subsequently prompted guideline updates worldwide, formally incorporating dapagliflozin into standard HF therapy and shifting the treatment gold standard from the "golden triangle" to the "new quadruple therapy."

The DAPA-HF trial enrolled 4,744 HFrEF patients with or without T2DM, using worsening HF or cardiovascular death as the primary endpoint. After 18.2 months of follow-up, dapagliflozin reduced the risk of death and HF events by 26%. Dapagliflozin exerts multiple effects including diuresis, glucose and blood pressure reduction, promotion of ketone body production, and increased hemoglobin levels, though the specific mechanisms underlying its HF prognostic benefits remain unclear. A study by Liu et al. investigating dapagliflozin's effects on miRNA expression profiles in a rat HF model created by left anterior descending artery ligation found that dapagliflozin altered cardiac miRNA expression, significantly downregulating miR-671, whose low expression was associated with improved cardiac function. These findings suggest that dapagliflozin may exert its cardioprotective effects through modulation of microRNA expression.

MicroRNAs (miRNAs) are a class of non-coding RNAs approximately 20-24 nucleotides in length that play crucial roles throughout human growth and development. miRNAs are not only specifically expressed at particular disease stages but also regulate gene expression, thereby influencing key pathological processes in HF including cardiomyocyte injury, apoptosis, fibrosis, and angiogenesis [11,12]. Recent international studies have demonstrated elevated miR-423-5p expression in HF patients, with levels changing in parallel with HF progression and correlating with LVEF and NT-proBNP [15,16,21]. Our previous research also showed upregulated plasma miR-423-5p in HF patients, with ROC curve analysis demonstrating good specificity and sensitivity for CHF diagnosis. However, the regulatory effect of dapagliflozin on miR-423-5p expression and its relationship with cardiac function improvement have not been previously reported.

This study therefore enrolled patients with T2DM and chronic HF to investigate the effect of dapagliflozin on plasma miR-423-5p expression and its correlation with cardiac function, aiming to further clarify the mechanistic basis for dapagliflozin's therapeutic effects. The dapagliflozin and control groups showed no significant differences in personal history, past medical history, blood pressure, body mass index, lipid profile, creatinine, NYHA functional class, or concomitant medications including diuretics, β-blockers, RAAS inhibitors, nitrates, ARNI, antiplatelet agents, and trimetazidine ($P>0.05$), indicating well-matched baseline characteristics that exclude confounding clinical factors. Before treatment, no significant differences were observed between the dapagliflozin and control groups in FBG, HbA1c, LVEF, LVEDD, SV, LVFS, NT-proBNP, or plasma miR-423-5p expression, eliminating potential baseline differences that could affect outcomes.

After four weeks of dapagliflozin treatment added to conventional therapy, both the control and dapagliflozin groups showed significant reductions in NT-proBNP and plasma miR-423-5p expression ($P<0.05$), with the dapagliflozin group exhibiting more pronounced decreases ($P<0.05$). Plasma miR-423-5p expression showed a significant positive correlation with NT-proBNP levels. After four weeks, LVEF, SV, and LVFS increased while LVEDD decreased in both groups ($P<0.05$), and plasma miR-423-5p expression demonstrated a significant negative correlation with LVEF. However, no significant differences were observed between the dapagliflozin and control groups at this early time point. After six months, left ventricular systolic function continued to improve, with both groups showing significant decreases in LVEDD and increases in LVEF, SV, and LVFS compared to baseline ($P<0.05$). The dapagliflozin group demonstrated more significant improvements in all these parameters compared to the control group ($P<0.05$).

These findings further confirm the diagnostic significance of plasma miR-423-5p expression in HF and demonstrate that dapagliflozin improves cardiac function in patients with T2DM and chronic HF. The mechanism may involve regulation of plasma miR-423-5p expression, providing a novel direction for investigating

dapagliflozin's cardioprotective mechanisms. Zhou et al. reported that miR-423-5p regulates the PI3K/AKT pathway in rat HF models, suggesting this pathway may play a key role in miR-423-5p-mediated HF progression, warranting further mechanistic investigation. This study had a relatively small sample size, and future research should expand the cohort to strengthen the conclusions. Subsequent studies should also investigate downstream targets of miR-423-5p and other related miRNAs through clinical trials and basic research to elucidate the molecular mechanisms underlying dapagliflozin's beneficial effects on HF prognosis, potentially contributing to improved HF diagnosis and treatment.

References

[1] Ge JB, Xu YJ, Wang C, et al. Internal Medicine [M]. 9th ed. Beijing: People's Medical Publishing House, 2018: 978-7-117-26541-6.

[2] Seferovic PM, Petrie MC, Filippatos GS, et al. Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology[J]. Eur J Heart Fail, 2018,20(5):853-872. DOI: 10.1002/ejhf.1170.

[3] Dunlay SM, Givertz MM, Aguilar D, et al. Type 2 Diabetes Mellitus and Heart Failure: A Scientific Statement From the American Heart Association and the Heart Failure Society of America: This statement does not represent an update of the 2017 ACC/AHA/HFSA heart failure guideline update[J]. Circulation, 2019,140(7):e294-e324. DOI: 10.1161/CIR.0000000000000691.

[4] Fang LG. New era of chronic heart failure therapy[J]. Chin J Cardiovasc Med, 2021,26(1):1-4. DOI: 10.3969/j.issn.1007-5410.2021.01.001.

[5] Kapila V, Topf J. Sodium-Glucose Co-transporter 2 Inhibitor-Associated Euglycemic Diabetic Ketoacidosis After Bariatric Surgery: A Case and Literature Review[J]. Cureus, 2021,13(8):e17093. DOI: 10.7759/cureus.17093.

[6] López-de-Andrés A, de Miguel-Díez J, Muñoz-Rivas N, et al. Impact of type 2 diabetes mellitus in the utilization and in-hospital outcomes of surgical mitral valve replacement in Spain (2001-2015)[J]. Cardiovasc Diabetol, 2019,18(1):60. DOI: 10.1186/s12933-019-0866-5.

[7] McDonagh T, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure[J]. Eur Heart J. 2021;42(36):3599-3726.

[8] Curtain JP, Docherty KF, Jhund PS, et al. Effect of dapagliflozin on ventricular arrhythmias, resuscitated cardiac arrest, or sudden death in DAPA-HF[J]. European Heart Journal. 2021;42(36):3727-3738.

[9] Lin YW, Chen CY, Shih JY, et al. Dapagliflozin Improves Cardiac Hemodynamics and Mitigates Arrhythmogenesis in Mitral Regurgitation-Induced

Myocardial Dysfunction[J]. Journal of the American Heart Association. 2021;10(7):e019274.

[10] Wang H, Zhu LQ, Peng DM. Meta evaluation of efficacy and safety of SGLT2 inhibitors in the treatment of heart failure[J]. International Journal of Biomedical Engineering, 2021,44(2):124-132.

[11] Topkara VK, Mann DL. Role of microRNAs in cardiac remodeling and heart failure[J]. Cardiovasc Drug Ther, 2011,25(2):171-182.

[12] Thum T, Galuppo P, Wolf C, et al. MicroRNAs in the human heart: a clue to fetal gene reprogramming in heart failure[J]. Circulation. 2007,116(3):258-267.

[13] Tan H, Li YM, Zhang HM, et al. The expression changes of plasma miR-423-5p and miR-210-3p in chronic congestive heart failure patients[J]. Journal of Clinical Cardiology, 2014,30(12):1081-1085.

[14] Chinese Diabetes Society. Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes Mellitus (2020 edition)[J]. International Journal of Endocrinology and Metabolism, 2021,41(05):482-548.

[15] Tijsen AJ, Creemers EE, Moerland PD, et al. MiR-423-5p as a circulating biomarker for heart failure[J]. Circ Res, 2010,106:1035-1039.

[16] Fan KL, Zhang HF, Shen J, et al. Circulating microRNAs levels in Chinese heart failure patients caused by dilated cardiomyopathy[J]. Indian Heart J, 2013,65(1):12-16.

[17] Li YM, Zhang HM, Tan H, et al. Clinical significance of plasma miR-423-5p expression in chronic congestive heart failure patients[J]. International Journal of Cardiovascular Disease, 2014,41(03):189-191.

[18] Packer M. Lessons learned from the DAPA-HF trial concerning the mechanisms of benefit of SGLT-2 inhibitors on heart failure events in the context of other large scale trials nearing completion[J]. Cardiovasc Diabetol. 2019,18(1):129-132.

[19] Liu DP. Role of sodium-dependent glucose cotransporter 2 inhibitors in heart failure[J]. Chinese Journal of Cardiovascular Medicine, 2020,25(01):1-3.

[20] Liu HL, Zhang L, Hu TT, et al. Study on the micro RNA expression profile in rats with ischemic heart failure treated by dapagliflozin[J]. Chinese Journal of Cardiovascular Medicine, 2021,26(5):477-482.

[21] Jiang YS, Tan H, Li XY, et al. Effects of perindopril on the expression of plasma miR-423-5p and cardiac function in patients with heart failure[J]. Journal of Shandong University (Health Sciences), 2016,54(08):55-59.

[22] Zhou YM, Shu Y, Tang JY, et al. Study of the effect and mechanism of microRNA-423-5p in heart failure through regulation of the PI3K/AKT signal-

ing pathway[J]. Journal of Clinical and Experimental Medicine, 2019,18(02):128-133.

Data Availability Statement

The scientific data supporting this study have been publicly released in the Science Data Bank of the Chinese Academy of Sciences.
Dataset CSTR: 31253.11.sciencedb.j00150.00037
Dataset DOI: 10.57760/sciencedb.j00150.00037
Dataset Private Access Link: https://www.scidb.cn/s/6ZFvMr
Anonymous Private Link: https://www.scidb.cn/anonymous/NlpGdk1y

Note: Figure translations are in progress. See original paper for figures.

Source: ChinaXiv — Machine translation. Verify with original.