

Anti-Oxidative Effect of Dapagliflozin, a Selective Sodium Glucose Transporter-2 Inhibitor, for Cardio-Renal Protection in Patients With Heart Failure With Reduced Ejection Fraction

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Abstract

Background: Selective sodium glucose transporter-2 inhibitor (SGLT2i) has cardio-renal protective effects via osmotic diuresis and natriuresis, and other pleiotropic effects, such as anti-oxidative, anti-fibrotic, and anti-senescence effects, have been suggested. However, those pleiotropic effects have not yet been fully elucidated in a clinical study.

Methods: We investigated the effects of SGLT2i in patients with heart failure with reduced ejection fraction (HFrEF). Twenty-five HFrEF patients who were initially treated with dapagliflozin from 2021 to 2023 at Fukuoka University Hospital were enrolled and we investigated their baseline characteristics, medications, clinical laboratory examination findings, echocardiography findings, and additional pleiotropic serum markers before administration of dapagliflozin and 6 months later.

Results: The patients were 67.0 ± 13.6 years old, 64.0% were male, and their body mass index was 24.0 ± 4.5 kg/m². Only four patients (16.0%) had diabetes mellitus. With regard to medications, 64.0%, 76.0%, and 60.0% were already taking renin-angiotensin aldosterone system inhibitors, beta-blockers, and mineralocorticoid receptor antagonists, respectively, and these medications did not change significantly for 6 months.

After treatment with dapagliflozin for 6 months, serum brain natriuretic peptide, left ventricular ejective function, hemoglobin, and urinary N-acetyl- β -D-glycosaminidase were significantly improved. In addition, high-sensitivity C-reactive protein and oxidative stress markers including myeloperoxidase, matrix metalloproteinase-1, and matrix metalloproteinase-9 significantly improved, while anti-fibrosis and anti-senescence markers did not.

Conclusions: Dapagliflozin had anti-oxidative effects in patients with HFrEF, in addition to cardio-renal protective effects. These anti-oxidative effects could be related to the cardio-renal protective effects of SGLT2i, even in a clinical setting.

Keywords: Selective sodium glucose transporter-2 inhibitor; Anti-oxidative effect; Heart failure with reduced ejection fraction

Introduction

Selective sodium glucose transporter-2 inhibitor (SGLT2i) is a class of antidiabetic agents that lower blood glucose by inhibiting renal glucose reabsorption [1]. Beyond glycemic control, SGLT2i has demonstrated beneficial effects in heart failure, attributable to natriuresis, osmotic diuresis, and potential pleiotropic actions [2]. Dapagliflozin, a type of SGLT2i, has been shown to have cardioprotective effects in patients with heart failure with reduced ejection fraction (HFrEF) [3], and heart failure with preserved ejection fraction [4]. Against this background, current guidelines for the treatment of heart failure now recommend the use of SGLT2i, regardless of the presence of type 2 diabetes or left ventricular ejection fraction (LVEF) [5]. Dapagliflozin also has renal protective effects [6]. However, the extrarenal effects of SGLT2i remain unclear.

Studies have indicated that SGLT2i reduces endothelial dysfunction in diabetic patients [7, 8], and several mechanisms have been proposed to explain this effect. These mechanisms include anti-oxidant properties [9-11], enhanced nitric oxide

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production [12, 13], and anti-inflammatory actions [14, 15]. However, the supporting evidence is primarily derived from animal and *in vitro* studies. In animal models, dapagliflozin has been shown to reduce markers associated with endothelial aging, such as senescence-associated β -galactosidase, p21, and p53 [13]. A comprehensive elucidation of these mechanisms could pave the way for the development of more effective therapeutic strategies for cardiovascular disease. In this study, we conducted an exploratory analysis of the effects of dapagliflozin in patients with HFrEF, focusing on a broad panel of pleiotropic markers to understand its potential non-glycemic benefits in a clinical setting.

Materials and Methods

Study protocol

The protocol for this clinical study was approved by the Institutional Review Board Committee of Fukuoka University in accordance with the Declaration of Helsinki (#U19-07-012). This was a single-center, prospective cohort study. A total of 25 HFrEF patients who were initially treated with dapagliflozin 10 mg between June 2021 and June 2023 were included. We selected patients who were aged 20 years or older, of either gender, and who survived until discharge. Eligible subjects were investigated with respect to their baseline characteristics, medications, clinical laboratory examinations, echocardiography, and additional pleiotropic serum markers before the administration of dapagliflozin and 6 months later.

Baseline characteristics

Age, sex, body height, body weight, body mass index, blood pressure, underlying diseases, including hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, and cardiovascular disease, including ischemic heart disease, cardiomyopathy, and atrial fibrillation, were investigated. Body mass index was calculated as weight divided by height $\times$ height. With regard to medications, renin angiotensin aldosterone system inhibitors including angiotensin receptor neprilysin inhibitor, beta-blocker, mineralocorticoid receptor antagonist, pimobendan, calcium channel blocker, and diuretics were investigated.

Clinical laboratory examinations

We investigated the results of blood examinations before dapagliflozin treatment and after 6 months. White blood cell, red blood cell, hemoglobin, platelet, hematocrit, total protein, albumin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, blood urea nitrogen, creatinine, ferritin, C-reactive protein (CRP), and brain natriuretic peptide were investigated. We also investigated the results of urine examinations, including N-acetyl- β -D-glycosaminidase, microalbumin, and liver-type fatty acid binding protein.

Echocardiography

We investigated the results of echocardiography before dapagliflozin administration and 6 months later. Left atrial dimension, aortic dimension, interventricular septum, left ventricular posterior wall, left ventricular end-diastolic dimension, left ventricular end-systolic dimension, LVEF, left ventricular end-diastolic volume, left ventricular end-systolic volume, ratio of early to late diastolic filling velocities, ratio of early diastolic filling velocity to early diastolic mitral annular velocity, and tricuspid regurgitation pressure gradient were investigated.

Enzyme-linked immunosorbent assay

To examine the pleiotropic effects of dapagliflozin, serum biomarkers were measured in duplicate following the manufacturers' instructions. Enzyme-linked immunosorbent assays (ELISAs) were used for galectin-3 (Cat. #DGAL30, R&D Systems Inc.), procollagen type I C-terminal propeptide (Cat. #SEA-570Hu, Cloud-Clone Corp.), procollagen type III N-terminal propeptide (Cat. #SEA573Hu, Cloud-Clone Corp.), endotrophin (Cat. #MBS1608767, MyBioSource), myeloperoxidase (MPO; Cat. #KR6631B, Immundiagnostik AG), and α -Klotho (Cat. #JP27998, IBL International).

Multiplex bead-based immunoassays (Luminex[®] MAGPIX[®] system, Luminex Corp., Austin, TX, USA) were used to quantify fibroblast growth factor-21 (FGF-21) and growth differentiation factor-11 (GDF-11) (MILLIPLEX[®] MAP Human Adipokine Magnetic Bead Panel, Cat. #HAGE1MAG-20K-04, Millipore-Sigma), as well as matrix metalloproteinase-1 (MMP-1), MMP-2, and MMP-9 (MILLIPLEX[®] MAP Human MMP Magnetic Bead Panel 2, Cat. #HMMP2MAG-55K-03, MilliporeSigma).

Statistical analysis

All data analyses were performed using SAS (version 9.4, SAS Institute Inc., Cary, NC, USA) at Fukuoka University (Fukuoka, Japan). Continuous variables are expressed as the mean $\pm$ standard deviation for normally distributed data, and as the median (interquartile range) for non-normally distributed data. For continuous variables, those with normal distributions were analyzed using the paired *t*-test, while those with non-normal distributions were analyzed using the Wilcoxon signed-rank test. Categorical variables were analyzed using McNemar's test for paired binary data. P values were two-sided and considered statistically significant if $P < 0.05$. No adjustments for multiple comparisons were made given the exploratory nature of the study.

Results

Patient characteristics

Table 1 shows the baseline characteristics of all patients ($n = 25$). In this study group, the mean age was 67.0 ± 13.6 years and 64.0%

Table 1. Baseline Characteristics (n = 25)

Characteristics	
Age, years	67.0 ± 13.6
Male, n (%)	16 (64.0)
Smoking, n (%)	19 (76.0)
Hypertension, n (%)	14 (56.0)
Diabetes mellitus, n (%)	4 (16.0)
Dyslipidemia, n (%)	12 (48.0)
CKD, n (%)	7 (28.0)
Cardiovascular disease	
IHD, n (%)	9 (36.0)
Cardiomyopathy, n (%)	6 (24.0)
AF, n (%)	13 (52.0)

Continuous variables are expressed as mean ± SD. AF: atrial fibrillation; CKD: chronic kidney disease; IHD: ischemic heart disease.

were male. Approximately half of the patients had hypertension and dyslipidemia. Only four patients (16.0%) had diabetes mellitus and were not being treated with SGLT2i. With regard to cardiovascular disease, the percentages of patients with ischemic heart disease, cardiomyopathy, and atrial fibrillation were 36.0%, 24.0%, and 52.0%, respectively. Table 2 shows the changes in vital signs and medications after treatment with dapagliflozin for 6 months. Body weight and body mass index were significantly reduced and blood pressure did not show significant changes under treatment with dapagliflozin. Excluding dapagliflozin, there were no significant changes in the medications used for 6 months.

Changes in the results of biochemical examinations after treatment with dapagliflozin for 6 months

Table 3 shows the changes in biochemical examination re-

sults between before and after treatment with dapagliflozin. Red blood cells, hemoglobin, hematocrit, total protein, and albumin all significantly increased after treatment with dapagliflozin. On the other hand, white blood cells, alanine aminotransferase, ferritin, CRP, brain natriuretic peptide, urinary N-acetyl-β-D-glycosaminidase, and urinary creatinine significantly decreased after treatment.

Changes in transthoracic echocardiography after treatment with dapagliflozin for 6 months

Table 4 shows the changes in transthoracic echocardiography parameters between before and after treatment with dapagliflozin. After treatment, left ventricular end-systolic dimension, end-diastolic volume, end-systolic volume, the ratio of early to late diastolic filling velocities, the ratio of early diastolic filling velocity to early diastolic mitral annular velocity, and tricuspid regurgitation pressure gradient significantly decreased. LVEF was significantly increased.

Changes in serum markers of fibrosis after treatment with dapagliflozin for 6 months

Figure 1 shows the changes in serum markers of fibrosis between before and after dapagliflozin. There were no significant decreases in galectin-3, procollagen I C-terminal propeptide, or procollagen III N-terminal propeptide after treatment. Endotrophin levels significantly increased. On the other hand, endotrophin levels significantly increased.

Changes in serum markers of anti-oxidative effects after treatment with dapagliflozin for 6 months

Figure 2 shows the changes in serum markers of anti-oxidative

Table 2. Changes in Vital Signs and Medications After Treatment With Dapagliflozin for 6 Months (n = 25)

	Before treatment	After treatment for 6 months	P-value
BW, kg	63.4 ± 12.4	60.2 ± 11.8	< 0.001
BMI, kg/m ²	24.0 ± 4.5	22.3 ± 4.1	< 0.001
SBP, mm Hg	123 ± 24	117 ± 21	0.17
DBP, mm Hg	79.3 ± 15.0	74.7 ± 12.6	0.10
Medications			
ARB/ACEi/ARNi, n (%)	16 (64.0)	18 (72.0)	0.31
β-blocker, n (%)	19 (76.0)	20 (80.0)	0.65
MRA, n (%)	15 (60.0)	15 (60.0)	1.0
Pimobendan, n (%)	3 (12.0)	3 (12.0)	1.0
CCB, n (%)	6 (24.0)	5 (20.0)	0.56
Diuretics, n (%)	16 (64.0)	14 (56.0)	0.32
Statin, n (%)	9 (36.0)	10 (40.0)	0.56

Continuous variables are expressed as mean ± SD. ACEi/ARB/ARNi: angiotensin-converting-enzyme inhibitor/angiotensin II receptor blocker/angiotensin receptor neprilysin inhibitor; BMI: body mass index; BW: body weight; CCB: calcium channel blocker; DBP: diastolic blood pressure; MRA: mineralocorticoid receptor antagonist; SBP: systolic blood pressure.

Table 3. Changes in the Results of Biochemical Examinations

	Before treatment	After treatment for 6 months	P-value
Blood findings			
WBC, $\times 10^3/\mu\text{L}$	6.70 ± 1.83	5.88 ± 1.65	0.01
RBC, $\times 10^6/\mu\text{L}$	4.34 ± 0.71	4.74 ± 0.62	0.002
Hb, g/dL	13.0 ± 2.2	14.0 ± 1.7	0.003
Plt, $\times 10^3/\mu\text{L}$	221 (179 - 262)	228 ± 89	0.95
HCT, %	39.7 ± 6.6	43.3 ± 5.1	< 0.001
TP, g/dL	6.8 ± 0.8	7.2 ± 0.6	0.008
Alb, g/dL	3.8 ± 0.6	4.2 ± 0.3	0.002
AST, U/L	23 (20 - 34)	25.7 ± 9.3	0.14
ALT, U/L	22 (14 - 34)	14 (10-27)	0.03
LDH, U/L	227 (177 - 249)	207 ± 61	0.12
BUN, mg/dL	18.6 ± 7.7	19.2 ± 5.7	0.69
Cre, mg/dL	1.01 (0.85 - 1.07)	1.02 ± 0.22	0.47
eGFR, mL/min/1.73 m ²	56.3 ± 17.8	54.4 ± 15.2	0.43
Ferritin, ng/mL	147 ± 108	83 (29 - 154)	0.01
CRP, mg/dL	0.33 (0.05 - 1.67)	0.08 (0.06 - 0.20)	0.04
BNP, pg/mL	280 (169 - 537)	229 ± 171	0.03
Urinary findings			
NAG, IU/L	15.1 ± 10.9	5.9 (2.8 - 10.8)	0.03
Cre, mg/dL	121 ± 59	76.2 ± 45.9	0.005
Microalbumin, mg/L	19.5 (6.0 - 52.0)	10 (5 - 28)	0.34
L-FABP, ng/mL	3.23 (1.30 - 6.82)	2.41 ± 2.40	0.13

Continuous variables are expressed as mean $\pm$ SD if they are parametric, and as median (interquartile range) if they are non-parametric. Alb: albumin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BNP: B-type natriuretic peptide; BUN: blood urea nitrogen; Cre: creatinine; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; Hb: hemoglobin; HCT: hematocrit; LDH: lactate dehydrogenase; L-FABP: liver-type fatty acid binding protein; NAG: N-acetyl- β -D-glycosaminidase; Plt: platelet; RBC: red blood cell; TP: total protein; WBC: white blood cell.

Table 4. Changes in Transthoracic Echocardiography Findings

	Baseline	Post-treatment	P value
LAD, mm	44.4 ± 11.2	43.0 ± 9.1	0.43
AOD, mm	32.1 (29.7 - 33.3)	32.0 ± 3.2	0.44
IVS, mm	9.72 ± 2.51	9.38 ± 2.55	0.35
LVPW, mm	10.6 ± 1.6	10.2 (9.4 - 10.8)	0.37
LVDd, mm	56.3 ± 9.2	53.9 ± 9.4	0.048
LVDs, mm	48.5 ± 10.6	43.7 ± 11.1	0.005
LVEF, %	30.5 ± 11.3	39.9 ± 14.5	0.002
LVEDV, mL	137 ± 58	115 ± 53	0.02
LVESV, mL	98.0 ± 47.8	71.9 ± 46.0	0.009
E/A	1.4 (0.9 - 2.0)	0.7 (0.5 - 0.8)	0.026
E/e'	17.1 (12.2 - 24.0)	12.7 ± 5.3	0.04
TRPG, mm Hg	33.5 ± 23.3	17.5 (13.0 - 31.0)	0.04

Continuous variables are expressed as mean $\pm$ SD if they are parametric, and as median (interquartile range) if they are non-parametric. AOD: aortic dimension; E/A: ratio of early to late diastolic filling velocities; E/e': ratio of early diastolic filling velocity to early diastolic mitral annular velocity; IVS: interventricular septum; LAD: left atrial dimension; LVPW: left ventricular posterior wall; LVDd: left ventricular end-diastolic dimension; LVDs: left ventricular end-systolic dimension; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; TRPG: tricuspid regurgitation pressure gradient.

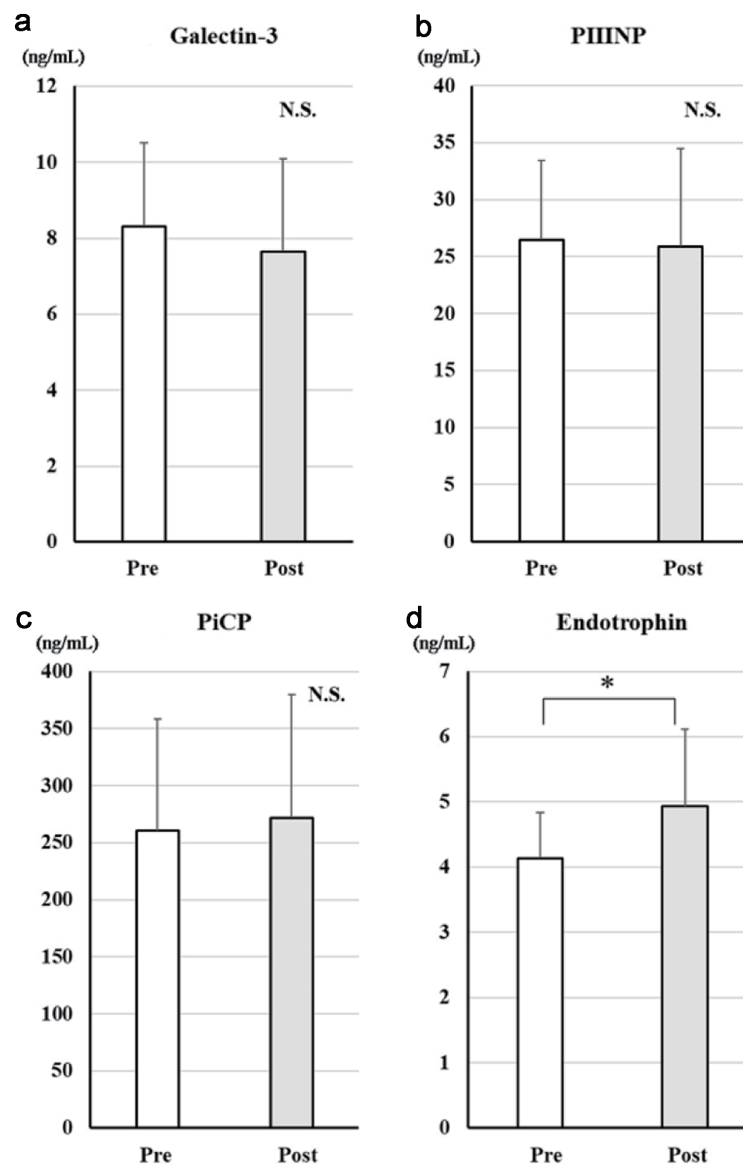


Figure 1. Changes in serum markers of fibrosis after treatment with dapagliflozin for 6 months. Changes in galectin-3 (a), PIIINP (b), PiCP (c), and endotrophin (d) before and after treatment with dapagliflozin. *Significant differences between before and after treatment. PIIINP: procollagen type III N-terminal propeptide; PiCP: procollagen type I C-terminal propeptide; NS: not significant.

effects between before and after treatment with dapagliflozin. After treatment, MPO (mean difference: +115 ng/mL, 95% confidence interval (CI): 39 to 191 ng/mL, $P = 0.0047$), MMP-1 (mean difference: +306 ng/mL, 95% CI: 124 to 488 ng/mL, $P = 0.0021$), and MMP-9 (mean difference: +6,196 ng/mL, 95% CI: 670 to 11,721 ng/mL, $P = 0.029$) levels significantly decreased, whereas MMP-2 (mean difference: +723 ng/mL, 95% CI: -1,280 to 2,726 ng/mL, $P = 0.46$) showed no significant change.

Changes in serum age-related proteins after treatment with dapagliflozin for 6 months

Figure 3 shows the changes in age-related proteins between

before and after treatment with dapagliflozin. There were no significant changes in these markers.

Discussion

In this study, treatment with dapagliflozin for 6 months had anti-oxidative effects in patients with HFrEF, in addition to cardio-renal protective effects. Anti-oxidative effects could be related to the cardio-renal protective effects of SGLT2i, even in clinical setting.

In this study, we confirmed that the improvements of 6 months of dapagliflozin treatment in patients with HFrEF were associated with improvements in cardiac function, reduc-

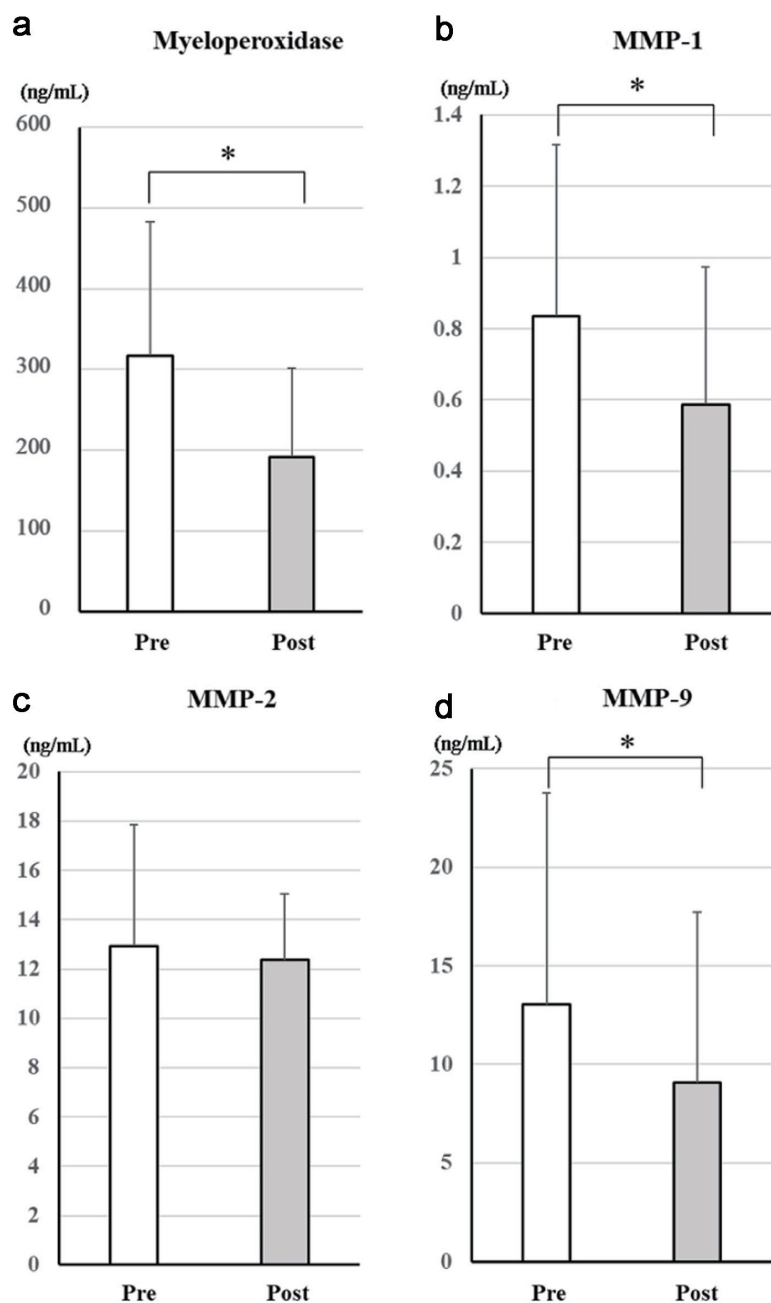


Figure 2. Changes in serum markers of antioxidative effects after treatment with dapagliflozin for 6 months. Changes in myeloperoxidase (a), MMP-1 (b), MMP-2 (c), and MMP-9 (d) between before and after treatment with dapagliflozin. *Significant differences between before and after treatment. MMP-1: matrix metalloproteinase-1; MMP-2: matrix metalloproteinase-2; MMP-9: matrix metalloproteinase-9; NS: not significant.

tions in oxidative stress markers, and renal protective effects. SGLT2i has been shown to have cardioprotective effects [16-18]. Treatment with empagliflozin for 6 months significantly improved left ventricular volume and LVEF in non-diabetic HFrEF patients [19]. The DAPA-MODA study showed that dapagliflozin improved left atrial and ventricular remodeling in chronic heart failure patients [20]. Our results were consistent with these previous reports.

We observed decreases in markers of proximal, tubule function, such as urinary N-acetyl- β -D-glycosaminidase and liver-type fatty acid-binding protein, confirming renal-protective effects. Although creatinine levels did not change, this may reflect recovery from the initial gap [21]. The increase in hematocrit might indicate an improvement in renal oxygenation and recovery of erythropoietin production. Previous studies have suggested that the process of glucose reabsorp-

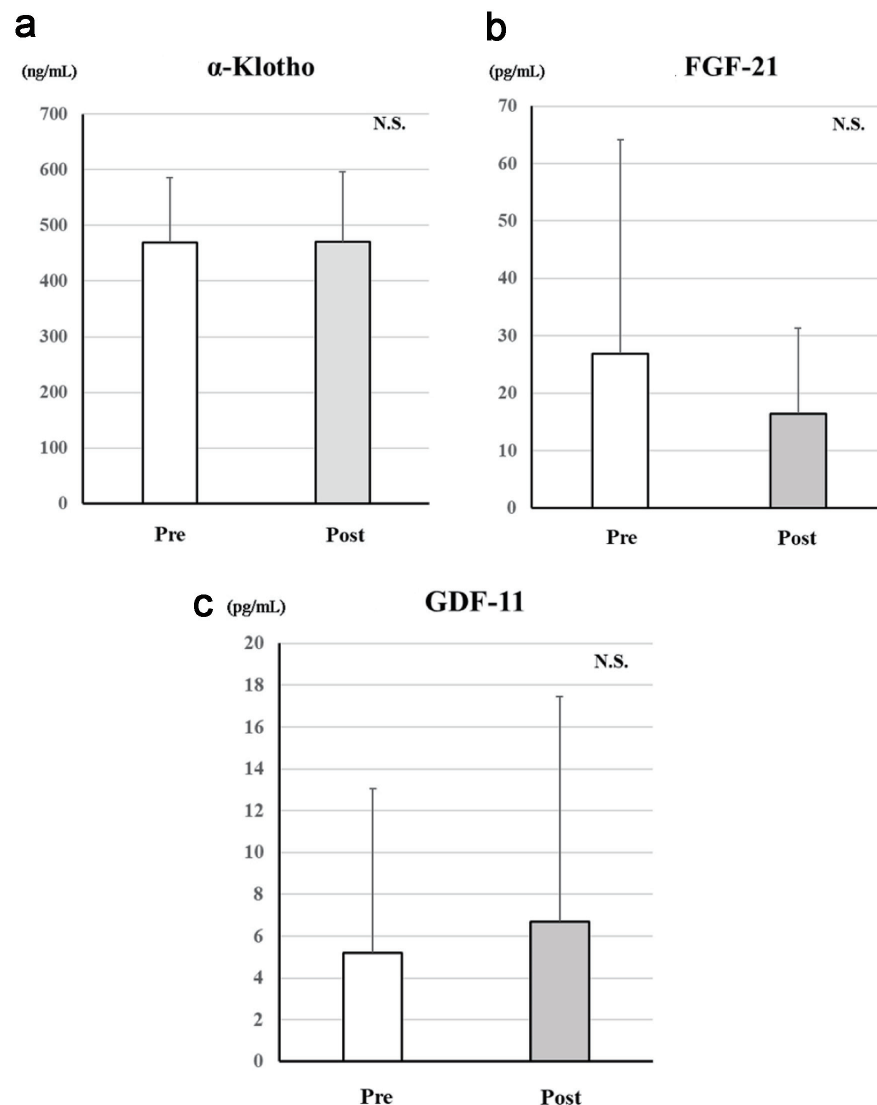


Figure 3. Changes in serum age-related proteins after treatment with dapagliflozin for 6 months. Changes in α -Klotho (a), FGF-21 (b), and GDF-11 (c) between before and after treatment with dapagliflozin. *Significant differences between before and after treatment. FGF-21: fibroblast growth factor-21; GDF-11: growth differentiation factor-11; NS: not significant.

tion from the renal tubules consumes a lot of energy, leading to decreased renal oxygen pressure [22, 23]. It has been reported that SGLT2i suppresses sodium and glucose reabsorption, improves renal oxygen supply, and subsequently recovers erythropoietin production, leading to an increased hematocrit level [24, 25]. Also, our study showed significant increases in red blood cells and hemoglobin, suggesting improved erythropoietin production [26]. The increase in hematocrit associated with SGLT2i is considered to be an important mediator of the cardiorenal-protective effects [27, 28].

SGLT2i has been reported to exert cardioprotective effects through anti-inflammatory and anti-oxidant mechanisms [29, 30]. Excessive reactive oxygen species (ROS) generated by mitochondria and nicotinamide adenine dinucleotide phosphate oxidase damage cardiomyocytes, disrupting excitation-contraction coupling and intracellular signaling. Persistent ROS eleva-

tion leads to contractile dysfunction, structural remodeling, and progression of heart failure [31]. Oxidative stress and chronic inflammation contribute to vascular endothelial dysfunction and vascular aging. ROS impair endothelial progenitor cells, reduce nitric oxide bioavailability, and diminish endothelium-dependent vasodilation. Additionally, ROS increase the expression of vasoactive molecules such as MMPs and vascular endothelial growth factor, promoting vascular remodeling [32].

Reducing oxidative stress helps prevent cardiovascular disease progression, particularly in the development of heart failure [33, 34]. In our study, MPO, a marker of oxidative stress, was significantly reduced following treatment with dapagliflozin. We also observed significant decreases in MMP-1 and MMP-9. MMPs degrade extracellular matrix proteins and are involved in inflammatory processes. ROS are known to enhance MMP-1 transcription [35], and the reduction in MMP-1

observed in our study suggests that SGLT2i can attenuate oxidative stress. MMP-9 has been associated with adverse post-myocardial infarction remodeling [36], and its reduction may contribute to the cardioprotective effects of SGLT2i. Although MMP-2 has been linked to inflammation, immune responses, and impaired cardiac function [37], no significant change was detected in our study.

Inflammation is also implicated in the pathogenesis of heart failure [38]. Previous clinical studies have demonstrated a reduction in CRP in diabetic patients treated with dapagliflozin [39]. In our study, significant reductions in both white blood cell count and CRP were observed after treatment with dapagliflozin, supporting the anti-inflammatory effects of SGLT2i. A major strength of our study is that we have demonstrated the anti-oxidant effects of SGLT2i in humans. However, we cannot exclude the possibility that systemic glucose excretion contributed to these effects.

In this study, there were no significant decreases in markers of fibrosis, and endotrophin even increased. Previous reports have described the antifibrotic effects of SGLT2i, but these were based on cell and animal experiments and have certain limitations. One study reported that inhibition of the transforming growth factor- β 1/Smad signaling pathway suppresses cardiac fibrosis [40]. Another study showed that empagliflozin inhibited the transforming growth factor- β 1/Smad pathway and activated the nuclear factor erythroid 2-related factor 2/anti-oxidant response element signaling pathway, thereby suppressing oxidative stress and fibrosis [41]. In a clinical study, canagliflozin did not have antifibrotic effects [42]. We measured the age-related protein α -Klotho, FGF-21, and GDF-11, but no significant differences were observed. The unexpected increase in endotrophin should be interpreted with caution. It may reflect the short observation period, heterogeneity of the patient population, or fluctuation through pathophysiological pathways independent of those related to oxidative stress. Given the current data, these possibilities cannot be excluded, and further studies with longer follow-up and more homogeneous cohorts are warranted.

This study has several limitations. First, the sample size was limited because it was from just one center and included only a small number of enrolled patients. Despite this, our exploratory research showed meaningful results. Second, the study period may have been too short to detect other pleiotropic effects, such as those on fibrosis and longevity. Further research will be needed.

Conclusions

Dapagliflozin showed anti-oxidative effects in patients with HFrEF, in addition to cardio-renal protective effects. These anti-oxidative effects may be related to the cardio-renal protective effects of SGLT-2i, even in a clinical setting.

Limitations

This study has several limitations. First, it was a single-center

investigation with a small sample size ($n = 25$), which limits statistical power and generalizability. Second, the absence of a control group makes it difficult to attribute causality solely to dapagliflozin, as effects may have been influenced by background medical therapy, weight loss, or regression to the mean. Third, multiple biomarker and echocardiographic comparisons were made without adjustment for multiple testing, raising the risk of type I error. Finally, the observation period of 6 months may be too short to detect changes in certain pleiotropic pathways such as fibrosis or cellular senescence. Furthermore, long-term, larger-scale studies are warranted to determine whether the observed effects persist over time and whether their magnitude increases with prolonged treatment.

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Financial Disclosure

None to declare.

Conflict of Interest

The authors declare no conflict of interest.

Informed Consent

Written informed consent was obtained from all participants.

Author Contributions

RT and YS contributed to the conception and design of the work. KT, AI, MM, YY, TA, TH, and KF were responsible for the acquisition of data and cleaned the data. RT and YS performed all data analyses. RT and YS drafted the manuscript. SM checked statistical analysis and revised the manuscript critically. SM critically reviewed the manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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