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ORIGINAL ARTICLE

Effects of Sodium-glucose Co-transporter-2 Inhibitors on Pulmonary Hypertension in Heart Failure with Preserved Ejection Fraction

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ABSTRACT

Background: Treatment options for pulmonary hypertension (PH) associated with heart failure (HF) with preserved ejection fraction (HFpEF) remain limited. Sodium-glucose co-transporter-2 inhibitors (SGLT2i) are a novel class of medications for HF, demonstrating efficacy regardless of diabetes status. These agents may lower left ventricular filling pressures, potentially reducing pulmonary pressure and enhancing right ventricular function. This study assessed the impact of SGLT2i on PH-HFpEF.

Aim: The aim of this study is to assess the impact of SGLT2i on echocardiographic and biochemical markers in patients with PH associated with HFpEF.

Study Design: This is a retrospective cohort study involving nine patients diagnosed with PH-HFpEF, treated at Pamukkale University. The study examines the changes in echocardiographic parameters and biochemical markers, specifically NT-proBNP levels, following long-term treatment with SGLT2i.

Methods: A retrospective analysis was conducted on nine patients with PH-HFpEF between April 2018 and October 2020. All exhibited echocardiographic features of HFpEF, had both pre- and postcapillary PH, and were treated with SGLT2i for a median duration of 27 months following standard HF therapy. Seven patients had a history of HF-related hospitalization, and PH was confirmed via right heart catheterization in five cases. Follow-up echocardiography was performed after at least 12 months of SGLT2i treatment.

Results: The mean patient age was 67 years, with a predominance of women (66%), and all had diabetes. Following SGLT2i initiation, none required hospitalization for HF. Hemodynamic parameters improved, including reductions in mean right atrial and pulmonary arterial pressures, decreased pulmonary vascular resistance, and enhancements in cardiac index and oxygen saturation. Additionally, tricuspid regurgitation velocity and N-terminal pro-brain natriuretic peptide levels significantly declined, indicating improved cardiac function.

Conclusion: Despite the high morbidity and mortality associated with this patient population, the findings suggest that SGLT2i may alleviate ventricular filling pressures, thereby reducing pulmonary pressures and potentially improving right ventricular function. Larger randomized trials are necessary to confirm these results.

Keywords: Heart failure with preserved ejection fraction, sodium-glucose co-transporter-2 inhibitors, pulmonary hypertension, echocardiography

INTRODUCTION

Pulmonary hypertension (PH) is a progressive pulmonary vascular disease characterized by increased pulmonary vascular resistance and elevated pulmonary artery pressure (PAP) due to vascular remodeling. This condition inevitably leads to right heart failure (HF) and, in severe cases, death.[1] While the exact pathogenesis of PH remains unclear, multiple mechanisms contribute to its development.[2] Among these, inflammation plays a key role in pulmonary vascular remodeling. The involvement of inflammation in PH has been recognized for nearly 30 years.[3] Pulmonary vascular cells release inflammatory mediators that attract inflammatory cells, which in turn promote the secretion of cytokines, chemokines, and growth factors. This cascade triggers vascular cell proliferation and collagen deposition, ultimately leading to pulmonary vascular remodeling.[4,5]

Sodium-glucose co-transporter-2 inhibitors (SGLT2i) are a class of medications that enhance glucose excretion through urine and were initially developed for diabetes mellitus (DM) management. However, recent research has identified them as a key treatment for HF, demonstrating benefits in patients both with and without DM, regardless of ejection fraction (EF). Notably, findings from the EMPEROR-Preserved and DELIVER randomized trials have shown that SGLT2i therapy can lower all-cause mortality and reduce hospitalizations in HF patients with mildly reduced or preserved EF.[6,7] N-terminal pro-brain natriuretic peptide (NT-proBNP), a commonly used biomarker in HF studies, is closely associated with ventricular wall tension and pressure

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increases. It serves as the indicator of functional and hemodynamic impairment in PH patients and is widely recognized as a prognostic marker in current guidelines.[8]

The poor prognosis associated with HF with preserved EF (HFpEF) is largely attributed to PH. PH is defined by a mean PAP exceeding 20 mmHg at rest, as measured by cardiac catheterization.[9] In HFpEF patients, the presence of PH is linked to worse clinical outcomes.[10] The reported prevalence of PH in HFpEF ranges from 31% to 88%, depending on disease severity, diagnostic criteria, and the method of assessment, whether echocardiography or cardiac catheterization.[11,12]

In addition to their primary glucosuric, natriuretic, and diuretic effects, SGLT2i have been found to directly inhibit the Na-H exchanger 1 receptor on the cell surface, leading to increased intracellular sodium and calcium levels.[13] Experimental studies have also demonstrated that SGLT2i therapy reduces cardiac fibrosis and oxidative stress.[14] Other benefits include improved endothelial function, decreased secretion of pro-inflammatory chemokines, and lower adipokine levels.[15,16] Beyond these effects, SGLT2i therapy enhances energy metabolism by increasing ketone body production, reduces atherosclerosis, influences the renin-angiotensin system, and elevates glucagon levels.[17] Although these mechanisms contribute to improved clinical outcomes, the exact mode of action of SGLT2i remains incompletely understood.

Subgroup analyses from the EMBRACE HF study have demonstrated that empagliflozin treatment significantly reduces pulmonary artery diastolic pressure.[18] Additionally, the study indicated that pulmonary pressure remained low even one week after discontinuing SGLT2i therapy, suggesting a mechanism of action beyond its diuretic effect. Ongoing research continues to explore new hypotheses regarding the efficacy and potential mechanisms of SGLT2i therapy.

The aim of this study was to evaluate the clinical response to SGLT2i therapy in patients with PH and HFpEF and to assess its effects on cardiac function.

The findings of this study have been previously presented in abstract form.[19]

METHODS

Study Design and Setting

This retrospective study was conducted at the Cardiology and Endocrinology Clinics of Pamukkale University between April 2018 and October 2020. Patients who met the inclusion criteria and did not meet the exclusion criteria during this period were enrolled. The study aimed to assess the effects of SGLT2i in patients with PH associated with HFpEF.

Participants

Participants with DM were eligible for inclusion if they met the following criteria:

- DM was diagnosed based on one of the following: fasting plasma glucose ≥126 mg/dL, 2-h plasma glucose ≥200 mg/dL during a 75-g oral glucose tolerance test, random plasma glucose ≥200 mg/dL accompanied with classic hyperglycemic symptoms, or HbA1c ≥6.5%.[20]

- Diagnosis of HFpEF with echocardiographic evidence of combined pre- and postcapillary PH.

- Initiation of SGLT2i therapy at least 3 months before inclusion and continued use throughout the study.

- Availability of complete medical records and follow-up data for at least 1 year after starting SGLT2i therapy.

Patients were excluded if they:

- Had PH classified as groups 1, 3, 4, or 5.

- Did not have a follow-up period of at least 12 months after initiating SGLT2i therapy.

Interventions and Measurements

SGLT2i therapy included various agents prescribed as part of standard HF treatment protocols, without preference for a specific drug. The primary interventions consisted of:

- Routine HF therapy, including beta-blockers (BB), renin-angiotensin-aldosterone system inhibitors, and mineralocorticoid receptor antagonists, administered according to the latest guidelines before and during the study. No patient received pulmonary arterial hypertension therapy.

- Echocardiographic and right heart catheterization assessments performed as part of routine clinical care.

Intervention Details

- Echocardiography: Assessments included left ventricular EF, PAP estimates, and diastolic dysfunction parameters (E/é ratio, left atrial volume index). Echocardiographic evaluations were conducted at baseline and 12 months after initiating SGLT2i therapy.

- Right heart catheterization: Performed before study enrollment to confirm the diagnosis of PH. This procedure provided measurements of PAP, right atrial (RA) pressure, and cardiac output.

Data Collection

Patient medical records were reviewed retrospectively to gather data on demographics, medical history, HF management, and outcomes related to hospitalization and echocardiographic changes. The duration of SGLT2i therapy was documented, with an average use of 27 months (range: 15-45 months).

Our study was conducted with the approval of Pamukkale University's Medical Ethics Committee (decision no. 60116787-020/32203, date: 08.05.2018).

Statistical Analysis

Data analysis was performed using Statistical Package for the Social Sciences version 25.0. Continuous variables were reported as mean±standard deviation or median (minimum-maximum), while categorical variables were expressed as frequencies and percentages. The Shapiro-Wilk test was used to assess data distribution normality. For dependent group comparisons, the paired t-test was applied when parametric assumptions were met, whereas the Wilcoxon matched-pairs signed-rank test was used otherwise. A p value of <0.05 was considered statistically significant for all tests.

RESULTS

Demographic and Clinical Characteristics

The study included nine patients with a mean age of 67 years, the majority of whom were female (66%). All patients had a history of DM and multiple risk factors for PH associated with HFpEF. Detailed demographic and clinical characteristics are presented in Table 1.

Following the initiation of SGLT2i therapy, none of the patients required hospitalization due to HF. The majority were classified as World Health Organization functional class III. The mean hemodynamic parameters were as follows: RA pressure, 10.8±3.27 mmHg; pulmonary arterial pressure, 35.6±5.59 mmHg; pulmonary vascular resistance, 3.6±1.34 WU; Fick cardiac index, 3±0.87 l/min/m^2; and mixed venous oxygen saturation, 68.2±9.44%.

Notably, treatment with SGLT2i led to a significant reduction in tricuspid regurgitation velocity (TRV) from 3.6±0.7 m/s to 3.09±0.53 m/s (p=0.019). Additionally, NT-proBNP levels showed a significant decline from 2650.44 ng/L to 1288.67 ng/L (p=0.028) (Table 2). However, no significant changes were observed in systolic PAP and RA pressure.

These findings highlight significant improvements following SGLT2i therapy, supporting its potential benefits oin patients with PH-HFpEF.

DISCUSSION

Our study demonstrated notable improvements in TRV and NT-proBNP levels following SGLT2i therapy in patients with HFpEF and PH. These results align with previous research supporting the efficacy of SGLT2i in enhancing cardiac function and hemodynamics. For example, a retrospective study reported improved right ventricular (RV) systolic function and reduced pulmonary arterial stiffness after 6 months of SGLT2i therapy in patients with HF with reduced EF (HFrEF).[21]

Additionally, another study observed significant enhancements in RV systolic functions within three months of adding SGLT2i to optimal medical therapy in HFrEF patients.[22] Experimental models further support these findings, showing that dapagliflozin can improve echocardiographic parameters and reduce cardiomyocyte apoptosis, which may aid in pulmonary artery remodeling and alleviate RV dysfunction.[23] The same study suggested that these benefits could be attributed to reduced apoptosis in RV cardiomyocytes. Previous research has emphasized the role of apoptosis in RV remodeling, indicating that increased apoptosis contributes to the progression of right HF.[24] These findings suggest that the antiapoptotic properties of SGLT2i therapy may play a role in improving clinical outcomes in this patient population.

An experimental PH model study found that combining dapagliflozin with sildenafil may be beneficial for pulmonary vascular remodeling. The study showed that dapagliflozin lowered RV systolic pressure, reduced RV hypertrophy and pulmonary vascular remodeling, and suppressed inflammatory mechanisms.[25] Consistent with these findings, our study also observed a significant reduction in the TRV values following SGLT2i treatment.

Additionally, a subgroup analysis of the multicenter, randomized, double-blind EMBRACE-HF study demonstrated that empagliflozin significantly lowered pulmonary artery diastolic pressure in patients with HFpEF or HFrEF who had CardioMEMS PAP sensors, compared to placebo.[18] While that study did not find a significant change in NT-proBNP levels, our study observed a notable reduction in NT-proBNP following SGLT2i therapy.

Table 1. Demographic and clinical characteristics of patients

Patient	Sex	Age	HT	DM	CKD	COPD	CAD	AF	OSAS	Treatment (month)	Med	Pre TRV	Pre sPAP	Pre SAA	Pre NT-proBNP	Pre VKI	Post TRV	Post sPAP	Post RAA	Post NT-proBNP	Post VCI	mSAP	PVR	fCI	mVO2	mPAP
1	F	66	+	+	-	+	-	-	-	27	Empa	3.3	48	25	129	18	3,2	47	25	110	15	7	3	NR	75	35
2	F	67	+	+	-	-	+	+	-	27	Empa	3.6	60	30	4284	21	3,4	65	27	2399	NR	12	3	2.4	73	33
3	M	67	+	+	-	-	-	-	-	29	Empa	3.3	47	22	103	15	3,2	45	NR	32	18	8	3	4	75	28
4	F	71	+	+	-	-	+	+	-	38	Empa	3.5	52	20	572	22	2,9	39	17	742	14	15	6	2.6	65	40
5	M	66	-	+	-	-	+	-	-	45	Empa	2.63	31	NR	1964	NR	2,1	NR	NR	1026	NR	NR	NR	NR	NR	NR
6	M	70	+	+	+	+	-	+	-	38	Empa	3.7	61	20	3724	NR	2,9	39	NR	3701	18	NR	NR	NR	NR	NR
7	F	67	+	+	+	-	+	+	-	16	Dapa	3	46	NR	3372	19	3	45	32	2048	22	NR	NR	NR	NR	NR
8	F	62	-	+		+	-	-	-	15	Dapa	4.7	90	NR	8092	NR	3	42	14	268	13	NR	NR	NR	NR	NR
9	F	67	+	+	+	-	-	-	+	16	Dapa	4.7	100	25	1614	22	4,1	77	NR	1272	22	12	3	NR	53	42

F: Female, M: Male, HT: Hypertension, DM: Diabetes mellitus, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease, AF: Atrial fibrillation, OSAS: Obstructive sleep apnea syndrome, Pre: Pre-treatment with sodium-glucose co-transporter 2 inhibitor (SGLTi), Post: Post-treatment with sodium-glucose co-transporter 2 inhibitor (SGLTi), TRV: Tricuspid regurgitation velocity, SPAP: Systolic pulmonary artery pressure, RAA: Right atrium area, NT-proBNP: N-terminal Pro B-type natriuretic peptide, VCI: Inferior vena cava, mSAP: Mean right atrium pressure, PVR: Pulmonary vascular resistance, fCI: Fick cardiac index, mVO2: Mixed venous oxygen saturation, mPAP: Mean pulmonary artery pressure, Dapa: Dapagliflozine, Empa: Empagliflozine

Table 2. Echocardiographic changes before and after SGLT2i treatment

		Before treatment	After treatment	p	Delta
TRV (n=9)	Mean±SD	3.6±0.7	3.09±0.53	0.019*	0.51±0.53
	Med (min-max)	3.5 (2.63-4.7)	3 (2.1-4.1)		0.53 (0-1.7)
NT-proBNP (n=9)	Mean±SD	2650.44±2565.75	1288.67±1225.11	0.028*	13.13±17.48
	Med (min-max)	1964 (103-8092)	1026 (32-3701)		342 (170-7824)
sPAP (n=8)	Mean±SD	63±20.71	49.88±13.73	0.071	1361.78±2521.48
	Med (min-max)	56 (46-100)	45 (39-77)		7.5 (5-48)
RA (n=3)	Mean±SD	25±5	23±5.29	0.157	2±1.73
	Med (min-max)	25 (20-30)	25 (17-27)		3 (0-3)

*p<0.05 indicates statistical significance. Delta, difference before and after treatment. Post-treatment, after treatment with the SGLT2i. Pre-treatment, before treatment with the SGLT2i.
NT-proBNP: N-terminal B-type natriuretic peptide (pg/mL), TRV: Tricuspid regurgitation velocity (m/sn), RA: Right atrium (mm), sPAP: Systolic pulmonary artery pressure (mmHg), SD: Standard deviation, Mean: Average, Med: Median, SGLT2i: Sodium-glucose co-transporter-2 inhibitors, min-max: Minimum-maximum

The benefits of SGLT2 inhibitors go beyond simple intravascular decongestion. Research by Pabel et al.[26] has shown that empagliflozin can reduce myocardial filament passive stiffness and improve diastolic function. These effects are believed to result from decreased oxidative stress and inflammation, increased nitric oxide availability, and reduced myocardial fibrosis and hypertrophy.[27-29] These molecular mechanisms may explain the pathophysiological improvements observed in our study participants, highlighting a broader impact on cardiac function in HFpEF with PH.

In HFpEF, while multiple factors contribute to disease pathogenesis, diastolic dysfunction remains a key underlying cause.[30] Elevated left ventricular filling pressures lead to passive pulmonary venous congestion and postcapillary PH.[31] This progression triggers pulmonary vasoconstriction and hypertension, ultimately placing increased strain on the right ventricle. Pulmonary arteriolar resistance plays a central role in these pathological processes, raising the question of whether pharmacological treatment can slow or reverse this deterioration. Our findings suggest that SGLT2i therapy may influence these mechanisms, potentially preventing the progression of PH and RV overload—both of which contribute to worsening clinical outcomes in these patients. To date, therapies such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, and BB have been explored, but with limited effectiveness. In particular, BB have not been demonstrated improvements in mortality or hospitalization rates among patients with HFpEF.[32]

Treatment with SGLT2i has shown significant benefits in patients with HFpEF, both through its molecular effects on key pathophysiological processes and in clinical trials such as EMPEROR-PRESERVED and DELIVER.[33] These studies have provided strong evidence supporting the role of SGLT2i therapy in managing this complex condition. Consistent with these findings, our study further highlights the efficacy of SGLT2i, demonstrating significant reductions in TRV and NT-proBNP levels—markers of reduced cardiac stress and improved heart function in patients with HFpEF and PH. These results not only reinforce previous research but also contribute to a deeper understanding of the potential mechanisms through which SGLT2i may slow the progression of PH and RV overload, both of which are key factors in worsening clinical outcomes for this patient group.

Study Limitations

Despite the promising results, our study has several limitations. As a pilot study assessing the potential effects of SGLT2i in a specific patient population, it included only nine patients, which restricts its generalizability and statistical power. All eligible patients who met the inclusion criteria and did not meet the exclusion criteria were included; therefore, a power analysis was not conducted. Additionally, the retrospective design limits the ability to establish direct causality. Since the study was conducted at a single center, the findings may not be broadly applicable to other clinical settings. These limitations highlight the need for future research, particularly prospective, multicenter studies with larger sample sizes, to confirm and expand upon our results. Such studies would provide a more comprehensive evaluation of the efficacy and safety of SGLT2i and further clarify their mechanisms of action.

Furthermore, the absence of a control group and the relatively short follow-up period restricted the ability to compare different treatment groups and assess long-term outcomes. Due to the small sample size, comparisons between different SGLT2i, such as empagliflozin and dapagliflozin, were not conducted. Additionally, no significant renal side effects or decline in estimated glomerular filtration rate were observed, which aligns with existing literature indicating that such effects are uncommon. However, the short follow-up period and limited sample size may have prevented the detection of rarer or delayed adverse effects.

CONCLUSION

This study demonstrated the efficacy of SGLT2i therapy in patients with HFpEF and PH, as evidenced by significant improvements in TRV and NT-proBNP levels. However, the study's retrospective design, single-center setting, and small sample size represent key limitations. The

study specifically included diabetic patients with echocardiographic evidence of combined pre- and postcapillary PH who had received SGLT2i therapy for at least one year, with follow-up echocardiographic assessments conducted after one year of treatment.

These findings may provide valuable insights for future large-scale studies focused on HFpEF patients with PH. Further prospective research with larger sample sizes could help validate and expand upon these results, potentially revealing more significant clinical outcomes. Additionally, this study highlights the need for further investigation into the impact of SGLT2i therapy on the necessity and outcomes of invasive right heart catheterization, which is traditionally used for PH management. Experimental models of PH could also be developed to explore the early effects of SGLT2i treatment in a controlled setting.

Ethics Committee Approval: Our study was conducted with the approval of Pamukkale University's Medical Ethics Committee (decision no. 60116787-020/32203, date: 08.05.2018).

Informed Consent: Because it is a retrospective study, informed consent is not required.

Authorship Contributions: Concept: I.T., Y.T.Y., G.F.Y., Design: I.T., Y.T.Y., G.F.Y., Data Collection or Processing: Y.T.Y., G.F.Y., Analysis or Interpretation: Y.T.Y., Literature Search: I.T., Writing: I.T.

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