Ref: Ro J Med Pract. 2024;19(1)
DOI: 10.37897/RJMP.2024.1.2

The role of sodium glucose cotransporter or glucagon-like peptide-1 receptor agonists in treating heart failure with preserved ejection fraction in patients with type 2 diabetes mellitus

Laura LUNGEANU-JURAVLE[1], Mirela TACHE[2], Ana RADU[2], Carmen DOBJANSCHI[2], Petrisor ADAMESCU[2], Andra NICA[3], Emilia RUSU[3], Gabriela RADULIAN[3]

[1]Department of Cardiology, "Nicolae Malaxa" Clinical Hospital, Bucharest, Romania
[2]Department of Diabetology, "Nicolae Malaxa" Clinical Hospital, Bucharest, Romania
[3]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

Background. *Heart failure with preserved ejection fraction is not a single disease but a clinical syndrome secondary to important comorbidities, is increasing in prevalence, and is associated with high functional impairment. This study aimed to compare the results of treating patients with heart failure with preserved ejection fraction and type 2 diabetes mellitus with sodium-glucose cotransporter inhibitors (SGLT-2 inhibitors) or Glucagon-like peptide-1 receptor agonists (GLP-1 RAs).*

Methods. *Observational trial in one medical center with assessments at baseline and 6 months. Participants were patients with type 2 diabetes mellitus and heart failure with preserved ejection fraction. The primary endpoint was to measure the impact of treatment on weight loss, diastolic dysfunction, Kansas City Cardiomyopathy Questionnaire. We performed anthropometric measurements, blood samples and transthoracic echocardiography for systolic and diastolic dysfunction.*

Results. *After 6 months of intervention, both groups had a significant increase in results of Kansas City Cardiomyopathy Questionnaire, and the mean change in the group treated with GLP-1 Ras was 15.88 ± 7.7 points (95% confidence interval[CI], 19.7-12.7, p<0.01) while in the group treated with sodium-glucose cotransporter inhibitors was 13.57 ± 7.96 points (95% confidence interval[CI], 16.22-10.91, p<0.01) so the quality of life was better. The weight loss was more important in the group with GLP-1 Ras with 5.8 ± 1.8 kg (95% confidence interval [CI], 4.7-7.0, p<0.01) while in the other group was 1.37 ± 1.4 kg (95% confidence interval [CI], 0.54-2.21, p<0.01). Diastolic dysfunction was improved in monitoring E/E' lateral and was 3.28 ±1.27 less (95% confidence interval [CI], 2.75-3.80, p<0.01) in the GLP-1 Ras group and 2.93 ± 2.15 less (95% confidence interval [CI], 2.21-3.64, p<0.01) in the SGLT-2 inhibitors group.*

Conclusions. *The present study establishes an improvement in symptoms, diastolic dysfunction, and weight loss in patients with type 2 diabetes mellitus and heart failure with preserved ejection fraction and treatment with GLP-1 Ras or SGLT-2 inhibitors.*

Keywords: heart failure with preserved ejection fraction (HFpEF), diabetes mellitus type 2 (T2DM), N-terminal pro–B-type natriuretic peptide (NTproBNP), Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), sodium glucose cotransporter inhibitors (SGLT-2 inhibitors)

Corresponding author:
Emilia Rusu
E-mail: emiliarusumd@yahoo.com

Article History:
Received: 20 March 2024
Accepted: 30 March 2024

BACKGROUND

Heart failure with preserved ejection fraction (HFpEF) is a pathology with increasing prevalence, considered responsible for half of heart failure cases. A significant percentage is also associated with obesity, with current evidence suggesting that they are not simply coexisting comorbidities, excess adiposity playing a role in the development of HFpEF [1-4]. HFpEF is common in obese patients due to common underlying mechanisms, including modulation of cardiac filling (altered in obese individuals), plasma volume, increased filling pressures, sympathetic nervous system activation, cardio-renal interactions, and accumulation of lipids and adipose cells. Essential is the inflammatory cascade that determines microvascular dysfunction, endothelial dysfunction, atrial fibrosis, hypertension, diabetes, chronic kidney disease, and most importantly HFpEF [5].

Starting from 2023, according to the focus on the heart failure guideline, treatment with SGLT2 inhibitors in HFpEF is recommended [6]. Obesity is frequently associated with type 2 diabetes, both pathologies being implicated in the onset of HFpEF. Another class of drugs, GLP1 receptor agonists, initially developed as therapy for type 2 diabetes, has proven benefits in weight loss and glycemic control.

The definition of HFpEF from the heart failure guideline is the presence of signs and symptoms of heart failure, EF > 50%, structural and functional cardiac changes consistent with left ventricular diastolic dysfunction/ increased left ventricular filling pressures, including elevated natriuretic peptides [6]. Diastole is the cardiac cycle component where optimal ventricular filling determines the stroke volume ejected at the next systole [7]. Many factors contribute to cardiac filling, including venous return, atrial filling from the pulmonary circulation, and effective emptying into the left ventricle. Ventricular filling is also influenced by cavity emptying function and synchronous function, which can be affected by early changes in diastolic filling in severe dyssynchrony [7]. Incomplete emptying of the left atrium leads to increased intracavitary pressure with secondary dilatation and increases the risk of atrial arrhythmias including atrial fibrillation [7]. The described mechanism is involved in the development of HFpEF, and this patient population presents for medical evaluation complaining of dyspnea on exertion. Doppler echocardiography is a safe, non-invasive method that can be used to measure ventricular filling and assess diastolic function [8].

In the diagnostic protocol of HFpEF, echocardiography also determines left ventricular hypertrophy and left atrial dilatation. Left ventricular hypertrophy is a strong predictor of cardiovascular morbidity and mortality independent of blood pressure and other cardiovascular risk factors [9]. The prevalence of left ventricular hypertrophy increases with the severity of hypertension, age, and obesity [10]. Left atrial dilatation has been demonstrated as a barometer of diastolic dysfunction and a predictor for atrial fibrillation, ischemic stroke, heart failure and cardiovascular death [11]. Left atrial volume is a more robust marker for cardiovascular events than area or diameter in patients with sinus rhythm [12].

OBJECTIVES

The objective of this study is to monitor the treatment outcomes with SGLT2 inhibitors versus GLP1 receptor agonists in HFpEF in patients with type 2 diabetes, aiming to find new therapeutic classes for this condition.

METHODS

Study design

The study was single center, conducted from January 2023 to March 2024, and was prospective observational.

Participants

Participants were patients included in the national diabetes program referred to a clinical hospital with a diabetes department. Inclusion criteria were: age over 18 years, with a diagnosis of heart failure class I-IV NYHA according to ECG, clinical, and biological criteria; with type 2 diabetes requiring initiation of specific therapy with SGLT2 inhibitors/GLP1 receptor agonists according to guideline recommendations, in sinus rhythm.

Exclusion criteria were: hemodynamically unstable patients, moderate-severe valvular heart disease, difficult 2D echocardiographic window, lack of compliance and severe comorbidities with a life expectancy less than 1 year. Approval was obtained from the Ethics Committee of the center where the study was conducted in advance. All patients who met the inclusion criteria agreed to participate, and signed informed consent were enrolled.

Eligibility was established through inter-clinic diabetes-cardiology consultation: patients requiring augmentation of antidiabetic therapy with either SGLT2 inhibitors or GLP1 receptor agonists were clinically, biologically, and echocardiographically evaluated. The recommendation for SGLT2 inhibitors or GLP1 receptor agonists was at the discretion of the diabetologist according to the patient's particularities as standard of care.

Anthropometric evaluation

Anthropometric measurements were performed: weight, height, BMI (body mass index), BSA (body surface area), arm circumference, and leg circumference (at one-third proximal) at both visits: initiation and visit two. For BMI calculation, the formula weight/height² was used. The recommendation of the World Health Organization was followed: BMI ≥ 30 kg/m² was considered obesity and between 25-29.9 kg/m² overweight. Blood pressure values were monitored with two measurements in the seated position at the end of the objective examination.

Laboratory analyses

Blood samples were collected at the hospital, in the local laboratory after 12 hours of fasting, and included: lipid profile (LDL cholesterol calculated by the Friedwald formula), fasting glucose, HbA1c, urea, creatinine, sodium, potassium, complete blood count, ESR, fibrinogen, C-reactive protein, thyroid stimulating hormone, AST, ALT, urine analysis, uric acid, NTproBNP. The entire mentioned set was collected at both study visits.

Transthoracic cardiac ultrasound

Transthoracic echocardiographic evaluation was performed using the apparatus (MY GOLDEN LAB 25-ESAOTE) available in the hospital's echocardiography laboratory where the study was conducted. Classic structural parameters included: cardiac chamber dimensions, interventricular septal wall thickness, M-mode assessment of IVC, assessment of valvular structure and function, and estimation of mitral/tricuspid regurgitation according to current guidelines. Classic indices of systolic function included cardiac output measurement, EF by Simpson's method, MAPSE of the LV lateral wall using M-mode at the mitral annulus as a marker of LV longitudinal systolic function, TAPSE of the RV lateral wall using M-mode at the tricuspid annulus as a marker of RV longitudinal systolic function. Classic indices of diastolic function included: E, A, E/A, TdE, A duration (obtained at the peak of the mitral/tricuspid valves), filling time (FT) (time from the onset of the E wave to mitral valve closure), biplane LA volume obtained from dedicated LA images in apical 4- and 2-chamber views. Passive, conduit, and active LA functions were assessed by measuring LA volumes at the time of the MV closure (minimal volume) and end-systolic (maximal volume).

The RV-RA gradient and calculated PAPs using continuous-wave Doppler envelope of the tricuspid valve estimated RA pressure (by dimensions and respiratory variation of IVC). Tissue Doppler echocardiography assessing LV longitudinal systolic function with systolic velocities in longitudinal axis (S) by color-guided pulsed tissue Doppler at basal segments in apical 4C (lateral wall, posterior IVS), 2C (inferior wall, anterior) and 3C (anterior IVS and posterior wall). RV longitudinal systolic function with systolic velocity in longitudinal axis (S) in color-guided pulsed tissue Doppler imaging at basal and mid RV free wall segments in apical 4C. Longitudinal diastolic function assessed by DTI with lateral E/E' Doppler.

Quality of life assessment

The Kansas City Cardiomyopathy Questionnaire was used as a tool for assessing quality of life and monitoring the symptomatic status of patients at both study visits: baseline and follow-up. For objective evaluation of patient strength, handgrip strength was measured at both study visits using an approved dynamometer.

RESULTS

Demographic characteristics of participant groups

A total of 25 patients were included in the GLP1 receptor agonist-treated group, of which 52% were female and 48% were male. The cohort of patients on SGLT2 inhibitor therapy consisted of 37 patients, of which 54% were female and 46% were male. In the GLP1 receptor agonist-treated group, 92% were obese and only 8% were overweight. In the SGLT2 inhibitor-treated group, only 73% were obese, with the remaining 27% being overweight. The mean BMI at baseline visit was 36.68 ±5.2 kg/m² in the GLP1 receptor agonist group and 33.57±5.9 kg/m² in the SGLT2 inhibitor group.

The mean age at study inclusion was 60.68 ±10.2 years in the GLP1 receptor agonist group and 64.3±7.2 years in the SGLT2 inhibitor group. The mean duration of diabetes was 8.2 years ±4 years in the GLP1 receptor agonist group and 12 ±11.6 years in the SGLT2 inhibitor group.

In the GLP1 receptor agonist-treated group, 24% were smokers, while in the SGLT2 inhibitor-treated group, 24.3% were actively smoking. All study participants had lipid profile values classifying them as dyslipidemic.

Regarding medical history: in the GLP1 receptor agonist-treated group, 12% had a history of myocardial infarction, 0% had revascularized peripheral arterial disease, and 4% had a history of ischemic stroke; in the SGLT2 inhibitor-treated group, 19% had a history of myocardial infarction, 5.4% had revascularized peripheral arterial disease, and 13.5% had a history of ischemic stroke. From the study population, there was a total percentage of 16% myocardial infarction, 3.2% revascularized peripheral arterial disease (PAD), and 9.7% ischemic stroke.

Associated comorbidities

One of the main causes of chronic kidney disease (CKD) is diabetes mellitus with the development over time of diabetic nephropathy [13]. It is estimated that half of diabetic patients also have CKD, with the elderly, those with long-standing type 2 diabetes, and certain ethnic groups being more predisposed [14]. In the study population, patients with stage 1 CKD predominated: 72% of those treated with GLP1 receptor agonists and 67% of those treated with SGLT2 inhibitors. Another frequent association is type 2 diabetes, CKD, and hypertension, with blood pressure values sometimes even harder to control than glycemic values in these patients [15].

Associated antidiabetic therapy

The addition of GLP1 receptor agonist or SGLT2 inhibitor treatment was performed in addition to preexisting antidiabetic background therapy. Regarding insulin therapy, 36% of the GLP1 receptor agonist-treated group associated with it, while 64.9% of the SGLT2 inhibitor-treated group did so. For oral antidiabetic drugs (OADs), 92% of the GLP1 receptor agonist group were on treatment, while only 72% of the SGLT2 inhibitor-treated group were.

Cardiovascular therapy

Study participants received targeted therapy based on associated cardiovascular comorbidities, including beta-blockers (BBs), angiotensin receptor blockers (ARBs), and angiotensin-converting enzyme inhibitors (ACEIs).

TABLE 1. *Characteristics of the study population*

Variable	SGLT-2 inhibitors	GLP-1 RAs	p
Obesity	24(73%)	23(92%)	0.059
Smoking	9(24.3%)	6(24%)	0.611
History of MI	7(19%)	3(12%)	0.055
History of stroke	1(4%)	5(13.5%)	0.387
History of PAD	2 (5.4%)	0(0%)	0.352
Insulin therapy	24(64.9%)	9(36%)	0.038
OADs	27(72%)	23(92%)	0.101
ARBs	11(29.7%)	5(20%)	0.556
ACEIs	22(59.5%)	16(64%)	0.794
BBs	31(83.8%)	19(76%)	0.521

Objective clinical examination

The clinical evaluation included two blood pressure measurements. An EKG was performed at each visit since one of the inclusion criteria was the presence of sinus rhythm on the EKG.

TABLE 2. *Clinical features*

Variable	GLP-1 RAs	SGLT-2 inhibitors
Systolic blood pressure mmHg	137.5±16.8 SD	140±18.3 SD
Diastolic blood pressure mmHg	81.4±10 SD	79.3±10.6 SD
Heart Rate bpm	74±9.43 SD	72±9.97 SD

Echocardiographic parameters of systolic and diastolic function

For the assessment of systolic function, left ventricular ejection fraction (LVEF) was measured using the Simpson method and basal tissue systolic velocities. Calculating the left ventricular ejection fraction by evaluating left ventricular volumes is the most used method [16]. At the baseline visit, the mean LVEF was 60.8%±6.4% in the GLP1 receptor agonist-treated group and 60.5%±7.5% in the SGLT2 inhibitor-treated group.

Stroke volume is the sum event of the cardiac cycle and represents the most pragmatic indicator by which the clinician can determine, regardless of other 2D results, whether cardiac pathophysiology contributes to the patient's clinical status. An estimated stroke volume is quickly useful, providing valuable information about hemodynamics and causality [17]. The mean stroke volume in the study was 43.9±9.48 ml in patients treated with GLP1 receptor agonists and 44.6±12.43 ml in the second group.

The diastolic profile was of type I in the study, with a mean E/A ratio of 0.72±0.15 in the GLP1 receptor agonist-treated group and 0.66±0.14 in the SGLT2 inhibitor-treated group. Another echocardiographic parameter determined for diastolic function was E/E' lateral, with a mean of 11±1.2 in the GLP1 receptor agonist-treated group and 9.4±2.2 in the SGLT2 inhibitor-treated group.

A prognostic parameter in congestive heart failure is the tricuspid annular systolic excursion (TAPSE) to pulmonary artery systolic pressure (PAPs) ratio [18]. Right ventricular longitudinal function was assessed by TAPSE with mean values of 24.2±3.3 in the first group and 23.4±3.5 in the second group. PAPs values were categorized as normal-low, which is why they were not further detailed.

Biological profile

Patients in the study cohorts had the specified set of analyses collected at both visits as mentioned in the study protocol. In terms of glycemic control, the GLP1 receptor agonist-treated group had an average blood glucose level of 219±77 mg/dl and glycated hemoglobin of 8.9%±1%, while in the SGLT2 inhibitor-treated group, the average blood glucose level was 199±70 mg/dl and glycated hemoglobin was 8.8%±2.3%. Regarding

TABLE 3. *Echocardiographic parameters in study population*

	GLP-1 RAs (n=25)		SGLT2 inhibitors (n=37)		Total (n=62)		p
	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation	
FEVS (%)-v1	0.61	0.06	0.61	0.08	0.61	0.07	0.88
E/A-v1	0.72	0.15	0.66	0.15	0.69	0.15	0.12
E/E' lateral-v1	11.12	1.20	9.44	2.29	10.12	2.08	0.00
SV-v1	43.96	9.49	44.62	12.43	44.35	11.26	0.82
TAPSE - v1	24.20	3.32	23.46	3.57	23.76	3.46	0.41

TABLE 4. *Distribution of left ventricle hypertrophy and left atrium dilatation in the study group*

Variable	GLP-1 RAs	SGLT-2 inhibitors	p
Left ventricle hypertrophy	18(72%)	31(83.8%)	0.501
Left atrium volume >45 ml	21(84%)	28(75.7%)	0.534

metabolic control in the study population, the mean total cholesterol in the GLP1 receptor agonist-treated group was 213±55 mg/dl, and in the SGLT2 inhibitor-treated group, it was 196±42.7 mg/dl.

The inflammatory syndrome, especially highly sensitive C-reactive protein (hs-CRP), has an additional role in stratifying the risk for patients with heart failure [19]. Data from a systematic review and meta-analysis suggest the possibility of using hs-CRP as a biomarker not only for predicting the development of new cases of HFpEF but also for long-term prognosis in this pathology [20]. In the GLP1 receptor agonist-treated group, the average hs-CRP was 1.08±1.03 mg/dl, while in the SGLT2 inhibitor-treated group, it was 1.3±1.1 mg/dl. Slightly higher values were recorded in the SGLT2 inhibitor group, where patients with a higher NYHA class were enrolled, but without statistical significance. This result would probably confirm the prognostic role of hs-CRP in the group with more advanced pathology if the patient cohorts were larger.

In the diagnostic protocol of HFpEF, the biomarker NT-proBNP is also included. Limitations related to this biomarker in the current study population, which largely associates obesity are related to falsely normal values. This situation was frequently found in other studies with a similar population. In one such study conducted at the Mayo Clinic, a substantial percentage of patients with HFpEF had NT-proBNP within normal limits. The pathophysiology of this phenotype is unknown [21] but frequently encountered in patients with obesity. Patients with HFpEF and normal NT-proBNP usually have mild diastolic dysfunction with normal cardiac output during physical exertion, although they have significantly increased cardiac filling velocities. This group has an increased risk of death or readmission for heart failure compared to those without heart failure [22]. The NT-proBNP level is lower in overweight/obesity, even in those with type 2 diabetes. Insulin resistance and low-grade chronic inflammation associated with such patients are implicated [23,24].

The mean NT-proBNP value in the study population treated with GLP1 receptor agonists was 63.5±41, with this group having obesity associated in 92% proportion. In the SGLT2 inhibitor-treated group, the mean NT-proBNP value was 189±272, with this group having obesity associated in a smaller percentage, namely 73%.

Quality of life and NYHA class

The NYHA class has remained a prognostic factor for morbidity and mortality in patients with heart failure over time [25]. Discrepancies between NYHA class and the Kansas City Cardiomyopathy Questionnaire (KCC-QS) score have been common. Compared, KCC-QS has been more significantly associated with subsequent mortality, particularly at 4 years [26]. KCC-QS, initially created with 23 questions, was reconfigured to 12 questions to be used as an evaluation tool in heart failure studies [26]. In the GLP1 receptor agonist-treated group, 68% of patients were classified in NYHA class II, and 0% in NYHA class III. In the SGLT2 inhibitor-treated group, 43% were in NYHA class II, and 19% in NYHA class III.

Upon applying the KCC-QS questionnaire, the mean result in the GLP1 receptor agonist-treated group was 60.5±16.7 points, while in the SGLT2 inhibitor-treated group, it was 48.7±26 points. These results reflect a more deteriorated symptomatic status and a lower quality of life than the NYHA class mentioned earlier in both treatment groups.

Another test that was performed is the handgrip test using a dynamometer to evaluate muscle blood flow and endothelium-dependent vasodilation in the peripheral blood vessel during dynamic gripping effort in patients with HFpEF. Although the contribution of non-cardiac comorbidities to the pathophysiology of HFpEF has been recognized, changes in peripheral vascular control are still under observation [27]. A reduction in blood flow and vascular conductance during dynamic handgrip exercise was found in patients with HFpEF compared to patients who have comorbidities such as obesity and hypertension but without HFpEF [27].

DISCUSSIONS

The effects of SGLT2 inhibitors or GLP1 receptor agonists on diastolic dysfunction, quality of life, and weight impact were evaluated.

Improvement in diastolic dysfunction at 6 months was observed by monitoring the lateral E/E' ratio, with a better ratio of 3.28 ± 1.27 (95% confidence interval [CI], 2.75-3.80, p<0.01) in the GLP1 receptor agonist-treated group. In the SGLT2 inhibitor therapy group, the lateral E/E' ratio improved to 2.93 ± 2.15 (95% confidence interval [CI], 2.21-3.64, p<0.01) at visit 2. Regarding the E/A ratio: the result in the GLP1 receptor agonist-treated group was -0.5±1.27 (95% confidence interval [CI], -0.08-0.16, p at the significance limit of 0.05), and in the SGLT2 inhibitor-treated group, the result was -0.06+0.11 (95% confidence interval [CI], -0.09-0.02, p:0.03). HFpEF represents an underdiagnosed pathology, often associated with obesity because some of the pathophysiological mechanisms such as central adiposity with increased inflammation, left ventricular hypertrophy, peripheral insulin resistance, and diastolic dysfunction are common and implicated in the pathogenesis of both comorbidities [2-4]. The coexistence of these 2 conditions, HFpEF, and obesity, with unfavorable prognosis is well known, but data from prospective observational studies aiming to decrease weight and its underlying impact on diastolic dysfunction and beyond in HFpEF are lacking [28].

After 6 months of treatment initiation, both groups showed improvement in the Kansas City Cardiomyopathy Questionnaire score, with an average of 15.88 ± 7.7 points (95% confidence interval [CI], 19.7-12.7, p<0.01) in the GLP1 receptor agonist-treated group and 13.57 ± 7.96 points (95% confidence interval [CI], 16.22-10.91, p<0.01) in the SGLT2 inhibitor-treated group, indicating an improvement in quality of life. In the STEP-HFpEF study, a randomized, double-blind study monitoring the effects of GLP1 receptor agonist treatment (subcutaneous semaglutide)/placebo in a population of patients with obesity and HFpEF, where the Kansas City Cardiomyopathy Questionnaire score was applied as an evaluation tool for quality of life, the improvement was 16.6 points, similar to that found in the current study [1]. SGLT2 inhibitor treatment has proven effective in HFpEF and is included in current guideline recommendations. Evidence from 2 randomized studies—Deliver (dapagliflozin in HFpEF) and Emperor (empagliflozin in HFpEF)—has led to this recommendation recently introduced into standard therapy [29, 30]. Both studies were double-blind, randomized trials with the primary endpoint of heart failure worsening and cardiovascular death. In Deliver, as a secondary objective, the Kansas City Cardiomyopathy Questionnaire score was followed up at 1 month when was better than baseline. In Deliver, the predominant NYHA class at inclusion was II with a percentage of 75%, similar to Emperor. In the current study, 43% of the SGLT2 inhibitor group were in NYHA II, but the mean KCC-QS score at baseline was 48 points, whereas in Deliver, the mean KCC-QS score at baseline was 70 points. In conclusion, in the current study, the patients were at a more advanced stage of heart failure compared to Deliver.

Weight loss at the 6-month visit was more significant in the GLP1 receptor agonist-treated group with an average of 5.8 ± 1.8 kg (95% confidence interval [CI], 4.7-7.0, p<0.01). In the SGLT2 inhibitor-treated group, it was 1.37 ± 1.4 kg (95% confidence interval [CI], 0.54-2.21, p<0.01). The mean BMI decrease was 1.44±0.06 kg/m² (95% confidence interval [CI], 0.05-0.11, p<0.01) in the GLP1 agonist group and 0.37±0.41 kg/m² (95% confidence interval [CI], 0.05-0.71, p<0.01) in the second group. A reduction in arm circumference of 0.86±0.6 cm (95% confidence interval [CI], 0.61-1.1, p<0.01) was recorded in the first group and 0.28 ± 0.67 cm (95% confidence interval [CI], 0.05-0.5, p<0.015) in the SGLT2 inhibitor-treated group.

The limitations of the current study are related to the small number of participants, but the current results recommend extension to a larger sample size for significant statistical power. Additional limitations are related to the short follow-up period: in the current study of 6 months compared to an average of 2 years in Deliver and Emperor, as well as the small participant pool.

CONCLUSIONS

The current study has revealed improvement in symptoms, quality of life, diastolic dysfunction, and weight loss in patients with type 2 diabetes and heart failure with preserved ejection fraction (HFpEF) treated with GLP1 receptor agonist or SGLT2 inhibitor. Further studies are needed in this direction to establish whether GLP1 receptor agonists represent a new therapeutic class for HFpEF in patients with type 2 diabetes and obesity.

Conflict of interest: none declared
Financial support: none

REFERENCES

1. Kosiborod MN, Abildstrøm SZ, Borlaug BA, Butler J, Rasmussen S, et all. STEP-HFpEF Trial Committees and Investigators. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. *N Engl J Med.* 2023 Sep 21;389(12):1069-1084. doi: 10.1056/NEJMoa2306963. Epub 2023 Aug 25. PMID: 37622681.
2. Haass M, Kitzman DW, Anand IS, Miller A, Zile MR, et al. Body mass index and adverse cardiovascular outcomes in heart failure patients with preserved ejection fraction: results from the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. *Circ Heart Fail.* 2011 May;4(3):324-31. doi: 10.1161/Circheartfailure.110.959890. Epub 2011 Feb 24. PMID: 21350053; PMCID: PMC3100162.
3. Newman AB, Lee JS, Visser M, Goodpaster BH, Kritchevsky SB, et al. Weight change and the conservation of lean mass in old age: the Health, Aging and Body Composition Study. *Am J Clin Nutr.* 2005 Oct;82(4):872-8; quiz 915-6. doi: 10.1093/ajcn/82.4.872. PMID: 16210719.
4. Haykowsky MJ, Nicklas BJ, Brubaker PH, Hundley WG, Brinkley TE, et al. Regional Adipose Distribution and its Relationship to Exercise Intolerance in Older Obese Patients Who Have Heart Failure With Preserved Ejection Fraction. *JACC Heart Fail.* 2018 Aug;6(8):640-649. doi: 10.1016/j.jchf.2018.06.002. Epub 2018 Jul 11. PMID: 30007558; PMCID: PMC6086374.
5. Kato ET, Lewis BS, Ono K. GLP-1 receptor agonists: new game changing drugs in patients with heart failure with preserved ejection fraction and obesity. *Eur Heart J Cardiovasc Pharmacother.* 2023 Dec 14;9(8):679-680. doi: 10.1093/ehjcvp/pvad072. PMID: 37777847
6. Theresa A McDonagh, Marco Metra, Marianna Adamo, Roy S Gardner, Andreas Baumbach, et al. ESC Scientific Document Group, 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2023 Oct 1;44(37):3627-39. doi: 10.1093/eurheartj/ehad195.
7. Henein MY, Lindqvist P. Diastolic function assessment by echocardiography: A practical manual for clinical use and future applications. *Echocardiography.* 2020 Nov;37(11):1908-18. doi: 10.1111/echo.14698. Epub 2020 May 19. PMID: 32426907.
8. Vlahović A, Popović AD. Procena dijastolne funkcije leve komore Dopler-ehokardiografijom [Evaluation of left ventricular diastolic function using Doppler echocardiography]. *Med Pregl.* 1999 Jan-Feb;52(1-2):13-8. Croatian. PMID: 10352498.
9. Agabiti-Rosei E, Muiesan ML. Left ventricular hypertrophy: how to influence an important risk factor in hypertension. *J Hypertens Suppl.* 1998 Jan;16(1):S53-8. PMID: 9534098.
10. Ruilope LM, Schmieder RE. Left ventricular hypertrophy and clinical outcomes in hypertensive patients. *Am J Hypertens.* 2008 May;21(5):500-8. doi: 10.1038/ajh.2008.16. Epub 2008 Mar 13. PMID: 18437140.
11. Družbacká L, Valočik G, Jakubová M, Stančák B, Fojtíková L. Klinické dôsledky zväčšenia ľavej predsiene [Clinical implications of enlargement of left atrium]. Vnitr Lek. 2012 Feb;58(2):118-22. Slovak. PMID: 22463091.
12. Tsang TS, Abhayaratna WP, Barnes ME, Miyasaka Y, Gersh BJ, et al. Prediction of cardiovascular outcomes with left atrial size: is volume superior to area or diameter? *J Am Coll Cardiol.* 2006 Mar 7;47(5):1018-23. doi: 10.1016/j.jacc.2005.08.077. Epub 2006 Feb 9. PMID: 16516087.
13. Lv JC, Zhang LX. Prevalence and Disease Burden of Chronic Kidney Disease. *Adv Exp Med Biol.* 2019;1165:3-15. doi: 10.1007/978-981-13-8871-2_1. PMID: 31399958.
14. Thomas MC, Cooper ME, Zimmet P. Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease. *Nat Rev Nephrol.* 2016 Feb;12(2):73-81. doi: 10.1038/nrneph.2015.173. Epub 2015 Nov 10. PMID: 26553517.
15. Corcillo A, Pivin E, Lalubin F, Pitteloud N, Burnier M, Zanchi A. Glycaemic, blood pressure and lipid goal attainment and chronic kidney disease stage of type 2 diabetic patients treated in primary care practices. *Swiss Med Wkly.* 2017 Jul 6;147:w14459. doi: 10.4414/smw.2017.14459. PMID: 28695552.
16. Li T, Wei B, Cong J, Hong Y, Li S. Direct estimation of left ventricular ejection fraction via a cardiac cycle feature learning architecture. *Comput Biol Med.* 2020 Mar;118:103659. doi: 10.1016/j.compbiomed.2020.103659. Epub 2020 Feb 15. PMID: 32174330.
17. Sattin M, Burhani Z, Jaidka A, Millington SJ, Arntfield RT. Stroke Volume Determination by Echocardiography. *Chest.* 2022 Jun;161(6):1598-1605. doi: 10.1016/j.chest.2022.01.022. Epub 2022 Jan 24. PMID: 35085589.
18. Tello K, Axmann J, Ghofrani HA, Naeije R, Narcin N, Rieth A et al. Relevance of the TAPSE/PASP ratio in pulmonary arterial hypertension. *Int J Cardiol.* 2018 Sep 1;266:229-235. doi: 10.1016/j.ijcard.2018.01.053. PMID: 29887454.
19. Agabiti-Rosei E, Muiesan ML. Left ventricular hypertrophy: how to influence an important risk factor in hypertension. *J Hypertens Suppl.* 1998 Jan;16(1):S53-8. PMID: 9534098.
20. Lakhani I, Wong MV, Hung JKF, Gong M, Waleed KB, et al. Diagnostic and prognostic value of serum C-reactive protein in heart failure with preserved ejection fraction: a systematic review and meta-analysis. *Heart Fail Rev.* 2021 Sep;26(5):1141-50. doi: 10.1007/s10741-020-09927-x. PMID: 32030562; PMCID: PMC8310477.
21. Verbrugge FH, Omote K, Reddy YNV, Sorimachi H, Obokata M, Borlaug BA. Heart failure with preserved ejection fraction in patients with normal natriuretic peptide levels is associated with increased morbidity and mortality. *Eur Heart J.* 2022 May 21;43(20):1941-51. doi: 10.1093/eurheartj/ehab911. PMID: 35139159; PMCID: PMC9649913.
22. Baldassarre S, Fragapani S, Panero A, Fedele D, Pinach S, et al. NTproBNP in insulin-resistance mediated conditions: overweight/obesity, metabolic syndrome and diabetes. The population-based Casale Monferrato Study. *Cardiovasc Diabetol.* 2017 Sep 25;16(1):119. doi: 10.1186/s12933-017-0601-z. PMID: 28946871; PMCID: PMC5613356.
23. Gaborit FS, Kistorp C, Kümler T, Hassager C, Tønder N, et al. Early Stages of Obesity-related Heart Failure Are Associated with Natriuretic Peptide Deficiency and an Overall Lack of Neurohormonal Activation: The Copenhagen Heart Failure Risk Study. *Glob Heart.* 2020 Mar 25;15(1):25. doi: 10.5334/gh.776. PMID: 32489798; PMCID: PMC7218759.
24. Lindberg F, Lund LH, Benson L, Dahlström U, Karlström P, et al. Trajectories in New York Heart Association functional class in heart failure across the ejection fraction spectrum: data from the Swedish Heart Failure Registry. *Eur J Heart Fail.* 2022 Nov;24(11):2093-2104. doi: 10.1002/ejhf.2644. Epub 2022 Aug 23. Erratum in: *Eur J Heart Fail.* 2023 Mar;25(3):444. PMID: 35999668; PMCID: PMC10087442.
25. Huo X, Pu B, Wang W, Peng Y, Li J, et al. New York Heart Association Class and Kansas City Cardiomyopathy Questionnaire in Acute Heart Failure. *JAMA Netw Open.* 2023 Oct 2;6(10):e2339458. doi: 10.1001/jamanetworkopen.2023.39458. PMID: 37874564; PMCID: PMC10599126.
26. Spertus JA, Jones PG. Development and Validation of a Short Version of the Kansas City Cardiomyopathy Questionnaire. *Circ Cardiovasc Qual Outcomes.* 2015 Sep;8(5):469-76. doi: 10.1161/CIRCOUTCOMES.115.001958. PMID: 26307129; PMCID: PMC4885562.
27. Ratchford SM, Clifton HL, La Salle DT, Broxterman RM, Lee JF, et al. Cardiovascular responses to rhythmic handgrip exercise in heart failure with preserved ejection fraction.

J Appl Physiol (1985). 2020 Dec 1;129(6):1267-76. doi: 10.1152/japplphysiol.00468.2020. Epub 2020 Sep 17. PMID: 32940557; PMCID: PMC7792839.

28. Kitzman DW, Brubaker P, Morgan T, Haykowsky M, Hundley G, et al. Effect of Caloric Restriction or Aerobic Exercise Training on Peak Oxygen Consumption and Quality of Life in Obese Older Patients With Heart Failure With Preserved Ejection Fraction: A Randomized Clinical Trial. *JAMA.* 2016 Jan 5;315(1):36-46. doi: 10.1001/jama.2015.17346. PMID: 26746456; PMCID: PMC4787295.
29. Vaduganathan M, Claggett BL, de Boer RA, DeMets Det all. Baseline Characteristics of Patients With HF With Mildly Reduced and Preserved Ejection Fraction: DELIVER Trial. *JACC Heart Fail.* 2022 Mar;10(3):184-97. doi: 10.1016/j.jchf.2021.11.006. PMID: 35241246.
30. Anker SD, Butler J, Filippatos G, Ferreira JP, et al. EMPEROR-Preserved Trial Investigators. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med.* 2021 Oct 14;385(16):1451-1461. doi: 10.1056/NEJMoa2107038. Epub 2021 Aug 27. PMID: 34449189.