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Impact of sodium glucose co-transporter-2 inhibitors on left atrial functions in patients with type-2 diabetes and heart failure with mildly reduced ejection fraction

Shaimaa B. El-Saied, Wafaa S. El-Sherbeny *, Sara I. El-sharkawy

Cardiovascular Medicine Department, Faculty of Medicine, Tanta University, Tanta, Egypt

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ABSTRACT

Background: We aimed to assess the impact of adding sodium glucose co-transporters-2 inhibitors (SGLT-2I) on cardiac remodeling in type 2 diabetic patients with heart failure with mildly reduced ejection fraction (HFmrEF) that had been under-represented in most clinical trials through the analysis of left atrial (LA) phasic functions with 2-D speckle tracking echocardiography (2D- STE

Methods: We enrolled 70 patients with type 2 diabetes (T2DM) and stable HFmrEF (35 patients received one of SGLT-2I either empagliflozin or dapagliflozin). Laboratory assessment and echocardiographic evaluation were carried out at baseline and after 6 months. LA volumes and deformation analysis were conducted using 2D-STE. Three LA strain parameters were obtained (LA reservoir strain, contractile strain, and conduit strain).

Results: After 6 months of SGLT-2 I treatment, there was better control of HbA1C and improvement of diastolic functions (E/e′ ratio and LAV-I significantly decreased. $P < 0.001$*). LVGLS increased, LA functions and all LA strain curve values improved, LA reservoir increased from 17.3 ± 2.0 to 23.8 ± 3.6, LA conduit from 11.0 ± 2.2 to 13.7 ± 2.8 and LA contractile from 6.5 ± 1.4 to 10.5 ± 2.6, $P < 0.001$* for all. Changes in LA strain values were significantly associated with the changes in LVGLS, LAEF %, E/ e′ ratio, and LAV-I.

Conclusion: Adding SGLT-2I to existing guideline-directed medical therapy in patients with T2DM and HFmrEF is associated with favorable clinical outcomes and significant improvement of LA volume and functions, with further improvement of LV diastolic and longitudinal functions.

1. Introduction

Sodium-glucose co-transporter type 2 (SGLT2) inhibitors were initially used as a class of anti-hyperglycemic agents managing Type II diabetes mellitus (T2DM), which proved to reduce heart failure (HF) hospitalization and provide mortality benefits in T2DM and cardiovascular disease [1]. It gained a class IA recommendation for the management of patients with Heart Failure with reduced Ejection Fraction (HFrEF) in addition to B- blockers, ARNI, and MRA, irrespective of the presence or absence of DM [2].

T2DM is a well-known independent predictor of mortality as well as a major risk factor for the development of all cardiovascular (CV) events, including heart failure, across all its grades. T2DM related cardiac affection is primarily diastolic dysfunction, and it is considered the earliest functional impairment during diabetes-related cardiac dysfunction [3].

Heart Failure with Mildly Reduced Ejection Fraction (HFmrEF), is a unique group of heart failure, first earned its official title in the 2016 ESC guideline for the diagnosis and treatment of acute and chronic HF. It was defined as patients with clear clinical, biological, and imaging criteria of

Abbreviations: AF, Atrial fibrillation; ARNI, Angiotensin receptor-Nibrilysin inhibitors; BSA, Body surface area; DM, Diabetes mellitus; E/ e′, peak early diastolic mitral flow velocity/pulsed-wave tissue Doppler-derived early diastolic velocity from the septal mitral annulus ratio; eGFR, Estimated glomerular filtration rate; HF, Heart failure; HFmrEF, Heart failure with mildly reduced ejection fraction; HFpEF, Heart failure with preserved ejection fraction; HFrEF, Heart failure with reduced ejection fraction; HTN, Hypertension; IHD, Ischaemic heart disease; LA, Left atrial; LAEF- %, Left atrial emptying fraction (%); LAEV- ml, Left atrial emptying volume; LAVI, Left atrial volume index; LV, Left ventricular; LVEF, Left ventricular ejection fraction; LV-GLS, Left ventricular- global longitudinal strain; MRA, Mineralcorticoid receptors antagonists; PASP, pulmonary artery systolic pressure; QOL, Quality of life; SGLT-2I, Sodium-glucose cotransporter type 2 inhibitors; TTT, Treatment; TVR, tricuspid valve regurgitation.

* Corresponding author.
E-mail address: wfelsherbeny@gmail.com (W.S. El-Sherbeny).

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HF with an intermediate EF of 40–49 % [4].

Despite being a separate group, it shares similar diagnostic features with Heart Failure with Preserved Ejection Fraction (HFpEF), and the 2021 ESC guideline for the diagnosis and treatment of acute and chronic HF recommended to be treated as those with HFpEF [2]. In contrast, some studies compared both and showed some differences [5,6]. Specific therapeutic agents for them were lacking for a long time, and the main management strategy of both groups focused on the control of congestive symptoms and comorbidities, either cardiovascular or non-cardiovascular comorbidities [2].

The recommendations for SGLT2 inhibitors in the HFmrEF and HFpEF were a class IIa recommendation in the previous guidelines [2]. The recently published 2023 focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure gave class IA recommendation for SGLT2 inhibitors as the first specific therapeutic agents to be used in both types of HF irrespective of the diabetic state [7].

SGLT2 inhibitors can significantly improve cardiac remodeling in patients with T2DM, with significant reductions in E/e' and LAVI levels after treatment [8].

The left atrium (LA) has the main role in mastering LV filling during the whole diastole. Its dysfunction is a powerful predictor of heart failure (HF), myocardial infarction, atrial fibrillation, and cardiovascular death [9,10].

Despite the use of the LA Volume Index (LAVI) as a marker of LA function, it lacks sensitivity as a marker of improvement of diastolic dysfunction [11,12].

Two-dimensional speckle-tracking echocardiography (2D-STE) proved to be more accurate in the quantitative assessment of myocardial deformation for the LV, RV, and LA in the last few years [13], providing an angle- free assessment of the atrial deformation [14]. The assessment of LA strain using 2D-STE improves the sensitivity for early detection as well as the prognosis of diastolic dysfunction [9,12].

Since diastolic dysfunction is the main pathology in diabetic patients with HFmrEF, our study aims to investigate the impact of treatment with SGLT-2 inhibitors on diastolic functions in diabetic patients with HFmrEF through the assessment of LA function by 2D-STE.

2. Methods

This prospective non-randomized single centre study was carried out on 70 patients presented to a specific heart failure clinic in the Cardiology Department, Faculty of Medicine, Tanta University Hospital. Patients who met the inclusion criteria were initially selected through the revision of patients' medical records based on their previous echocardiographic examination that confirmed the diagnosis of HFmrHF. Then, we revised their clinical data and repeated the echocardiographic study before enrolment to confirm previous findings. At this point, we categorized patients into two groups. The study was carried out between December 2022 and July 2023. Informed consents was obtained from all patients.

Inclusion criteria: The sample of patients was divided into two groups. Group I: SGLT-2I users were those patients with established T2DM with clinical and echocardiographic evidence of the presence of stable HFmrEF (40 %–50 %), and they were suitable candidates as per our protocol to start treatment with one of the group medications SGLT-2 inhibitors (dapagliflozin 10 mg or empagliflozin 10 mg).

Group II = Non-SGLT-2I users: Were age and sex-matched group. They were studied as a comparable group, i.e., patient who were not suitable candidates to use any of SGLT-2 inhibitors.

Exclusion criteria: Patients less than 20 years, patients with type 1 DM or insulin- dependent DM, severe renal impairment (eGFR < 30 ml/min/1.73 m2), unstable heart failure patients (defined as an exacerbation of HF symptoms in the past 3 months), AF/atrial flutter or any significant rhythm disturbance, significant (moderate or severe) valvular heart disease, any recent cardiovascular disease (e.g., recent acute coronary syndrome or cerebral stroke), pregnancy or lactation, and poor echocardiographic views. **Specific precaution taken into consideration before the use of SGLT-2 I**: We did not prefer the use of SGLT-2 inhibitors in patients with optimally controlled diabetic states on their other glucose-lowering agents with HbA1C < 6.5. We did not start during fasting days if there was evidence of dehydration, concomitant genital or urinary tract infection, or a history of diabetic ketoacidosis or hypoglycemia.

All patients were subjected to:

Full history taking, including all demographic data (age, sex, BMI, and other risk factors), treatment history of concurrent or past medications, history of previous HF admission, and any new complaint or evidence of decompensating HF in each visit, full clinical assessment at baseline, 3 months, and 6 months after the start of SGLT2 inhibitors, laboratory assessment of diabetes state (FBS, 2hPP, and HbA1C) and renal functions (creatinine and eGFR) at baseline, 3 and 6 months and NT-pro-BNP at baseline and after 6 months, and ECG or any required added investigation according to clinical status of patients. All medical treatments were adjusted and titrated based on clinical evaluation and laboratory findings during each visit.

3. Echocardiography examination

All the following echocardiographic measurements were obtained in accordance with the current guidelines of the American Society of Echocardiography/European Association of Cardiovascular Imaging [11]. The Vivid E9 ultrasound system (GE Vingmed Ultrasound, Horten, Norway) equipped with an M5S phased array transducer (2.5–5.0 MHz) and a dedicated software package was used for the study. Images and data were digitally stored and then moved to an echo pack for offline analysis at baseline and 6 months following start of treatment (TTT) with empagliflozine or dapagliflozine. Three to five consecutive beats were recorded and averaged.

Left ventricle end-systolic and end-diastolic volumes and ejection fraction (EF) were estimated using Simpson's modified biplane method. LV diastolic function was determined using *trans*-mitral inflow velocities that were assessed by the pulsed-wave Doppler, the E/A ratio, and the pulsed (e′) diastolic velocity wave tissue Doppler. The E/e′ ratio was calculated as the index of the LV filling pressure. PASP was assessed through the evaluation of peak tricuspid regurgitation velocity (TRV). PASP = RA pressure + 4 V2, where V = TRV.

LA analysis:

1- LA strain: The deformation analysis of the LA mechanics was performed by elaborate 2DSTE on both focused 4-chambers and 2-chambers views that were acquired to avoid LA foreshortening. The frame rate was set between 60 and 80 frames/s. The LA analysis was established by Automated Function Imaging (AFI) software (GE Vingmed Ultrasound AS, Horten, Norway) dedicated to LA. After placing three landmarks, two at the mitral annulus and the other at the atrial roof, it traced the endocardium and defined the region of interest (ROI). The LA average strain is the combination of the three LA walls (left wall, right wall, and roof). LA strain curves were delivered from that average strain, and the software provided us with the left atrium strain values, including the LA reservoir strain (peak longitudinal strain), a contractile strain (active atrial contraction) and LA conduit strain (passive atrial emptying).The zero-baseline strain reference was set at ventricular end-diastole (ED) using R-R ECG gating [12].

2- LA volumes and functions: It also calculated the LA minimum (LAV-min), LA maximum (LAV-max), and pre-atrial contraction (LA VpreA) volumes for each single plane and biplane. LA-Vmax was indexed to the body surface area (BSA) to give LAVI max = LA Vmax / BSA. The LA emptying volume (LAEV) was calculated as LAV-max- LAV-min and LA emptying fraction (LAEF) was calculated as $\frac{LAVmax-LAVmin}{LAVmax} X100$ [12].

- **LV global longitudinal strain (LV-GLS):** The assessment of global longitudinal peak systolic strain was performed offline. Endocardial borders were traced manually. They were visualised as a color-coded sequence in the individual clips and then combined in a bull's-eye plot. The software then calculated the regional average of the apical two-chamber, four-chamber, and three-chamber views of the 17 segments at an end-systolic frame [15].

3.1. Statistical analysis

Statistical analysis was carried out using SPSS v26 (IBM Inc., Armonk, NY, USA). Qualitative variables were summarized as frequencies, and the association of the groups with categorical variables was assessed using Pearson's Chi-square test for independence test, Fisher-Freeman-Halton exact test, and Fisher's exact test as appropriate. Shapiro-Wilks test and histograms were used to evaluate the normality of data distribution. Quantitative parametric data were presented as mean and standard deviation (SD) and were analysed by unpaired student *t*-test. Moreover, quantitative non-parametric data were presented as the median and interquartile range (IQR) and were analyzed using the Mann-Whitney test. Spearman's rank-order correlation was performed to assess the direction, magnitude, and significance of the correlation between numerical variables. Independent associations of changes in LA strain curve parameters between baseline and 6 months after administration of SGLT-2I with clinical and echocardiographic parameters were evaluated using univariate and multivariate linear regression analyses. P-value < 0.05 was chosen to indicate the significance of statistical tests.

4. Results

The study included 70 diabetic patients; 35 patients used their anti-diabetic TTT and one of the available SGLT-2I in Egypt was added (23 patients used dapagliflozin, 12 used empagliflozin), while the remaining 35 patients used their usual anti-diabetic other than SGLT-2I group. Baseline characteristics (demographic data, associated comorbidities, clinical presentation and medication of the studied groups) were presented in Table 1.

Demographic data, associated comorbidities and history of previous HF admission before enrolment were comparable between both groups. Most patients in both groups were previously admitted due to previous acute ischaemic insult and others were for congestive symptoms like worsening dyspnoea and edema.

Full drug history taking regarding anti-diabetic TTT and other cardiac TTT with baseline clinical evaluation of the presenting symptoms were assessed in both groups, which showed no significant difference between the groups. Metformin and DPP-4 were the most prevalent anti-diabetic TTTs. Most of the patients were using, ACE-I or ARBS, B-blockers, and statin therapy.

Clinical outcome at follow-up: According to Table 1, patients were regularly assessed in each visit to a specific heart failure clinic for any clinical events during the 6-month follow-up, where no hospital re-admissions were seen in the SGLT-2I user group versus only 2 patients were re-admitted in the non-SGLT-2I group, one for worsening dyspnoea and edema and the other for hypertensive pulmonary edema. No one in both groups showed evidence of hypoglycemia or diabetic ketoacidosis. Despite most patients showing improved symptoms during follow-up, there was a statistically significant difference in patients showing improved symptoms in SGLT-2I users as compared to those non-SGLT-2I users (91.4 % versus 68.6 %, P value = 0.017*).

Clinical variables, laboratory findings in Table 2, as well as conventional echocardiographic parameters, LA functions, and strain parameters in Table 3, were collected and assessed at baseline and 6 months in both groups. Statistical significance was tested for the relative changes within each group (P1 for group I and P2 for group II) as well as between-group comparisons of baseline readings (P3) and of relative

Table 1
Baseline characteristics (Demographic data, comorbidities, admission and medication of the studied groups) and Clinical events at follow-up.

	SGLT-2I users	Non– SGLT-2I users	p-value		
Age (years)	Mean ± SD	59.0 ± 6.6	60.9 ± 6.2	0.221	
sex	Female	9 (25.7 %)	11 (31.4 %)	0.597	
	Male	26 (74.3 %)	24 (68.6 %)		
BMI (Kg/m2)	Mean ± SD	29.9 ± 2.6	30.1 ± 2.5	0.778	
Comorbidities	HTN	15 (42.9 %)	19 (54.3 %)	0.339	
	Dyslipidaemia	24 (68.6 %)	21 (60.0 %)	0.454	
	Prior IHD	22 (62.9 %)	18 (51.4 %)	0.334	
	Smoker	17 (48.6 %)	17 (48.6 %)	1.000	
Previous HF admission	Total numbers	18 (51.4 %)	17 (48.6 %)	0.811	
	Cause	ACS	12 (66.7 %)	11 (64.7 %)	0.903
		Others	6 (33.3 %)	6 (35.3 %)	
Anti-diabetic Medications	Metformin	25 (71.4 %)	21 (60.0 %)	0.314	
	Sulphonylurea	19 (54.3 %)	19 (54.3 %)	1.000	
	Thiazolidinoin	10 (28.6 %)	6 (17.1 %)	0.255	
	DPP-4	26 (74.3 %)	26 (74.3 %)	1.000	
	GLP-1 RA	0 (0.0 %)	2 (5.7 %)	0.239	
	SGLT-2I	**Dapagliflozin**	23 (66.7 %)	—	
		Empagliflozin	12 (34.3 %)		
Other cardiac medications	BB	26 (74.3 %)	28 (80.0 %)	0.569	
	ACE-I or ARB	29 (82.8 %)	29 (82.8 %)	1.000	
	Statin	31 (88.6 %)	27 (77.1 %)	0.205	
	Loop diuretics	17 (48.6 %)	21 (60.0 %)	0.337	
	MRA	9 (25.7 %)	10 (31.4 %)	0.956	
	DAPT	12 (34.3 %)	11 (31.4 %)	0.903	

(*continued on next page*)

Table 1 (*continued*)

		SGLT-2I users	Non– SGLT-2I users	p-value
clinical events& outcome at follow-up	HF re-admission	0 (0.0 %)	2 (5.7 %)	0.493
	worsening symptoms	3 (8.6 %)	9 (25.7 %)	0.057
	Improving symptoms	32 (91.4 %)	24 (68.6 %)	0.017*

Data are expressed as Mean ± standard deviation.* significant at p-value < 0.05. BMI: Body mass index, HTN: Hypertension, IHD: Ischaemic heart disease, HF: Heart failure, ACS: Acute coronary syndrome, DPP-4I: Dipeptidyl Peptidase-4 inhibitors, GLP-1RA: Glucagon-like peptide-1 Receptors agonist, SGLT-2I: Sodium-glucose cotransporter type 2 inhibitors, BB: B- blockers, ACEI: Angiotensin-converting enzyme inhibitors, ARBs: Angiotensin II receptor blockers, DAPT: Dual antiplatelet therapy.

(delta) changes at six-month follow-up (P4). See Table 3 and Fig. 1.

Baseline values for clinical variables were similar and there was a statistically significant improvement in SBP and HR in both groups.

In SGLT-2I users, we preferred to enrol patients who had not optimally controlled HbA1C and to select patients with safer or better renal function. Therefore, baseline values of HbA1C and eGFR were relatively higher in group I as compared to group II ($p < 0.001$* for both), HbA1C significantly decreased from 7.8 to 8.9 to 7.1–7.6 at 6 months, $P < 0.001$*). Similarly, the mean eGFR did not decline& even mildly improved from 68.7 ± 12.0 to 69.7 ± 11.5, $P = 0.035$* in SGLT-2I users, as compared to non-SGLT-2I users. Only 20 patients in group I and 16 patients in group II completed their baseline and follow-up results for NT-Pro-BNP. The results showed significant improvement in both groups at follow-up that was associated with improvement in the patient's clinical status.

Echocardiographic parameters were presented in Table 3**:** Baseline values for all echocardiographic variables were comparable in both groups (P3, all p-value > 0.5).

In non-SGLT-2 inhibitor users, there were no significant changes after 6 months in all echo-Doppler parameters (E/A, E/e′, PASP, LVGLS, LA functions, or volumes). Meanwhile, SGLT-2I users (group I) showed significant changes in most echo-Doppler variables at 6 months of follow-up, LVGLS showed significant improvement from −13.0 ± 1.6 to −17.4 ± 2.0 ($P < 0.001$*), and LVEF mildly improved. E/e′ significantly decreased from 13.1 ± 3.2 to 10.8 ± 2.2, $p < 0.001$*. LA volumes (LAVI and LAEV) both significantly decreased after 6 months, and LAEF % increased from 31.6 ± 4.2 to 43.2 ± 10.8. LA strain values significantly improved, LA reservoir from 17.3 ± 2.0 to 23.8 ± 3.6, LA conduit from 11.0 ± 2.2 to 13.7 2.8, and LA contractile from 6.5 ± 1.4 to 10.5 ± 2.6, all $P < 0.001$*, Figs. 2,3.

The relative changes (Delta) in the echocardiographic variables

Table 2
Comparison between Clinical variables and laboratory findings in both groups at baseline and after 6 months.

	SGLT-2I Users			Non SGLT-2I Users			Between groups comparison	
	Baseline	6 M	P1	Baseline	6 M	P2	P3	P4
SBP	133.1 ± 16.0	125.7 ± 7.4	0.003*	130.9 ± 17.6	125.1 ± 9.5	0.027*	0.571	0.614
DBP	78.4 ± 11.2	75.1 ± 8.2	0.095	78.6 ± 10.5	76.9 ± 7.9	0.317	0.956	0.429
HR	70.5 ± 6.1	65.2 ± 3.0	<0.001*	70.7 ± 5.7	65.3 ± 2.8	<0.001*	0.920	0.967
HbA1C	8.2 [7.8–8.9)	7.3 [7.1–7.6)	<0.001*	6.7 [6.5–6.8)	6.8 [6.6–6.9)	0.063	<0.001*	<0.001*
eGFR	68.7 ± 12.0	69.7 ± 11.5	0.035*	56.3 ± 14.7	56.8 ± 15.0	0.261	<0.001*	0.514
NT-Pro-BNP	452.5 ± 62.1	426.3 ± 76.2	0.007*	437.0 ± 87.8	427.0 ± 89.4	0.019*	0.608	0.531

Data are expressed as Mean ± standard deviation or Median [IQR].* significant at p-value < 0.05.
Abbreviations: SBP: Systolic blood pressure (mmHg), DBP: Diastolic blood pressure (mmHg), HR: Heart rate, HbA1C: Glycated Haemoglobin A1C, eGFR: estimated glomerular filtration rate (ml/min/1.73 m2), NT- pro-BNP: NT-pro plasma brain natriuretic peptide.
P1 = P value for Changes from baseline to 6 months follow-up of group 1 (SGLT-2I users).
P2 = P value for Changes from baseline to 6 months follow-up of group II (Non– SGLT-2I users).
P3: p-value from the between groups comparison of baseline values of the two groups, P4: p-value from the between groups comparison of the change from baseline to 6 M values.

Table 3
Comparison of Echocardiographic variables at baseline and follow-up between both groups.

	SGLT-2I users (Group I)			Non SGLT-2I users (Group II)			Between groups comparison	
	Baseline	6 M	P1	Baseline	6 M	P2	P3	P4
LV EF%	44.4 ± 2.5	45.2 ± 3.0	0.022*	44.6 ± 2.5	45.0 ± 2.5	0.136	0.699	0.574
E/A	1.0 ± 0.6	1.0 ± 0.5	0.639	1.1 ± 0.6	1.1 ± 0.6	0.619	0.791	0.99
LVGLS	−13.0 ± 1.6	−17.4 ± 2.0	<0.001*	−12.4 ± 1.6	−12.8 ± 1.8	0.054	0.114	<0.001*
E/e′	13.1 ± 3.2	10.8 ± 2.2	<0.001*	12.5 ± 3.0	12.2 ± 2.8	0.212	0.405	<0.001*
PASP (mmHg)	25.6 ± 4.4	25.4 ± 4.4	0.454	25.1 ± 4.7	24.9 ± 5.0	0.287	0.658	0.714
LAV-index	48.9 ± 5.7	42.6 ± 5.5	<0.001*	49.3 ± 6.1	48.6 ± 6.3	0.058	0.778	<0.001*
LAEV- ml	34.1 ± 6.2	35.6 ± 7.3	0.034*	34.4 ± 5.9	34.1 ± 5.8	0.443	0.813	0.079
LAEF- %	31.6 ± 4.2	43.2 ± 10.8	<0.001*	32.9 ± 4.7	33.2 ± 4.4	0.166	0.238	<0.001*
LA Reservoir	17.3 ± 2.0	23.8 ± 3.6	<0.001*	18.2 ± 2.1	18.3 ± 2.5	0.724	0.067	<0.001*
LA conduit	11.0 ± 2.2	13.7 ± 2.8	<0.001*	11.1 ± 2.2	11.1 ± 2.5	1.000	0.871	<0.001*
LA contractile	6.5 ± 1.4	10.5 ± 2.6	<0.001*	7.1 ± 1.4	7.3 ± 1.7	0.557	0.068	<0.001*

Data are expressed as Mean ± standard deviation; * significant at p-value < 0.05. P1, P2 as expressed before. Abbreviations: LVEF%: Left ventricular ejection fraction, E/A: peak early diastolic mitral flow velocity/ late atrial diastolic mitral flow velocity, LV-GLS: Left ventricular- global longitudinal strain, E/e′: peak early diastolic mitral flow velocity/ pulsed-wave tissue Doppler-derived early diastolic velocity from the septal mitral annulus ratio, PASP: pulmonary artery systolic pressure, LAVI: Left atrial volume index, LAEV- ml: Left atrial emptying volume, LAEF- %: Left atrial emptying fraction (%). P1: p-value from the within SGLT-2I users group comparison between baseline & 6 M values, P2: p-value from the within Non-SGLT-2I users group comparison between baseline & 6 M values, P3: p-value from the between groups comparison of baseline values, P4: p-value from the between groups comparison of the change from baseline to 6 M values.

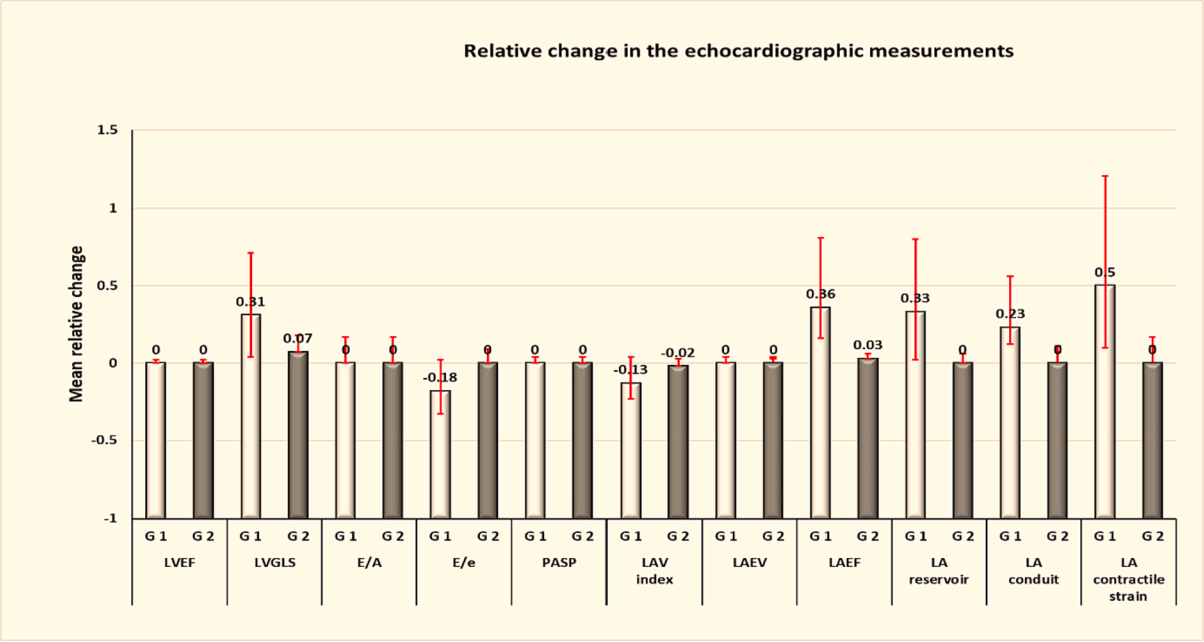

Fig. 1. Comparing the relative changes of different echo-Doppler parameters between the two groups.

between their baseline values and after 6 months in each group were studied and then compared between each other. The delta changes for (LVGLS, E/e′ ratio, LAVI, LA-EF and all 3 LA strain parameters) showed significantly favorable outcome in group I as compared to those in group II. (P4) and Fig. 1.

Tables 4 and 5 summarized the results of univariate and multivariate linear regression analysis of changes in left atrial strain parameters from baseline to 6 months (Delta) with different clinical, biochemical& echocardiographic variables. All left atrial strain parameters were significantly increased in SGLT-2I users as compared to the non-SGLT-2I group. The changes in LA reservoir and conduit strain were not significantly affected by the change in blood pressure, but both significantly increased with decreases in HbA1C (p value < 0.001 for both). On the contrary, the change of LA contractile strain was significantly affected by the change in systolic blood pressure ($P = 0.034$), but not by the change in HbA1C. None of the LA strain parameter changes were affected by changes in HR, eGFR, LVEF, E/A ratio, PASP or LA-EV. Meanwhile, there were significant positive impacts of Δ LVGLS and Δ LAEF on all LA strain values and significant negative impact of Δ E/ e′ ratio and Δ LAV-I on Δ LA reservoir and conduit strain. The changes in LA reservoir stain were the most significant determinant for the improvement in LA-EF after administration of SGLT2 inhibitors (coefficient correlation (rs) $= 0.634$, $P < 0.001$*), followed by delta LA contractile strain (rs $= 0.495$, $P = 0.002$*).

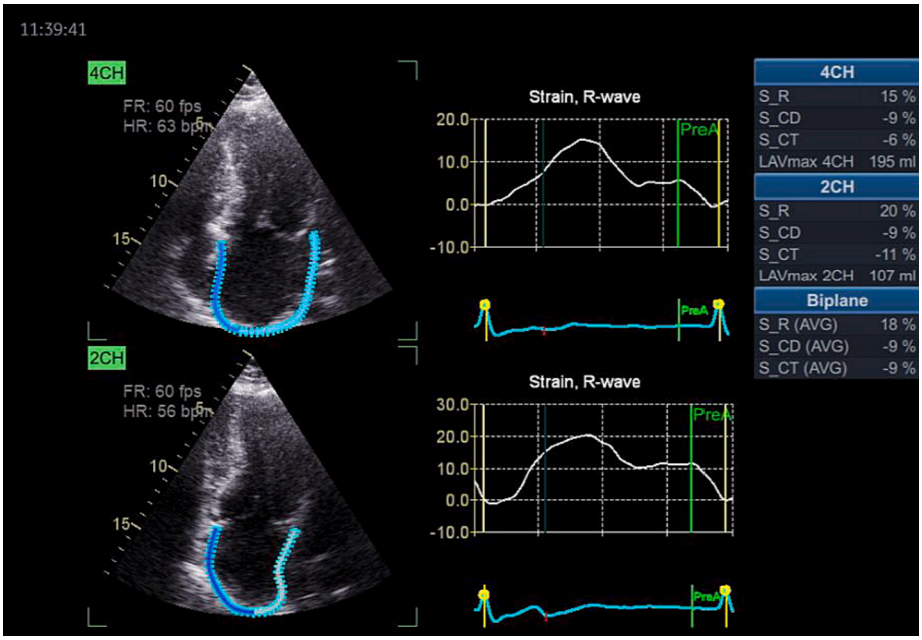

Fig. 2. Strain curve at baseline before treatment with SGLT-2I. Reservoir strain is measured as the difference between the peak strain curve value and baseline (positive value). Conduit strain is calculated as difference of the strain value at the onset of atrial contraction minus the peak strain value (negative value). Contraction strain is calculated as difference of the strain value at baseline minus the strain value at onset of atrial contraction (negative value).

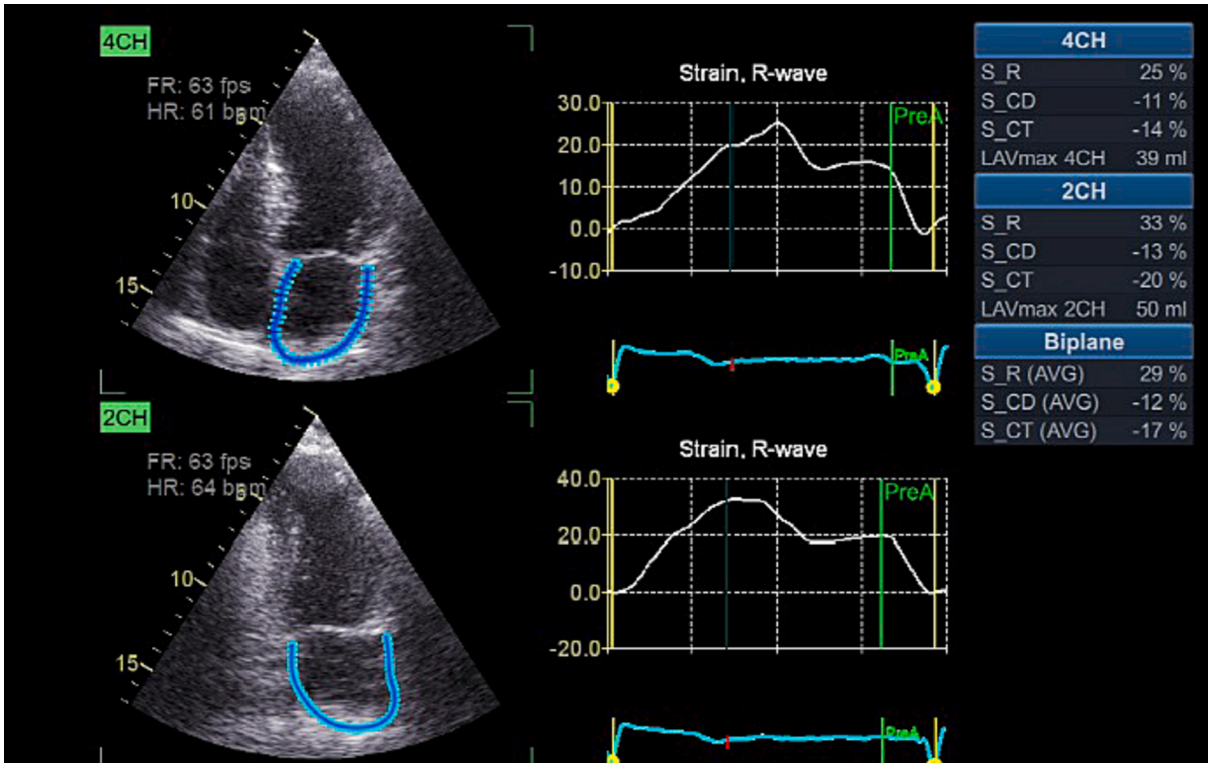

Fig. 3. Six months after treatment with SGLT-2I, average reservoir (peak longitudinal) strain changed from 18 to 29, Conduit strain increased from − 9 to −12& contraction strain also increased from −9 to −17.

Table 4
Univariate linear regression analyses for the impact of the relative changes (Delta) of different clinical, biochemical& echo-cardiographic variables on the relative changes of LA strain measurements.

	Δ LA reservoir strain		Δ LA conduit strain		Δ LA contractile strain	
	t-Value	P- value	t-value	p-value	t-value	p- value
Group I	10.872	<0.001*	4.650	<0.001*	3.093	0.003*
Δ SBP	1.419	0.160	0.772	0.443	2.159	0.034*
Δ DBP	−0.034	0.973	−0.200	0.842	−0.167	0.868
Δ HR	0.394	0.695	0.595	0.554	1.211	0.230
Δ HbA1C	−7.969	<0.001*	−4.854	<0.001*	−1.320	0.191
Δ eGFR	−0.027	0.978	0.918	0.362	−0.737	0.464
Δ LVEF	1.141	0.258	0.713	0.478	0.926	0.358
Δ LVGLS	6.757	<0.001*	4.096	<0.001*	2.409	0.019*
Δ E/A	0.741	0.461	0.005	0.996	0.449	0.655
Δ E/e′	−5.062	<0.001*	−4.264	<0.001*	−2.254	0.027*
Δ PASP	0.360	0.720	−0.503	0.616	1.153	0.253
Δ LAV-I	−4.332	<0.001*	−3.589	0.001*	−0.701	0.485
Δ LA-EV	1.686	0.096	1.747	0.085	−0.226	0.822
Δ LA-EF	8.854	<0.001*	3.517	0.001*	2.747	0.008*

* Significant at p-value < 0.05. Abbreviations: as before.
Δ: changes in the measurements between baseline and follow up.

By multivariate linear regression analysis, changes in the LA reservoir were the most predominant variable that significantly increased in group 1 as compared to group 2 and with the increase in LA-EF (P-value = 0.012* and < 0.001*, respectively). Changes in LA conduit and LA contractile were significantly affected by changes in E/e (P value = 0.027* for both).

Reproducibility: The correlation coefficient of inter-observer reproducibility of LVEF % was 0.954 (95 % confidence interval: 0.888–0.982), LV GLS was 0.923 (95 % confidence interval: 0.881–0.940), LA reservoir strain was 0.93 (95 % confidence interval: 0.894–0.957), LA conduit strain was 0.917 (95 % confidence interval: 0.872–0.946) and LA contractile strain was 0.915 (95 % confidence interval: 0.867–0.946). The correlation coefficient of intra-observer agreement of the studied echocardiographic parameters of interest was around 0.98 (95 % confidence interval: 0.969–0.988).

5. Discussion

In our study, we analysed the impact of adding one of the available SGLT-2I in Egypt (either empagliflozin or dapagliflozin) to diabetic patients on short-term clinical outcome (6 months follow-up), which was not new and was thoroughly investigated in patients with different cardiovascular diseases and different types and grades of heart failure [16]. HFmrEF is still under-represented in most clinical trials [17]. It is a heterogeneous group encompassing patients with phenotypic and clinical characteristics typical for both reduced and preserved EF. It may receive patients from HFrEF who have improved EF following specific anti-failure TTT or intervention, or it can include neglected or deteriorated patients from those with heart failure with HFpEF. In addition, their group of patients can progress to any one of the other two groups of HF [18].

To our knowledge, the impact of adding such a group of medicine on cardiac remodeling through the assessment of systolic and diastolic functions with the help of conventional echocardiographic parameters including LV-EF%, E/A, E/e′ ratios, LAV-I, and PASP, in addition to the relatively new, more specific 2-D speckle tracking echocardiography through evaluation of LV-GLS and LA functions including LA-EV, LA-EF, and LA strain parameters (reservoir, conduit, and contractile strain) in HFmrEF were not solely studied before.

In this study, adding SGLT-2I to usual anti-diabetic TTT in HFmrEF was associated with the improvement of symptoms, less worsening of presenting symptoms, no hospitalization better control of HbA1C (despite the higher baseline level), and no decline of eGFR as compared to those not using SGLT-2I. This could share the favorable outcomes with adding SGLT-2I. This has been confirmed in multiple trials. In Dapa-HF trial treatment with dapagliflozin in patients of HFrEF resulted

Table 5
Multivariate linear regression analysis.

LA Reservoir					
Independent variables	B	SE	95 % CI for B	t	p
Groups 1	0.172	0.066	0.039 to 0.305	2.587	0.012*
Delta HBA1C	−0.487	0.378	−1.242 to 0.269	−1.288	0.203
Delta LVGLS	0.031	0.098	−0.164 to 0.226	0.319	0.751
Delta E/e	−0.260	0.152	−0.565 to 0.044	−1.708	0.093
Delta LAV index	0.204	0.206	−0.208 to 0.616	0.991	0.326
Delta LAEV	−0.080	0.159	−0.397 to 0.238	−0.502	0.617
Delta LAEF	0.359	0.080	0.199 to 0.520	4.465	<0.001*
LA Conduit					
Group 1	−0.062	0.108	−0.278 to 0.154	−0.573	0.569
Delta HBA1C	−0.826	0.615	−2.056 to 0.404	−1.343	0.184
Delta LVGLS	0.155	0.159	−0.162 to 0.472	0.976	0.333
Delta E/e	−0.562	0.248	−1.057 to −0.067	−2.270	0.027*
Delta LAV index	−0.494	0.336	−1.166 to 0.179	−1.468	0.147
Delta LAEV	0.236	0.258	−0.280 to 0.752	0.914	0.364
Delta LAEF	0.046	0.133	−0.221 to 0.312	0.342	0.734
LA Contractile					
Groups 1	0.056	0.091	−0.126 to 0.238	0.614	0.542
Delta SBP	−0.017	0.270	−0.556 to 0.523	−0.061	0.951
Delta LVGLS	0.192	0.163	−0.134 to 0.518	1.177	0.243
Delta E/e	−0.574	0.254	−1.081 to −0.067	−2.260	0.027*
Delta LAEF	0.131	0.137	−0.143 to 0.404	0.955	0.343

Δ: Delta (Relative change from baseline to 6 months reading). B: unstandardized regression coefficient; CI: confidence interval; SE: standard error; * significant at $p < 0.05$.

in a 26 % reduction in worsening HF with alleviation of HF symptoms and improved physical function and quality of life (QOL) that was irrespective of the presence or absence of DM [19]. The EMPEROR-reduced trial found that empagliflozin reduced HF hospitalization by 25 % with improvements in QOL and a significant reduction in eGFR [20].

At the start of this study, HFpEF and HFmrEF still lacked class 1 recommendations for their use irrespective of diabetic state. But with overwhelming evidence of how much the clinical outcome has improved with these drugs across the spectrum of all heart failure types, the guidelines advise continuation of guideline-directed medical therapy even for patients who have an improved ejection fraction of greater than 40 % [21], additionally the recently published 2023 focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure gave class IA recommendation for their use [7].

In the DELIVER trial, they assigned 6,263 patients with heart failure and a left ventricular ejection fraction of more than 40 % to receive dapagliflozin (at a dose of 10 mg once daily) versus placebo. Dapagliflozin reduced the primary endpoint of CV death or worsening HF, and there was no reduction in CV death. Additionally it improved symptom burden. These effects were independent of T2DM status [22].

In the EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction), approximately 5,750 patients with preserved ejection fraction (defined as LVEF > 40 %), the use of empagliflozin showed a 29 % reduction in time to HF hospitalization, a decrease in the decline of eGFR, and a moderate improvement in QOL. These results were irrespective of the presence or absence of DM [23].

DECLARE-TIMI 58 assessed cardiovascular outcomes for 17,160 patients who were treated with dapagliflozin and followed-up for a median of 4.2 years. Dapagliflozin resulted in a lower rate of hospitalization for HF [24]. Similarly, the EMPA-REG OUTCOME trial found that T2DM patients with a high risk of cardiovascular events had cardiovascular benefits from empagliflozin as compared to placebo [1].

Our results revealed a statistically significant improvement in conventional echocardiographic parameters, including LVEF, E/e′& LAV-I, and LV-GLS, from baseline to 6-month readings in SGLT-2I users as compared to non-SGLT-2 I.

This result was consistent with some results published in the literature. For example, Tanaka et al. [25] studied the impact of adding dapagliflozin to usual anti-diabetic TTT in diabetic patients with different types of chronic stable heart failure. They found significant improvement of LV-EF %, LAV-I, and E/e′ from 9.3 (7.7–11.8) to 8.5 (6.6–10.7), P- value = 0.020, together with the improvement of LV-GLS from 15.4 ± 3.4 % to 16.8 ± 4.0 % ($p < 0.001$) after administration of dapagliflozin for all heart failure patients. However, this improvement was superior in HFpEF patients as compared to non-HFpEF patients. Of note, there was little representation of HFmrEF (17 %) in this study, and it was mainly HFpEF (69 %). Lan et al. [26] investigated the early use of empagliflozin following acute coronary syndrome, and it was associated with improvement in diastolic function, including E/e′ ratio, mitral valve peak E-wave velocity, LAV-I, and LV mass index.

In contrary, Roy et al. [27] studied the effect of using SGLT-2I in HFpEF patients with T2DM and did not show improvement in any of the LV diastolic functional parameters.

Sehly et al. [28] reported the impact of using empagliflozin early after acute coronary syndrome in diabetic patients and showed no significant improvement of LV-EF, LAV-I, or LV-GLS but there was significant improvement of E/e′ from 13.2 ± 5.1 to 11.1 ± 4.2, P value < 0.001* in the empagliflozine group.

Our study showed a significant improvement of all LA function parameters (LA-EV and LA-EF% as well as LA strain parameters) ($P < 0.001$* for all) in SGLT-2I users as compared to non-SGLT-2I users.

Sehly et al. [28] confirmed the beneficial effect of early use of empagliflozin on LA strain parameters in patients following acute coronary syndrome. LA reservoir strain improved from 28.0 ± 8.43 to 34.6 ± 12.2, $P < 0.001$*, LA conduit from 14.5 ± 5.4 to 16.7 ± 7.0P = 0.034* and LA contraction from 13.5 ± 5.2 to 17.9 ± 7.2, P = 0.006*.

Thiele et al. [29] results were consistent with our results, which enrolled 44 diabetic patients to receive empagliflozin 10 mg for 3 months. Even though there was no effect on hemodynamic parameters, there was a significant improvement in the E/e′ ratio, which was detected from the first day of treatment and maintained till the end of the study. In addition, empagliflozin significantly improved LA strain parameters after 3 months of treatment with LA reservoir and LA contraction phase values changed from 26.4 ± 8.0 % to 29.0 ± 7.4 %; P = 0.011 and from 10.9 ± 5.7 % to 12.5 ± 6.0 %; P = 0.008 respectively compared with placebo.

Our study found a significant positive association between the changes in LA strain parameters and the changes in LVGLS and LAEF. Additionally, our results revealed that there was a significant negative association between Δ LA strain parameters (reservoir and conduit strain) and Δ (E/e′ ratio, LAV-I).

This result was similar to the findings of Mălăescu et al. [30], who studied the association between LA strain parameters and LV systolic and diastolic parameters and showed that LA strain parameters correlated well with the corresponding LV strain and the changes of LA and LV volumes (LV-LA volume ratio, $R^2 > 0.78$), giving the unique power of LA strain to be a simple single measurement that integrated LA and LV functions and volumes.

6. Limitations

A number of limitations of this study should be acknowledged. First, it was a non– randomized single center study, with a small sample size and a relatively short follow-up of 6-months that preclude long-term prognostic implication. Also, the echocardiograms were not acquired nor analyzed blindly; nevertheless, the echocardiographic measurements were repeated by two observers to insure acceptable reproducibility of LA strain, which require good delineation of endocardial borders. Lastly, the enhancement in the diabetes control in the SGLT2i group may have contribute to the observed improvement in the cardiac functions of this group. Therefore, our findings should be confirmed in a well-designed prospective and randomized study.

Echocardiographic evaluation was not blindly. Nevertheless, we had to repeat the echocardiographic measurements by two observers to be sure this is our case. Measurements of LA strain require good delineation of endocardial borders, However the reproducibility of measurements was accepted. The relative significant improvement of diabetic status in SGLT-2I users group may participate the significant improvement in the cardiac functions of this group. Therefore, the clinical implications of our findings should be further studied.

7. Conclusion

Despite the vast, clear, well-studied evidence of benefits of SGLT-2 I in different categories of cardiovascular disease, we still in need to interpret and correlate these cardiovascular benefits on cardiac mechanics by different conventional echo-cardiographic parameters in addition to the newly, more specific, easily applicable 2-D speckle tracking deformation analysis of different cardiac chambers. Adding SGLT-2I to existing guideline-directed medical therapy in patients with T2DM and HFmrEF is associated with favorable clinical outcomes and significant improvement of left atrial volume, functions and strain values with further improvement of LV diastolic functions and LV longitudinal functions.

Author contributions

“SE” Design of the study, acquisition patient data, and drafting the manuscript.

“WE” Analysis and interpretation of data, revision of the manuscript and the results.

“SE” Acquisition of data, performing echocardiography for the patients and revision of the results.

All authors reviewed and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Not applicable.

Ethical consideration

This study was approved by the Ethics Committee in the Faculty of Medicine, Tanta University, reference number (36172/12/22) and with the Helsinki Declaration of 1975 and later revision.

Written informed consents were obtained from all patients of the study.

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