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# The effects of SGLT-2 inhibitors on echocardiographic indices and antioxidative properties in patients with heart failure with reduced ejection fraction and diabetes mellitus

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**ABSTRACT. – OBJECTIVE: Sodium-glucose co-transporter-2 inhibitors (SGLT-2i) are a new class of drugs that lower blood glucose and reduce mortality in heart failure patients with reduced ejection fraction (HFrEF). They also have antioxidant effects. The exact mechanism of SGLT-2i is unknown. This study investigated the effects of SGLT-2i on asprosin, matrix metalloproteinase (MMP), and tissue inhibitor of MMP (TIMP-1) concentrations and echocardiographic measurements of strain in the left heart chamber.**

**PATIENTS AND METHODS: This prospective follow-up study included 56 patients with HFrEF and diabetes mellitus (DM) who did not initially receive SGLT-2 inhibitors. The control group consisted of 30 healthy individuals. Patients with HFrEF were administered either empagliflozin (n=28) or dapagliflozin (n=28) in addition to their treatment. The patient group was evaluated for left ventricular global longitudinal strain (LVGLS), left atrial (LA) strain, and LA volumes at the beginning and third month of the study. The control group had blood collected once, while the patient group had it twice: at the start of the trial, on the same day as the echocardiographic evaluation, and at the end of the third month after starting an SGLT-2i. Serum levels of asprosin, MMP-1 and TIMP-1 were assessed.**

**RESULTS: LVGLS increased significantly in HFrEF patients at the third-month assessment compared to baseline (-8.6±2.3% *vs.* -9±2.5%, respectively; $p<0.001$), but there was no significant difference in LVEF ($p=0.593$). A substantial increase was observed in the left atrial ejection fraction (LAEF) compared to baseline values (36.3±9.4% *vs.* 42.1±8.7%, respectively; $p<0.001$), driven by a reduction in minimal LA volume [32.5 (19-96) ml *vs.* 32 (20-86) ml, respectively; $p=0.018$]. Compared to baseline evaluation, LA reservoir [13 (6-25) *vs.* 16.5 (2-26), respectively; $p<0.001$] and contraction strain (7.7±4.3 *vs.* 9.4±5.6, respectively; $p=0.014$) values were also enhanced at the third month. Between the baseline and the 3rd month, the patient group's LA conduit strain ($p=0.122$) and LA maximum volume ($p=0.716$) remained unchanged. Serum asprosin significantly increased (11.7±5.1 ng/mL *vs.* 14±9.4 ng/mL, respectively; $p=0.032$); however, no statistically significant alteration was detected in MMP ($p=0.278$) and TIMP-1 levels ($p=0.401$).**

**CONCLUSIONS: SGLT-2i are associated with elevated levels of LVGLS, LAEF, LA contraction strain, and LA reservoir strain. SGLT-2i medications may improve plasma asprosin levels to boost energy metabolism, reduce oxidative stress and reactive oxygen radicals.**

*Key Words:*
Asprosin, Diabetes mellitus, Heart failure with reduced ejection fraction, SGLT-2 inhibitors, Matrix metalloproteinases (MMP-1), Tissue inhibitor of metalloproteinase (TIMP-1).

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**Abbreviations**

ACEI: Angiotensin-Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; AF: Atrial Fibrillation; CRP: C-reactive protein; CMR: Cardiac Magnetic Resonance; ECM: extracellular matrix; ERK1/2: Extracellular Signal-Regulated Kinases 1/2; HbA1c: Glycated hemoglobin A1c; HCT: Hematocrit; HF: Heart failure; HFrEF: Heart failure with reduced ejection fraction; HFpEF: Heart failure with preserved ejection fraction; LA: Left Atrium; LGE: Late Gadolinium Enhancement; LV: Left Ventricle; LVEF: Left ventricular ejection fraction; LV GLS: Left ventricular Global Longitudinal Strain; MMP: Matrix Metalloproteinase Enzyme Family; MSC: Mesenchymal Stromal Cells; NHE: Na-H exchanger-1; NT-proBNP: N-terminal pro Brain Natriuretic Peptide; PALS: Photoacoustic lesion scoring; PLT: Platelet; ROS: Reactive oxygen species; SGLT-2: Sodium-Glucose Co-transporter-2; SOD: Superoxide Dismutase; TIMP-1: Matrix Metalloproteinase Tissue Inhibitors; TTE: Transthoracic Echocardiography; T2DM: Type 2 Diabetes Mellitus; WBC: White blood cell.

## Introduction

Heart failure (HF) is a complex medical condition that occurs when the heart is unable to pump enough blood to meet the metabolic requirements of tissues or can only do so by exerting abnormally high pressure during filling. Despite multiple therapeutic options, 60% of patients with HF die within five years of diagnosis, making it an important global health issue. Using left ventricular ejection fraction (LVEF), a typical echocardiographic measurement, the condition was divided into subgroups for the purpose of classification. Individuals who have an ejection fraction of the left ventricle (LVEF) that is lower than forty percent are classified as having heart failure with reduced ejection fraction (HFrEF). This condition accounts for more than half of all individuals who exhibit symptoms or signs of cardiac failure[1,2].

Diabetes mellitus (DM), a comorbidity that is becoming more common, is one of the most significant risk factors for the occurrence of cardiac failure. Observational studies[3,4] have demonstrated a significant elevation in the risk of HF in patients with diabetes, with a two to four-fold increase compared to those without diabetes. Diabetes is strongly associated with an increased risk of unfavorable effects in individuals suffering from heart failure, particularly those with cardiac failure with decreased ejection fraction (HFrEF).

Sodium-glucose co-transporter-2 inhibitors (SGLT-2i) are a new kind of medication designed to mainly lower blood glucose levels. These treatments have shown[5-7] the capacity to reduce mortality in people who have both diabetic mellitus (DM) and heart failure (HF). These medications have shown[1,2] a significant reduction in fatalities linked to cardiovascular issues, hospitalizations for heart failure, and overall mortality. These findings have had a considerable impact on the recommendations for managing heart failure. Although numerous trials[5-7] have confirmed their benefits in the cardiovascular system, the precise mechanisms by which SGLT-2 inhibitors promote cardiac health remain unclear. The potential cardioprotective actions of SGLT2i molecules in heart failure include inhibiting the Na-H exchanger-1 (NHE) receptor in the heart, which may lead to improved mitochondrial function by reducing cardiac inflammation, fibrosis, and oxidative stress[8,9].

To maintain the proper functioning of its essential metabolic processes, the human body must achieve a balance between the production of reactive oxygen species (ROS) and the reduction of free radicals. Increased concentrations of ROS in the heart directly disrupt the electrical activity and contraction of cardiomyocytes by altering essential proteins involved in the heart's excitation-contraction pathway. Calcium channels of the L-type, potassium channels, sodium channels and sodium-calcium exchanger channels are all included in this group of proteins. Uncompensated ROS cause cardiac fibroblast proliferation and the activation of matrix metalloproteinases, resulting in extracellular remodeling and an increase in fibrosis[10].

Asprosin is an adipokine that was initially identified in 2016 and is secreted by white adipose tissue[11]. Adipokines are biologically active compounds released by adipose tissue that have several roles in regulating hunger, energy levels, lipid and carbohydrate processing, blood pressure control, and inflammation. Its beneficial benefits on the heart are believed to be achieved by suppressing apoptosis through the extracellular signal-regulated kinase (ERK1/2) and superoxide dismutase (SOD-2) pathways, resulting in decreased reactive oxygen metabolites[12]. Matrix metalloproteinases (MMPs) are a group of zinc endopeptidases that are either secreted or anchored to the cell surface. They have many domains and are involved in the breakdown of the extracellular matrix, as well as various other biological activities. It is important to maintain a balance between MMPs and their primary natural protein inhibitor, the tissue inhibitors of metalloproteinases (TIMPs), in order to ensure proper cellular activities[13-15].

Strain echocardiography is widely used to detect reduced longitudinal LV systolic function and left atrial (LA) function in various heart diseases. Left ventricular global longitudinal strain (LVGLS) exhibits a greater predictive value than other echocardiographic measures in patients with HFrEF. A more precise assessment of LA function, which is a predictive indication for mortality in patients with heart failure, may also be obtained by the use of this recently developed ultrasound approach[16-19].

We performed a study to determine the effect of SGLT-2 inhibitors on multiple biochemical markers linked with inflammatory conditions, oxidative stress, and fibrosis in HFrEF patients. We conducted another research utilizing 2D and strain echocardiography to assess the effect of SGLT2 inhibitors on the structure and functionality of the left ventricle (LV) and left atrium (LA) in patients with heart failure defined as reduced ejection fraction (HFrEF).

## Patients and Methods

### Study Population

The research was designed as a single-center prospective cohort study and carried out from March 2021 to June 2021, which included 56 individuals. We prospectively screened 96 patients with HFrEF (LVEF≤40%) and type 2DM with a sinus rhythm who were naive to SGLT-2 inhibitors. The study excluded patients who had an estimated glomerular filtration rate (eGFR) of 30 ml/min/1.73 $m^2$ or lower (n=9), were pregnant or breastfeeding (n=1), had a history of malignancy (n=2), had endocrine disorders other than type 2 diabetes mellitus (n=4 with thyroid disorders, n=1 with adrenal adenoma), were scheduled for cardiac surgery or coronary intervention (n=8), had increased liver enzymes (n=4), had a history of myocardial infarction within the past six months (n=8), or had poor image quality that was rejected by the software (n=3). The remaining 56 patients with HFrEF formed the study population. Patients with HFrEF were receiving maximum tolerated HF medications, including angiotensinogen enzyme inhibitors and/or beta blockers and/or mineralocorticoid receptor antagonists, but were naïve to SGLT-2 inhibitors.

The control group consisted of medically unimpaired male and female participants aged 18-80 who voluntarily sought our clinic's facilities and exhibited no health complications following the tests and assessments.

The local Ethics Committee of the Medical Faculty at Gaziantep University approved the project after all the participants in the research study provided informed permission.

### Echocardiography Evaluation

Following the administration of an SGLT2 inhibitor as part of the optimally tolerated therapy for heart failure, all of the patients were evaluated with two-dimensional (2D) transthoracic echocardiography (TTE) imaging. During this imaging, tissue Doppler, tissue strain, and two-dimensional strain analysis were all performed. This was performed prior to the initiation of SGLT2i treatment and again three months later. The control group underwent only one transthoracic echocardiographic examination for normalization at the beginning of the study. The echocardiographic exams were conducted using commercially available ultrasound equipment, including a 5 MHz transducer and Vivid S90 device (GE-Vingmed Ultrasound AS, Horten, Norway). Three consecutive heart cycles were recorded to obtain echocardiographic cine loops. Subsequently, these cine loops were preserved in optical disks to perform the analysis offline. The two-dimensional echocardiography was performed according to the standards set by the American Society of Echocardiography and the European Association of Echocardiography[20]. The specified criteria were used to measure the dimensions of the left atrium (LA) and left ventricle (LV) at the end of diastole and end of systole. The LV ejection fraction (LVEF), LA maximal and LA minimal volumes (LA $V_{max}$ and LA $V_{min}$, respectively) have been calculated utilizing the biplane Simpson method[21]. The left atrial ejection fraction (LAEF) was determined using the formula [LAEF = LA $(V_{max}-V_{min})/V_{max}$], which was automatically calculated by a computer program[22-24]. A specialized software (Echo-PAC PC; GE Healthcare, Waukesha, WI, USA) was used to perform strain analysis. A single, skilled echocardiographer blinded to all other subjects' data conducted each study and off-line analysis.

To determine LV global longitudinal strain (LVGS) values, digital cine loops were collected during the end of expiration at frame rates that varied between 60 to 100 frames per second, beginning at the peak of the R-wave. The program autonomously generated a segmented area of interest by tracing the endocardial contour on a frame captured at end-diastole. The quality of myocardial tracking was evaluated visually. If the tracking was deemed inadequate, the procedure

was repeated by modifying the area of interest or straightening the contour manually. Graphics depicting the deformation parameter were automatically generated. The average segmental value was obtained using the apical four-chamber, apical two-chamber, and apical three-chamber images to calculate the LVGS.

Images of the strain were acquired from the apical four-chamber view and captured at a frame rate exceeding 110 frames per second to assess the function of the left atrium. Following the manual marking of the LA basal, lateral, and apical segments in the apical four-chamber view, the software automatically determined the strain values of LA. The quality of myocardial tracking was visually checked again. The onset of the QRS wave and ventricular end-diastole were marked as the zero point, and the peak positive longitudinal strain was calculated as the LA reservoir strain. Negative strain in early diastole was calculated as LA conduit strain and negative strain in late diastole was calculated as LA contraction strain (Figure 1)[23].

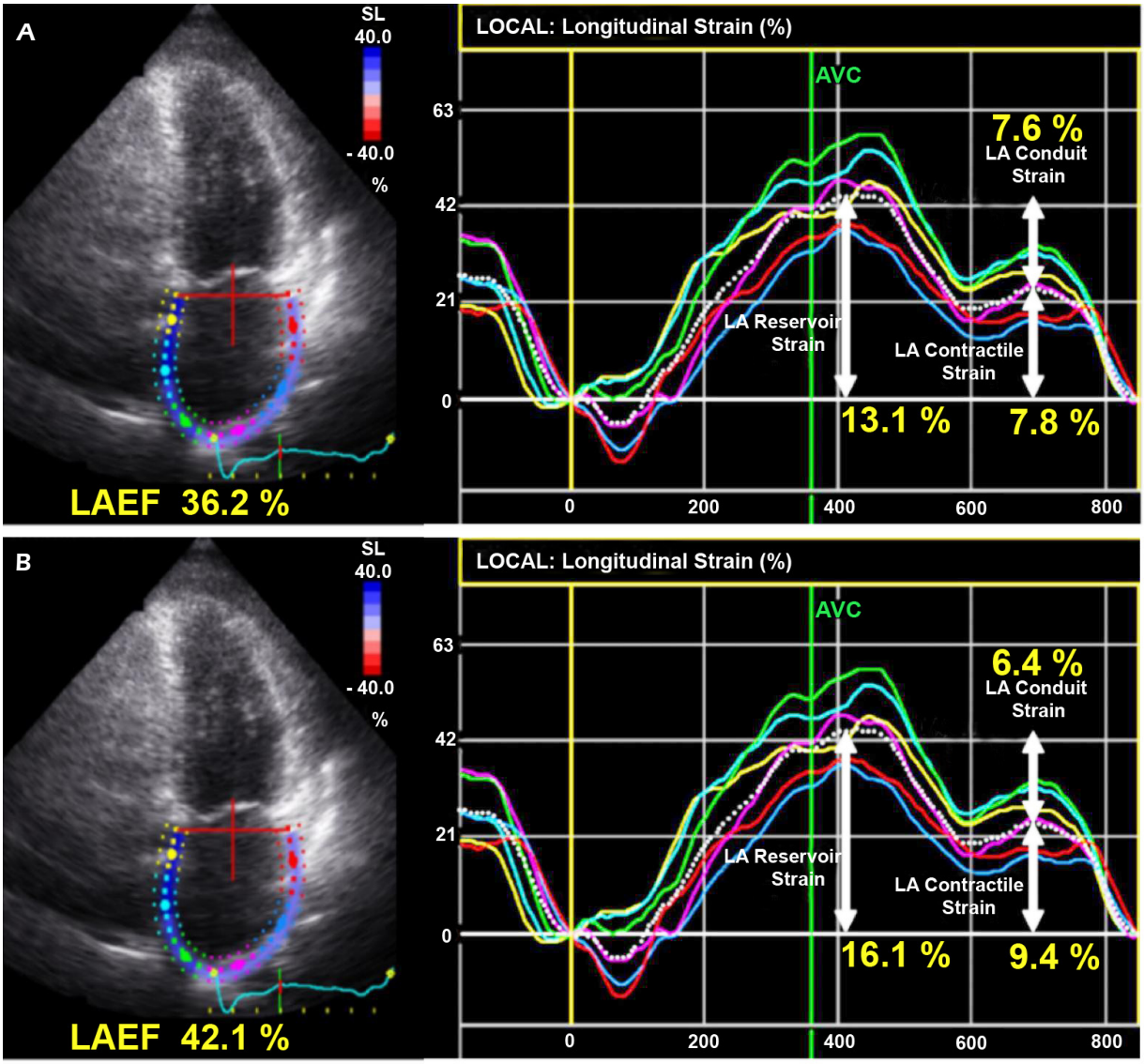


**Figure 1.** **A**, Displays the left atrial (LA) strain echocardiographic assessment conducted before the administration of SGLT-2 inhibitors, whereas (**B**) illustrates the echocardiographic assessment conducted three months following the administration of SGLT-2 inhibitors. Diabetic individuals with heart failure with reduced ejection fraction showed a significant increase in left atrial ejection fraction (LAEF), LA reservoir strain and LA contraction strain values, as seen by strain echocardiography when treated with SGLT-2 inhibitor molecules.

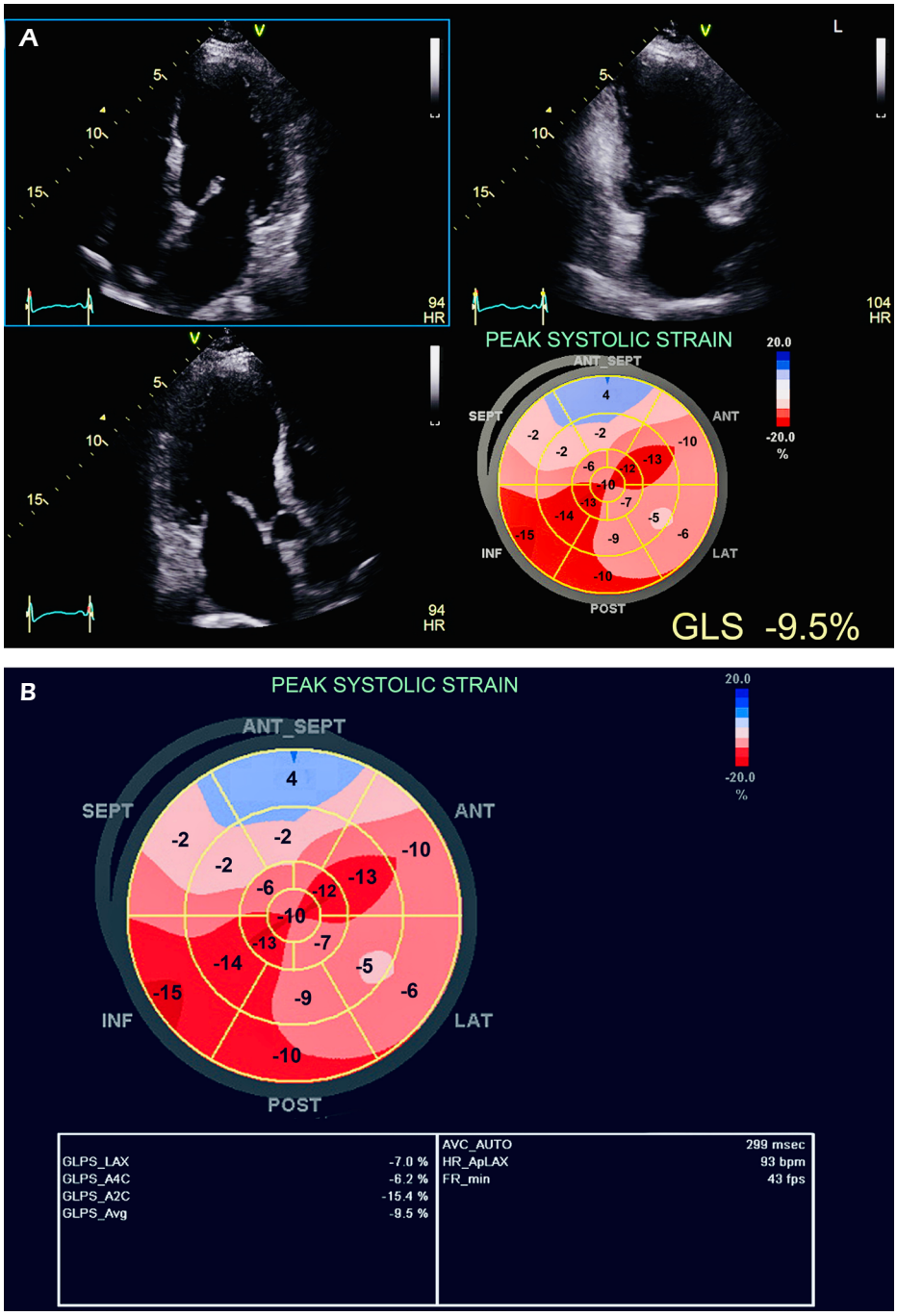


**Figure 2. A-B**, Display the echocardiographic assessment conducted before the administration of SGLT-2 inhibitors, whereas (**C-D**) illustrate the echocardiographic assessment conducted three months following the administration of SGLT-2 inhibitors. Administration of SGLT-2 inhibitor medication in individuals with diabetes and heart failure with reduced ejection fraction resulted in a notable improvement in left ventricular global longitudinal strain echocardiography (LVGLS) measures, as seen using echocardiography.

*Figure continued*

While the echocardiographic examination was performed once in the control group, it was performed twice (at the initiation of the study and at the third month of SGLT-2 inhibitor use) in patients with HFrEF.

### *Measurement of Strain Parameters Using Echocardiography*

Following the manual marking of the LA basal, lateral, and roof in the apical four-chamber pictures, the software automatically determined the

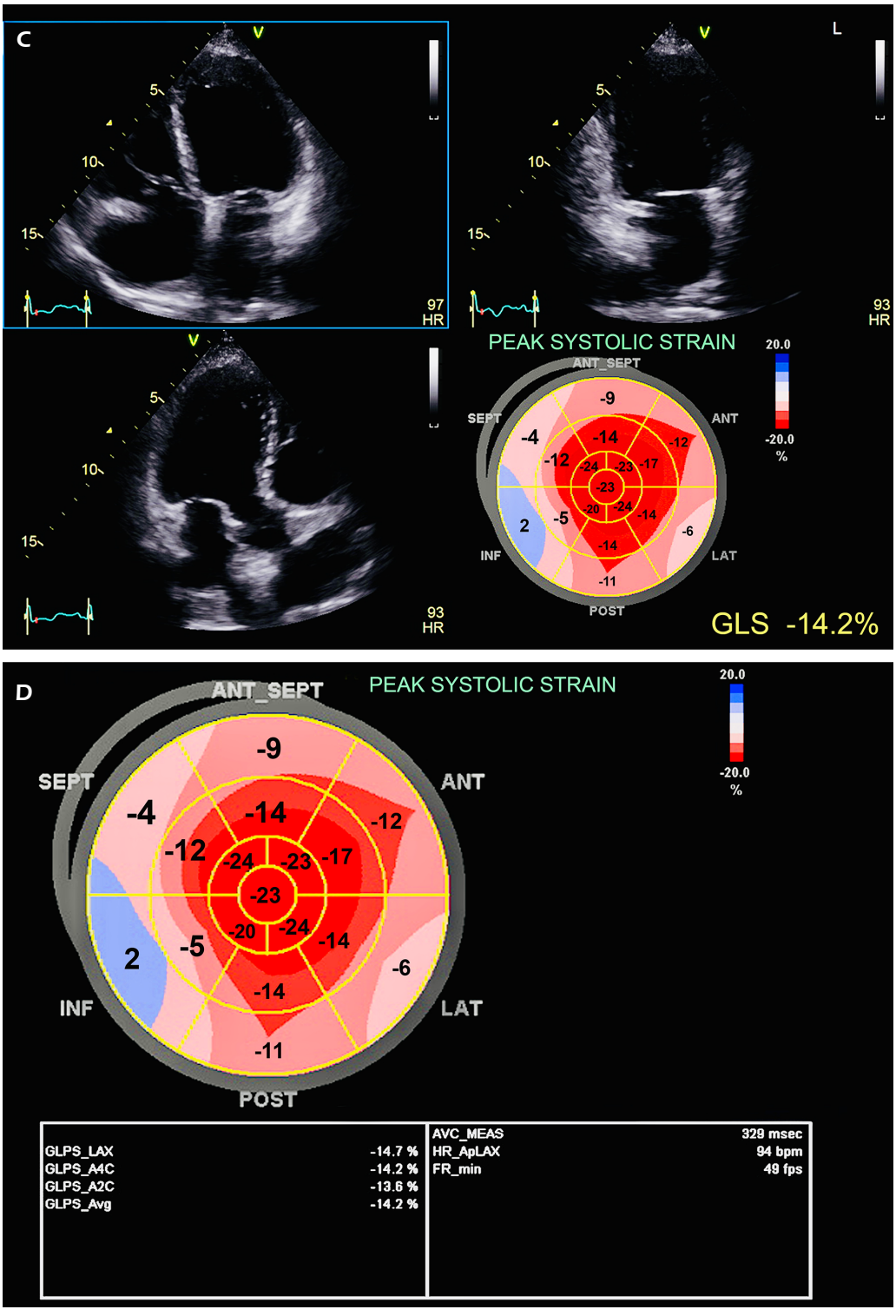


***Figure 2 Continued.*** **A-B**, Display the echocardiographic assessment conducted before the administration of SGLT-2 inhibitors, whereas (**C-D**) illustrate the echocardiographic assessment conducted three months following the administration of SGLT-2 inhibitors. Administration of SGLT-2 inhibitor medication in individuals with diabetes and heart failure with reduced ejection fraction resulted in a notable improvement in left ventricular global longitudinal strain echocardiography (LVGLS) measures, as seen using echocardiography.

strain values in LA. Within the LA strain curve, the different phases can be distinguished by three measurements. Specifically, when the atrial wall extends during the reservoir phase, the strain in this phase should be defined as a positive value. The narrowing of the LA wall during the other two phases suggests that they should be defined by negative values. The onset of the ventricular end-diastole was taken as the zero point, and the peak positive longitudinal strain was calculated as the LA reservoir strain. Negative strain in early diastole was calculated as LA conduit strain and negative strain in late diastole was calculated as LA contraction strain[25]. Among the LA strain values, reservoir strain, conduction strain, contraction strain, LAEF, and left atrial maximum and minimum volume index values were recorded (Figure 1).

Figure 1A depicts the echocardiographic assessment conducted before the administration of SGLT-2 inhibitors, whereas Figure 1B illustrates the echocardiographic assessment conducted three months following the administration of SGLT-2 inhibitors. Diabetic individuals with heart failure with reduced ejection fraction showed a significant increase in left atrial strain values, as seen by echocardiography when treated with SGLT-2 inhibitor molecules.

In LV strain measurements, the region from the left ventricular outflow tract to the anterior mitral annulus was marked with dots. The strain analysis was performed using apical 4-chamber, apical 3-chamber, and 2-chamber images obtained from three pulses, with a frame rate ranging from 50 to 100 fprs. During the measurements, a single point was identified at the apex of the mitral annulus, as well as one point from each corner. The computer autonomously scanned the boundaries of the myocardium. Following the implementation of manual corrections, the computer subsequently calculated the strain measurements automatically. Following the processing of images from three distinct cavities in the algorithm, a ''Bull's Eye'' model consisting of 17 segments was generated. After "Bulls Eye" was created, the GLS-average from LV global longitudinal strain (GLS) values was recorded for each participant (Figure 2)[26].

Figure 2 A-B displays the echocardiographic assessment conducted before the administration of SGLT-2 inhibitors, whereas Figure 2 C-D illustrates the echocardiographic assessment conducted three months following the administration of SGLT-2 inhibitors.

Administration of SGLT-2 inhibitor medication in people with diabetes and heart failure with reduced ejection fraction resulted in a notable improvement in left ventricular global longitudinal strain echocardiography (LV GLS) measures, as seen using echocardiography.

### Laboratory Study

The control group underwent blood sampling once, whereas the patient group underwent the procedure twice. The first blood sample was taken at the commencement of the study, which was also the day when the echocardiographic examination was performed. After starting treatment with an SGLT-2 inhibitor, the second blood sample was collected on the last day of the third month, which also coincided with the echocardiographic testing. All venous blood samples were collected after an overnight fasting. Heparin-containing tubes were used to collect blood samples. The serum samples were separated by centrifugation at a speed of 4,000 revolutions per minute for a duration of 10 minutes. Subsequently, the samples were stored at a temperature of -80°C until the assays were conducted. MMP-1/TIMPs-1 and asprosin levels were measured with an ELISA reader (BioTek ELx800; BioTek® Instruments Inc., Winooski, VT, USA) and the color intensity formed by the enzyme-linked immunosorbent assay (ELISA) method using Bioassay Technology Laboratory (BT LAB: Bioassay Technology Laboratory® Shanghai, China) kits. Results are expressed as ng/mL. White blood cell (WBC), hematocrit (HTC), and platelet (PLT) counts were performed with the Automated Hematology Analyzer XN 10 (Kobe, Japan). Serum Ferritin, serum creatinine, C-reactive protein (CRP), and C-peptide levels were measured with the Beckman Coulter UniCel DxI 800 (Brea, CA, USA). The levels of hemoglobin A1C (HbA1C) and N-terminal pro-B natriuretic peptide (NT-proBNP) were determined using the entirely automated hemoglobin analyzer and the UNICELL-S (Shenzhen, China) equipment.

### Statistical Analysis

An analysis of statistical significance was carried out using the MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013) program. The distribution of normality for continuous variables was checked using the Shapiro-Wilk test. Continuous variables were presented as means±standard deviations (SD) or as medians (minimum-maximum values) according to normality test results. Categorical variables are presented as numbers (n) and percentages. The comparison between two

independent variables with a normal distribution was examined with the Student's *t*-test, otherwise with the Mann-Whitney U test, appropriately. The comparison of baseline parameters with the third month corresponding was examined with a paired *t*-test, or Wilcoxon Signed Rank test. A $p<0.05$ was considered statistically significant.

## Results

Demographic characteristics of the study's participants and controls are presented in Table I. The control group was significantly younger than the patient group [30 (26-36) years *vs.* 68 (42-86) years, $p<0.001$]. The statistical analysis found no significant variations in male and female numbers across groups ($p=0.962$). The patients had a bigger body surface area than the controls (29±3.5 $m^2$ *vs.* 22.2±4 $m^2$; $p<0.001$). However, there was actually no statistically significant variance in diastolic or systolic blood pressure measures ($p=0.485$ and 0.582, respectively). The HF medications used by the patients are also presented in Table I. Among the patients with HF, 60.7% were receiving angiotensin-converting enzyme inhibitors (ACEi), 30.3% were receiving an angiotensin receptor blocker (ARB), and 92.8% were receiving beta-blockers. Among the two SGLT-2 inhibitors available in our country, half of the patients (n=28) received empagliflozin, and the other half received dapagliflozin. Table II presents a comparison of baseline echocardiographic measurements between patients and controls. Echocardiographic data revealed a higher LV end-diastolic diameter (LVEDD) (56.37±7.42 mm *vs.* 48.2±3.6 mm, respectively) and LV end-systolic diameter (34.85±3.54 mm *vs.* 29.9±3.4 mm, respectively) but lower LVEF values (33.3±6.9% *vs.* 59±1.8%, respectively) (all three *p*-values<0.001) in patients compared to controls. Strain echocardiographic assessment of the LV showed reduced LVGLS strain values in patients compared to controls (-8.6±2.3% *vs.* -21.3±1%, respectively, $p<0.001$). Assessment of LA demonstrated higher $V_{max}$ (60.2±21 ml *vs.* 22.3±2.3 ml, respectively; $p<0.001$) and $V_{min}$ (37.65±15.28 ml *vs.* 34.94±12.73 ml, respectively; $p=0.049$) but lower LAEF values (36.3±9.4% *vs.* 66.4±3.1%, respectively; $p<0.001$) in patients compared to controls. Strain echocardiographic assessment of LA displayed a lower LA reservoir strain [13 (27-25) *vs.* 40 (38-42), respectively], conduit strain (7.5±4.2 *vs.* 22.2±1.2, respectively), and contraction strain (7.7±4.3 *vs.* 17.8±1) functions in patients with HF than in controls (all three *p*-values<0.001). Patients with HF had lower baseline serum asprosin levels

**Table I.** Comparison of baseline demographic characteristics of the patients with heart failure with controls.

| Variable | Heart failure group (n=56) | Control group (n=30) | *p*-value |
|---|---|---|---|
| Age, years | 67±9.9 | 29.9±2.7 | **<0.001** |
| Men, % | 30 (53.6) | 30 (26-36) | **<0.001** |
| Body surface area, m² | 29±3.5 | 22.2±4 | **<0.001** |
| Systolic blood pressure, mmHg | 116.5±12.5 | 125.5±8.5 | 0.485 |
| Diastolic blood pressure, mmHg | 73.5±7.5 | 80.5±4.5 | 0.582 |
| Medications | | | |
| ACE inhibitor (n,%) | 34 (60.7) | - | NA |
| ARB (n,%) | 17 (30.3) | - | NA |
| ARNI (n,%) | 2 (0.3) | - | NA |
| B-blocker (n,%) | 52 (92.8) | - | NA |
| MRA (n,%) | 34 (64.2) | - | NA |
| SGLT-2 inhibitors | | | |
| Empagliflozin (n,%) | 28 (50) | - | NA |
| Dapagliflozin (n,%) | 28 (50) | - | NA |
| Digoxin (n,%) | 9 (16.7) | - | NA |
| Diuretic (n,%) | 23 (42.6) | - | NA |
| Antiaggregant (n,%) | 32 (59.3) | - | NA |
| Anticoagulant (n,%) | 3 (5.6) | - | NA |

ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker, ARNI: angiotensin receptor-neprilysin inhibitor, MRA: mineralocorticoid receptor antagonist, SGLT-2: sodium-glucose co-transporter-2, NA: non-applicable.

**Table II.** Baseline comparison of echocardiographic and laboratory variables between patients with heart failure and controls.

| Variable | Heart failure group (n=56) | Control group (n=30) | *p*-value |
|---|---|---|---|
| **Echocardiographic variables** | | | |
| LVEDD (mm) | 56.37±7.42 | 48.2±3.6 | **<0.001** |
| LVESD (mm) | 34.85±3.54 | 29.9±3.4 | **<0.001** |
| LVEF (%) | 33.3±6.9 | 59±1.8 | **<0.001** |
| LVGLS (%) | -8.6±2.3 | -21.3±1 | **<0.001** |
| LA $V_{max}$ (ml) | 60.2±21 | 22.3±2.3 | **<0.001** |
| LA $V_{min}$ (ml) | 37.65±15.28 | 34.94±12.73 | **0.049** |
| LAEF (%) | 36.3±9.4 | 66.4±3.1 | **<0.001** |
| LA reservoir strain (%) | 13 (27-25) | 40 (38-42) | **<0.001** |
| LA conduit strain (%) | 7.5±4.2 | 22.2±1.2 | **<0.001** |
| LA contraction strain (%) | 7.7±4.3 | 17.8±1 | **<0.001** |
| **Laboratory variables** | | | |
| Asprosin (ng/ml) | 11.7±5.1 | 20.9±13.3 | **<0.001** |
| MMP (ng/mL) | 6.3 (2.6-21.6) | 5.5 (2.2-16.3) | 0.278 |
| MMPTI (ng/mL) | 5±2.7 | 7.9±4.8 | **0.019** |

LVEDD: left ventricular end-diastolic diameter, LVEDD: left ventricular end-systolic diameter, LVGLS: left ventricular global longitudinal strain, LVEF: left ventricular ejection fraction, LA: left atrial, LAEF: left atrial ejection fraction, $V_{max}$: maximum volume, $V_{min}$: minimum volume, MMP: matrix metalloproteinase, MMTI: matrix metalloproteinase tissue inhibitor.

(11.7±5.1 ng/mL *vs.* 20.9±13.3 ng/mL, respectively; $p<0.001$) and MMPTI levels (5±2.7 ng/mL *vs.* 7.9±4.8 ng/mL, respectively; $p=0.019$) but similar MMP levels [6.3 (2.6-21.6) ng/mL *vs.* 5.5 (2.2-16.3) ng/mL; respectively $p=0.278$] compared to controls.

Table III compares baseline and third-month laboratory and echocardiographic data in the patient group before and after treatment with an SGLT-2 inhibitor. LVEF values were not considerably distinct (33.3±6.9% *vs.* 33.5±7.1%, respectively; $p=0.593$); however, there was a notable rise in the LV GLS values (-8.6±2.3% *vs.* -9±2.5%, $p<0.001$). LAEF increased significantly (36.3±9.4% *vs.* 42.1±8.7%) ($p<0.001$), owing to a decrease in $V_{min}$ [32.5 (19-96) ml *vs.* 32 (20-86) ml, respectively; $p=0.018$]. The third month of the examination showed substantial increases in LA reservoir [13 (6-25) *vs.* 16.5 (2-26), respectively; $p<0.001$] and contraction strain (7.7±4.3 *vs.* 9.4±5.6, respectively; $p=0.014$). Between the baseline assessment and the third-month evaluation, there was no statistically noteworthy difference in the LA conduit strain ($p=0.122$) or the LA $V_{max}$ ($p=0.716$) parameters in the patients (Table III).

A comparison of baseline biochemical parameter values with third-month values revealed a statistically noteworthy rise in serum asprosin levels (11.7±5.1 ng/mL *vs.* 14±9.4 ng/mL, respectively; $p=0.032$) but no statistically significant alteration in MMP ($p=0.278$) or MMTI levels ($p=0.401$) (Table III). There was a marked decrease in plasma N-terminal pro brain natriuretic peptide (Nt-proBNP) ($p=0.037$) and HbA1c ($p<0.001$) levels, but white blood cell count (WBC) ($p=0.075$), hematocrit (HCT) ($p=0.147$), platelet count ($p=0.527$), serum creatinine ($p=0.689$), eGFR ($p=0.567$), C-peptide levels ($p=0.502$), and ferritin ($p=0.119$) levels did not significantly change at the end of the third month (Table III).

## Discussion

Following three months of therapy with an SGLT2 inhibitor in addition to the conventional approach for HFrEF, our study observed no statistically significant changes in ejection fraction or conventional echocardiographic parameters. In addition, the LVGLS, left atrial reservoir, and conduit strain parameters improved. Additionally, serum asprosine levels improved, but NT-proBNP levels were reduced. However, there was no change in serum TIMMP and MMP-1 values after

three months. HbA1c ($p$<0.001), CRP ($p$=0.016), and NT-proBNP ($p$=0.037) all showed substantial reductions, as expected. Randomized controlled trials[27-29] have unequivocally shown that SGLT-2 inhibitors have significantly reduced hospitalization and mortality rates in individuals with HFrEF, irrespective of their diabetic status. The impact of SGLT2 inhibitors on the cardiovascular system cannot be primarily attributed to their influence on ejection fraction. LVGLS is an indicator that evaluates the left ventricle's systolic performance. It is used because of its high level of sensitivity. Some research[30,31] has demonstrated that it has a substantial influence on the long-term results in patients with HFrEF, and this correlation is unaffected by other variables. Incorporating LVGLS into the evaluation of patients with HFrEF offers a supplementary predictive capability that surpasses that of left ventricular ejection fraction (LVEF) alone[30,31]. Therefore, it is recommended that LVGLS be included in clinical practice in order to enhance the capability of classifying patients according to the amount of risk they present. SGLT-2 inhibitor molecules attach to the Na-H exchanger-1 (NHE) receptor in the heart and hinder its operation. This disturbs the equilibrium of sodium and calcium in the cytosol, leading to enhanced mitochondrial activity, reduced oxidative stress, and the cessation of cardiac fibrosis. It is possible that each of these modes of action is likewise accountable for the enhancement in GLS[9]. The study's limited duration of follow-up raises concerns about the observed alterations in strain levels during the first stage of the disease despite the standard echocardiographic data being unchanged. This raises doubts about the usefulness

**Table III.** Comparison of baseline and 3rd month echocardiographic and laboratory parameters in patients with heart failure.

| Variable | Baseline | 3rd month | *p*-value |
|---|---|---|---|
| **Echocardiographic parameters** | | | |
| LVEF (%) | 33.3±6.9 | 33.5±7.1 | 0.593 |
| LAEF (%) | 36.3±9.4 | 42.1±8.7 | **<0.001** |
| LA $V_{max}$ (mL) | 54 (36-157) | 55 (35-134) | 0.716 |
| LA $V_{min}$ (mL) | 32.5 (19-96) | 32 (20-86) | 0.018 |
| LA reservoir strain (%) | 13 (6-25) | 16.5 (2-26) | **<0.001** |
| LA conduit strain (%) | 7.5±4.2 | 6.3±4.3 | 0.122 |
| LA contraction strain (%) | 7.7±4.3 | 9.4±5.6 | **0.014** |
| LVGLS (%) | -8.6±2.3 | -9±2.5 | **<0.001** |
| **Laboratory parameters** | | | |
| WBC ($10^3$/μL) | 9.3±2.7 | 8.8±2.7 | 0.075 |
| Hct % | 40.2±4.7 | 41.1±4 | 0.147 |
| Plt ($10^3$/μL) | 255.5±74.6 | 252.5±79.3 | 0.527 |
| Creatinine (mg/dL) | 1.1±0.4 | 1.1±0.4 | 0.689 |
| eGFR (ml/min/1.73 $m^2$) | 73.7±24.8 | 72.5±24.2 | 0.567 |
| HbA1c (%) | 8.5 (5.7-14.8) | 7.7 (5.6-12.4) | **<0.001** |
| C-Peptide (μg/L) | 4 (0.6-16.3) | 3.8 (1-12.9) | 0.502 |
| CRP (mg/L) | 6 (0.5-168.7) | 4.4 (0.3-96.3) | **0.016** |
| Ferritin (ng/mL) | 81.1 (12-247.9) | 67.4 (1.5-291.2) | 0.119 |
| Nt-proBNP (pg/mL) | 955.4 (27.7-13,459.3) | 894.9 (43.2-15,150.4) | **0.037** |
| Asprosin (ng/mL) | 11.7±5.1 | 14±7.4 | **0.032** |
| MMP (ng/mL) | 6.3 (2.6-21.6) | 5.5 (2.2-16.3) | 0.278 |
| MMPTI (ng/mL) | 4.4 (1.9-14.8) | 3.9 (1.8-13.3) | 0.401 |

CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, HbA1c: glycated hemoglobin A1C, LA: left atrial, LVEF: left ventricular ejection fraction, LVGLS: left ventricular global longitudinal strain, MMP: matrix metalloproteinase, MMPTI: matrix metalloproteinase tissue inhibitor, Nt-proBNP: N-terminal pro natriuretic peptide, $V_{max}$: maximum volume, $V_{min}$: minimum volume, WBC: blood cell count.

of strain echocardiography as a standard tool for monitoring patients. While the ejection fraction did not change in our patients after receiving SGLT-2 inhibitors, there was a significant change in GLS values. On the basis of these findings, it would seem that GLS has the potential to function as a reliable tool for monitoring patients who are suffering from cardiac failure and have a reduced ventricular ejection fraction. LA reservoir peak longitudinal strain, inherent to its nature as a strain, is dependent on its baseline length, with maximal elongation of the LA during LV systole, suggesting its high dependence on LV longitudinal strain as well[32]. Carluccio et al[16] showed that LA reservoir strain was more strongly associated with LVGLS beyond LA volume and E/e' in patients with HFrEF, highlighting the substantial impact of left ventricular systolic dysfunction on left atrial dysfunction in individuals with HFrEF. The strain on the LA reservoir was significantly reduced in patients with HFrEF compared to patients with heart failure with preserved ejection fraction (HFpEF), despite the higher occurrence of atrial fibrillation (AF) in patients with HFpEF.

The presented explanation suggests that alterations in the LA, which serves as an intermediary chamber between the circulation of the pulmonary system and the left side of the heart (LV), might directly affect the functioning of the LV. LA dysfunction is an independent predictor of unfavorable outcomes, irrespective of the existence of LV hypertrophy and global longitudinal strain[33]. From this viewpoint, LA "remodeling" plays an active role in the pathophysiology of heart failure. The degeneration of the LA prior to its enlargement raises the probability of developing symptomatic HF and mortality. LA dysfunction may be the main source of clinical decompensation in HF, as several pathways of HFrEF include LA. Thus, patients with identically diminished LVEF may have different symptoms[30]. Indeed, atrial failure has been proposed as a distinct clinical condition encompassing any structural, functional, or electrical irregularity that impacts heart function and causes symptoms[34].

Left atrial strain in HFrEF patients can provide extra predictive insights on outcomes, outweighing those from commonly used clinical and cardiac magnetic resonance (CMR) risk indicators like late gadolinium enhancement (LGE).

Assessing peak atrial longitudinal strain (PALS) is a very useful predictive diagnostic in subjects with cardiac failure with a reduced ejection fraction. It remains consistent irrespective of the left atrial volume and the longitudinal contraction of the left ventricle[35].

SGLT-2 inhibitor molecules have been found[9,36,37] to enhance systolic and diastolic functions by reducing afterload due to decreased preload and blood pressure, as well as improving endothelial functions. These benefits are attributed to the osmotic diuresis and natriuresis effects they exert in the proximal tubule.

Based on our findings, we have determined that the use of SGLT2 inhibitors leads to improvements in mitochondrial activities, reduction in oxidative stress, and prevention of cardiac fibrosis. Therefore, we propose that the enhancement of left atrial systolic and diastolic function is directly associated with the use of SGLT2i. These improvements in left atrial function and structure may be responsible for the possible beneficial effects of SGLT2i in heart failure.

Asprosin is a kind of adipokine that is released by white adipose tissue. Adipokines are biologically active compounds released by adipose tissue that have several roles in regulating hunger, energy levels, lipid and carbohydrate processing, blood pressure control, and inflammation. In addition, the liver, pancreas, skeletal muscle, and heart are also impacted by the presence of circulating asprosin[11,12]. A study[38] conducted in living organisms discovered that asprosin has the ability to regulate the activity and longevity of mesenchymal stromal cells (MSC) in order to enhance cardiac function in cases of myocardial infarction. Within the ischemic microenvironment, asprosin served as a protective factor for MSCs by preventing the generation of reactive oxygen species and inhibiting apoptosis. The cytoprotective effect was achieved by increasing the production of superoxide dismutase (SOD)-2 protein and activating the ERK1/2-SOD2 (extracellular signal-regulated kinases) signaling pathway. Similarly, a clinical study[39] discovered that individuals with dilated cardiac myopathy who had elevated levels of asprosin experienced a decreased occurrence of adverse cardiovascular events compared to those with lower levels. In addition, another study[40] found that in hypoxic conditions, asprosin directly caused cardio-protective effects on H9c2 cell line myoblasts, resulting in the restoration of mitochondrial respiration. Heart failure results in a shift of mitochondrial energy production from fatty acids to glycolytic pathways. This change may require quick and accurate control of plasma glucose levels through the action of glucogenic adipokines[12]. This mechanism is crucial for meeting the energy demand of myocytes, particularly in response to hemodynamic stress[39].

Consequently, the rise in serum asprosin levels following the use of SGLT-2 inhibitors may be one of the potential beneficial mechanisms of action for these drugs in patients with HFrEF and DM.

Matrix metalloproteinases (MMPs) are a class of enzymes that include the capability to degrade the constituents of the extracellular matrix (ECM) and basement membrane. However, it is crucial to acknowledge that MMP species do not consistently increase in individuals with end-stage heart failure. This indicates that a distinct set of MMPs is expressed in the myocardium of patients with failing hearts. Tissue inhibitors of matrix metalloproteinases (TIMPs) are proteins that are produced in the local area and have the ability to bind to active MMPs, hence controlling the overall proteolytic activity[15,41].

Angiotensin II can inhibit MMP, thus, along with aldosterone, playing a role in myocardial collagen restructuring by preventing collagen breakdown and promoting production[42-44]. MMPs have been demonstrated[45] to be efficacious in treating heart failure by targeting angiotensin. According to our observations, we did not see the expected increase in TIMP-1 levels when MMP-1 levels decreased among the patients in the heart failure group in our research. It is possible that since our patients were using angiotensin II inhibitors or receptor blockers and mineral corticosteroid receptor antagonists, these patients already had low MMP levels, which did not change the addition of SGLT-2 inhibitors to the treatment. Consequently, it seems that SGLT2 inhibitors do not exert their effects through MMPs.

Elevated concentrations of CRP were additionally associated with an increased likelihood of hospital readmission and mortality, suggesting that, notwithstanding other variables, it might serve as a dependable indicator of recovery and readmission in instances of heart failure[46,47]. The observed reduction in C-reactive protein values after administration with SGLT2 inhibitors might be ascribed to the medicines' anti-inflammatory properties. The predictive significance of NT-proBNP levels is substantial in patients with heart failure and a reduced ejection fraction[48]. The reduction in NT-proBNP levels found after administering SGLT-2 inhibitors in our study may be seen as an additional beneficial outcome of these inhibitors in treating cardiac failure.

### Limitations of the Study

The primary limitation of our study is the comparatively limited sample size. Despite the small sample size, statistically significant results were obtained. Another constraint of the study is the limited duration of the follow-up period. As a result of our nation's health policy, the administration of SGLT-2 inhibitors is restricted to diabetic patients. Consequently, only individuals with diabetic heart failure were included in the research.

## Conclusions

The research found that when SGLT-2 inhibitor molecules were administered, the left ventricle and left atrium improved their systolic and diastolic functions. Additionally, the study identified an association between these improvements and increased values of LVGLS, LAEF, left atrial contraction strain, and left atrial reservoir strain. Furthermore, considering the notable alterations in plasma asprosin levels, it is believed that SGLT-2i molecules exert an influence on reactive oxygen radicals by diminishing oxidative stress and enhancing energy metabolism. However, it is important to carry out a more comprehensive study to have a more comprehensive knowledge of the impacts of these medications.

### Conflict of Interest

The authors declare that they have no conflict of interest.

### Ethics Approval

The study commenced prospectively after obtaining approval from the Ethics Committee of Gaziantep University Faculty of Medicine Ethics Committee on March 9, 2022, under reference number 2021/353.

### Informed Consent

Informed consent was acquired from all patients.

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### Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

### AI Disclosure

No artificial intelligence (AI) assisted technologies such as Large Language Models (LLMs), chatbots or image generators were used at any stage of this research.

### Authors' Contributions

Savcılıoglu M.D. and Duzen V. methodology and conceptualization, Tuluce S.Y. original draft preparation, S. Sucu M. biostatistics, software, Kaplan M. Altunbas G. and Vuruskan E., Savcılıoglu N. echocardiographic assessment, Taysi S. evaluation of blood tests, Tabur S. and Balcıoglu M. management of the endocrine arm of research. All authors read and approved the final manuscript.

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