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Original Article / Özgün Araştırma

Can Empagliflozin Improve Left Ventricular Strain Parameters in Patients with Type-2 Diabetes Mellitus and Normal Ejection Fraction?

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Abstract

Objectives: Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are known to improve symptoms and reduce mortality in patients with heart failure (HF). Empagliflozin is an SGLT-2 inhibitor. Although empagliflozin is beneficial in patients with type-2 diabetes mellitus (DM) with or without HF, data on how empagliflozin affects echocardiographic parameters are limited. We aim to evaluate the changes in left ventricular myocardial strain parameters with 2-dimensional speckle-tracking echocardiography (2D-STE) in patients with type-2 DM and normal ejection fraction (EF) after empagliflozin treatment.

Methods: A total of 92 participants were included in our study. Forty-eight of them had type-2 DM and 44 were the control group. The left ventricular ejection fraction (LVEF) of the type-2 DM patients was normal, and there were no HF symptoms and findings. Empagliflozin 10 mg once daily was given to the diabetic group. Initial and at the end of the 3rd month, the 2D-STE parameters of the diabetic group were compared.

Results: The median age of the study population was 52.0 (46.0-58.0, IQR), and 48 (52.1%) were female. The left ventricle global longitudinal strain (LV-GLS), left ventricle global circumferential strain (LV-GCS), and left ventricular global radial strain (LV-GRS) were less in the diabetic group than in the control group (p value < 0.001, < 0.001, and < 0.001, respectively). There was a significant increase in the LV-GLS and LV-GCS compared to before empagliflozin treatment (-20.0 [-17.6;-20.9] vs -19.2 [-17.5;-20.2], p= 0.005 and -18.9 [-16.0;-20.8] vs -17.1 [-15.8;-18.7], p= 0.003, respectively). Although the LV-GRS increased compared to baseline, the change was not significant (37.0 [31.0-41.6] vs 36.3 [32.4-40.3], p= 0.776).

Conclusion: In our study, after empagliflozin treatment left ventricular myocardial strain parameters such as LV-GLS and LV-GCS were improved in patients with type-2 DM and normal EF.

Keywords: Diabetes mellitus, Empagliflozin, Strain.

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Empagliflozin Tip-2 Diabetes Mellituslu ve Normal Ejeksiyon Fraksiyonu Olan Hastalarda Sol Ventriküler Strain Parametrelerini İyileştirebilir mi?

Öz

Giriş ve Amaç: Sodyum-glukoz kotransporter-2 (SGLT-2) inhibitörlerinin kalp yetmezliği (KY) hastalarında semptomları iyileştirdiği ve mortaliteyi azalttığı biliniyor. Empagliflozin bir SGLT-2 inhibitörüdür. KY olsun veya olmasın tip-2 diyabetes mellituslu (DM) hastalarda empagliflozinin yararları bilinse de, ekokardiyografik parametreleri nasıl etkilediği ile ilgili veriler kısıtlıdır. Amacımız, empagliflozin tedavisi sonrası normal ejeksiyon fraksiyonu (EF) olan tip-2 DM'li hastalarda 2 boyutlu speckle tracking ekokardiyografi (2D-STE) ile sol ventrikül miyokardiyal strain parametrelerindeki değişiklikleri değerlendirmektir.

Yöntemler: Çalışmamıza toplam 92 katılımcı dahil edildi. Bunların 48'i tip-2 DM tanılı hasta grubu ve 44'ü ise sağlıklı kontrol grubundan oluşmaktaydı. Tip-2 DM hastalarının sol ventrikül ejeksiyon fraksiyonu (LVEF) normaldi. Ayrıca bu hastalarda KY semptom ve bulguları yoktu. Diyabetik hasta grubuna günde bir kez 10 mg empagliflozin verildi. Bu hastaların başlangıç ve 3. ayın sonunda 2D-STE parametreleri karşılaştırıldı.

Bulgular: Çalışma popülasyonunun median yaşı 52.0 (46.0-58,0, IQR) olup, bunların 48'i (%52,1) kadındı. Sol ventrikül global longitüdinal strain (LV-GLS), sol ventrikül global sirkümferensiyal strain (LV-GCS) ve sol ventrikül global radyal strain (LV-GRS) diyabetik grupta kontrol grubuna göre daha düşüktü (sırasıyla p değeri <0.001, <0.001 ve <0.001). Empagliflozin tedavisi öncesine göre LV-GLS ve LV-GCS de önemli bir artış görüldü (sırasıyla; -20.0 [-17.6;-20,9] vs -19.2 [- 17.5;-20.2], p= 0,005 ve -18,9 [-16.0;-20,8] vs -17,1 [-15.8;-18.7], p= 0,003). LV-GRS başlangıca göre artmış olsa da bu anlamlı değildi (37.0 [31.0-41.6] vs 36.3 [32.4-40.3], p= 0.776).

Sonuç: Çalışmamızda, EF'si normal olan tip-2 diyabeti olan hastalarda empagliflozin tedavisi sonrası LV-GLS ve LV-GCS gibi sol ventrikül miyokardiyal strain parametrelerinde iyileşme görülmüştür.

Anahtar kelimeler: Diyabetes mellitus, Empagliflozin, Strain.

INTRODUCTION

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are a new class of oral anti-hyperglycemic drugs that increase urinary glucose excretion by decreasing glucose reabsorption in the renal proximal tubules[1]. As well as antidiabetic features, their positive cardiac effects are also known. Large randomized and placebo-controlled studies in patients with type-2 diabetes mellitus (DM) who are at high cardiovascular risk have shown that SGLT-2 inhibitors reduce heart failure (HF) hospitalizations within months after treatment[2,3]. Although many hypotheses have been proposed, the basic mechanisms by which SGLT-2 inhibitors reduce the risk of HF in people with DM are not yet fully understood. Considering the reduction in hospitalization because of HF, it may be assumed that the benefits of SGLT-2 inhibitors are due to the positive hemodynamic and metabolic effects on left ventricle (LV) function[4].

Empagliflozin is an SGLT-2 inhibitor. Studies with empagliflozin have observed similar renal and/or extrarenal benefits as other SGLT-2 inhibitors. Recently, SGLT-2 inhibitors have been shown to reduce cardiovascular death and hospitalizations in patients with systolic and/or diastolic HF, with or without DM[5]. Although studies are showing the cardiac benefits of empagliflozin, there is no study in the literature with advanced echocardiographic evaluation such as 2-dimensional speckle tracking echocardiography (2D-STE) in type-2 diabetic patients with preserved ejection fraction (EF). In this study, we aim to examine the effect of empagliflozin on LV myocardial strain parameters before and after 3 months of treatment in patients with type-2 DM and normal LVEF.

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METHODS

Study design

Our study was designed as a prospective, single-center, and observational study. A total of 96 participants were included in our study, of which 52 were in type-2 DM (patient) group and 44 were in the non-diabetes (control) group. The patient group consisted of those who were followed up in Diyarbakır Gazi Yaşargil Training and Research Hospital Internal Medicine and Endocrinology outpatient clinics between September 1, 2019 - January 31, 2020. Patients of similar age without DM and HF were enrolled as the control group. All of the type-2 diabetic patients had an LVEF of more than 50% and had no symptoms or signs of HF. Other than HF, the exclusion criteria were atrial fibrillation, chronic renal failure, patients with pacemakers, history of moderate to severe valvular disease, presence of active infection, and pregnancy. Empagliflozin 10 mg daily was given to the 52 patients who remained after the exclusion criteria. Before starting empagliflozin, the patients' routine biochemical tests and glycosylated hemoglobin (HbA1c) levels were checked. Body mass index (BMI) and body surface area (BSA) were calculated. 12-lead surface electrocardiography and 2D-STE images were also examined. All procedures were repeated at the end of the 3rd month. Four patients who could not tolerate the drug were excluded from the study during follow-up. At the end of the 3rd month, the clinical, laboratory, and echocardiographic assessments of the patients at initial and after treatment were compared. Strain analysis by 2D-STE was performed by two independent of each other experienced cardiologists according to guidelines from 2D grayscale images recorded using EchoPAC software[6]. These experts then performed strain analysis again for intraobserver agreement. Then, two more experts, independent of each other and different from the first observers, performed strain analysis for the interobserver agreement. The ethics committee approval required for our study was obtained from the ethics committee of our hospital (Protocol no: 377, date: 29.11.2019).

Echocardiographic assessment

Vivid S70 systems (GE Healthcare, Horton, Norway) were used to obtain all echocardiographic images, which were then moved to the EchoPAC workstation. Three consecutive cardiac cycles were taken and images were recorded at a frame rate of 60-80 frames/sec. Conventional apical 4-chamber, apical 2-chamber, parasternal long-axis, and parasternal short-axis images were obtained for left ventricle and left atrium measurements, wall thickness, systolic and diastolic parameters. Pulse wave doppler velocity measurements were used for LV diastolic parameters. Biplane LVEF was measured by using the modified Simpson method. Analyzes were performed for 3-apical (LV 4-chamber, 2-chamber, and 3-chamber view) and 3 short-axis views (LV basal, mid and apical views). The program automatically tracked LV myocardium's boundaries, with manual adjustments as required. The program measured strain values in each view after manual adjustments. Aortic valve closure in the apical long-axis view was defined as end-systole. After processing all 3 apical views, a 17-segment bull's-eye view was created. Left ventricular global longitudinal strain-transmural, endocardial and epicardial measurements (LVGLS-trans, LVGLS-endo, and LVGLS-epi, respectively) were automatically calculated by the EchoPAC software. The average strain values for global circumferential strain (GCS) and global radial strain (GRS) were obtained by taking apical, mid-ventricular, and basal short-axis parasternal views[6]. The initial strain images of the same patient are shown in Figure 1 and the after-treatment strain images are shown in Figure 2.

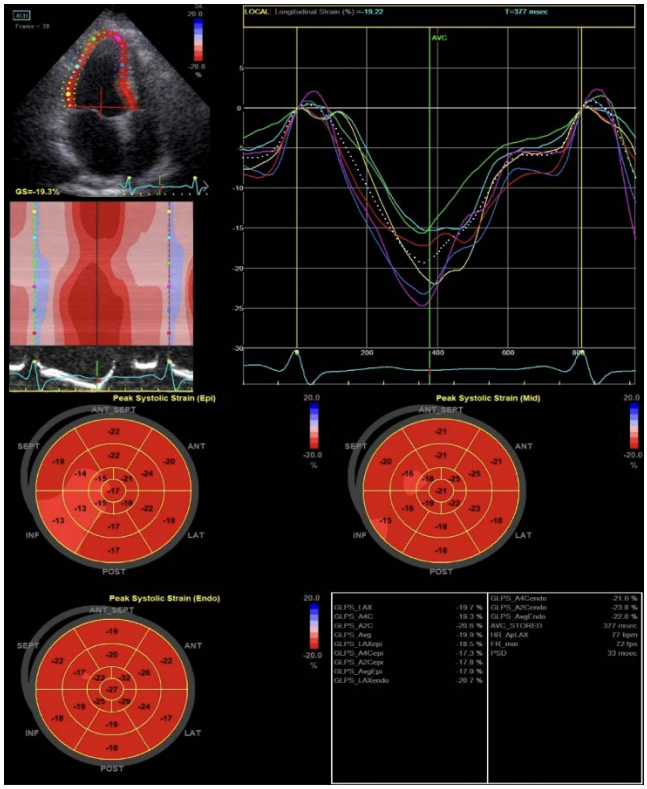

Figure 1. A sample of initial 2D-STE analysis of the same patient.

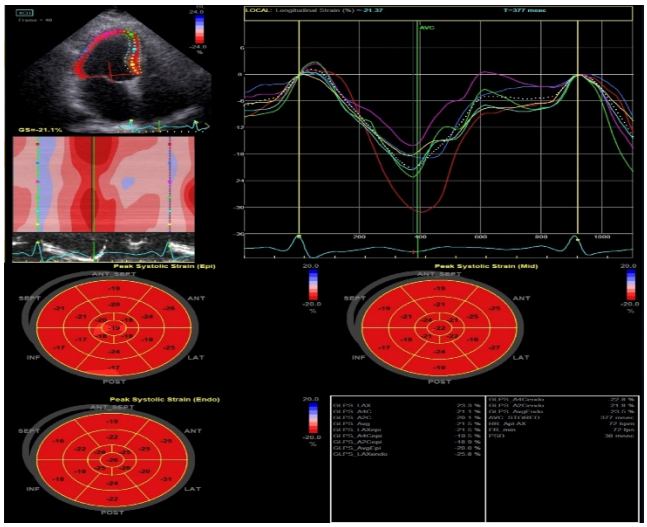

Figure 2. A sample of after empagliflozin treatment 2D-STE analysis of the same patient.

Statistics

The histogram and Shapiro-Wilks test were used to confirm the normal or non-normal distribution of data. The median value and interquartile range (IQR) (25-75 %) were used in the distribution of parametric variables. The categorical variables were expressed as percentages. Chi-square test was used to compare categorical variables between groups. Continuous variables were compared by the Mann-Whitney U test. Wilcoxon test was used to compare continuous variables. Intra and interobserver agreement were assessed using the intraclass correlation coefficient (ICC). There was perfect agreement when ICC > 0.74, good when ICC = 0.60–0.74, fair when ICC = 0.40–0.59, and poor when ICC < 0.4[7]. The statistical significance level of the obtained data was interpreted with the "p" value. Values of $p < 0.05$ were considered to be statistically significant. The analysis of the data was performed using SPSS (Statistical Package for Social Science for Windows)-24 packaged software.

RESULTS

Ninety-two participants were included in the study. The median age of the study population was 52.0 (46.0-58.0, IQR) and 48 (52.1%) were female. BMI ($p<0.001$), BSA ($p=0.011$) and mitral E/e' ($p=0.015$) were higher in the patient group, while left ventricle global longitudinal strain (LV-GLS), left ventricle global circumferential strain (LV-GCS) and left ventricle global radial strain (LV-GRS) were lower in the control group ($p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). Demographic, laboratory, and echocardiographic findings of patient and control groups are given in Table I. Almost all of the patients were using metformin (93.7%) and more than half were using insulin (52%). Medications of the patient group are given in Table II.

Table I: Comparison of demographic, laboratory, and echocardiographic findings of patient and control groups.

Variables	Patient group(n=48)	Control group(n=44)	p value
Age, years	55(45-62)	51(41-57)	0.105
Sex, female (%)	27(56)	21(48)	0.531
Hypertension, n (%)	23(47.9)	12(27.3)	0.060
Coronary artery disease, n (%)	12(25.0)	5(11.3)	0.112
Systolic blood pressure, mm/Hg	120(110-129)	115(105-120)	0.052
Diastolic blood pressure, mm/Hg	70(60-80)	70(60-80)	0.234
Body mass index, kg/m²	31.5(28.0-37.8)	24.6(23.2-26.8)	<0.001
Body surface area, m²	1.94(1.85-2.07)	1.88(1.68-1.97)	0.011
Creatinine, mg/dL	0.80(0.70-1.00)	0.82(0.67-0.97)	0.550
Potassium, meq/L	4.1(3.9-4.4)	4.2(4.0-4.50)	0.211
Hematocrit %	45.4(44.0-48.9)	45.0(40.0-47.0)	0.056
Heart rate, beat/min	84(74-91)	86(77-92)	0.194
Biplane ejection fraction (%)	64(62-66)	64(63-67)	0.108
Mitral E/e'	6.33(5.00-9.10)	5.00(4.42-6.38)	0.015
LV-GLS (%)	-19.2(-17.5;-20.2)	-20.6(-19.5;-21.8)	<0.001
LV-GCS (%)	-17.1(-15.8;-18.7)	-21.8(-21.0;-22.5)	<0.001
LV-GRS (%)	36.3(32.4-40.3)	45.3(38.3-49.3)	<0.001

Data are expressed as median interquartile range and categorical variables were expressed as numbers (%).

LV- GCS: Left ventricle global circumferential strain, LV-GLS: Left ventricle global longitudinal strain, LV-GRS: Left ventricle global radial strain.

At the end of the third month of empagliflozin treatment, the initial and after treatment parameters of the patient group were compared. Systolic blood pressure (p = 0.001), diastolic blood pressure (p = 0.012), BMI (p < 0.001), BSA (p < 0.001), alanine transaminase (p= 0.029), glucose (p< 0.001), HbA1c (p < 0.001), and triglyceride (p = 0.001) were significantly lower after empagliflozin treatment compared to baseline. Hematocrit (p = 0.001) and high density lipoprotein (p = 0.001) were significantly increase after treatment. Clinical and laboratory parameters of the patients before and after treatment are given in Table III.

Table II: Medications of the patient group.

Drugs	n	%
Beta-blocker	6	12.5
Statin-fibrates	13	27.0
Renin-angiotensin-aldosterone inhibitors	20	41.6
Calcium channel blockers	7	14.5
Mineralocorticoid receptor antagonists	2	4.1
Hydrochlorotiazid-indapamide	11	22.9
Insulin	25	52.0
Biguanide (Metformin)	45	93.7
Sulfonylureas	7	14.5
Thiazolidinediones	4	8.3
Dipeptidyl dipeptidase-4 inhibitors	26	54.1
Glucagon-like peptide-1 receptor agonist	2	4.1
Others	3	6.2

Table III: Clinical and laboratory parameters of the patients before and after empagliflozin treatment.

Variables	Before treatment	After treatment	p value
Body mass index, kg/m^2	31.5(28.0-37.8)	30.7(26.2-36.0)	<0.001
Body surface area, m^2	1.94(1.85-2.07)	1.93(1.80-1.99)	<0.001
Systolic blood pressure, mm/Hg	120(110-129)	115(110-125)	0.001
Diastolic blood pressure, mm/Hg	70(60-80)	70(60-78)	0.012
Aspartate transaminase, IU/L	17.0(15.0-24.7)	17.0(14.0-20.0)	0.116
Alanine transaminase, IU/L	20.0(15.0-28.7)	15.5(12.2-28.0)	0.029
Glucose, mg/dL	182(141-263)	147(114-179)	<0.001
HbA1c, %	9.15(7.05-10.57)	7.65(6.50-8.90)	<0.001
Potassium, meq/L	4.1(3.9-4.4)	4.1(3.9-4.4)	0.346
Creatinine, mg/dL	0.80(0.70-1.00)	0.76(0.70-1.00)	0.135
Hematocrit %	45.4(44.0-48.9)	46.0(44.0-50.0)	0.001
Total colesterol, mmol/L	196(157-227)	202(166-217)	0.337
High density lipoprotein, mmol/L	38(35-41)	40(37-50)	0.001
Low density lipoprotein, mmol/L	122(98-137)	116(104-137)	0.176
Triglyceride, mmol/L	150(123-242)	124(80-189)	0.001
White blood cell, 10^9/ L	8.45(8.00-9.71)	9.00(7.92-10.42)	0.253
Neutrophil, 10^9/ L	5.00(4.35-6.30)	5.35(4.32-6.55)	0.403
Lymphocyte, 10^9/ L	2.80(2.40-3.20)	2.90(2.22-3.30)	0.674
Platelet, 10^9/ L	251(226-307)	267(219-321)	0.242

Data are expressed as median interquartile range, HbA1c: glycosylated hemoglobin

In echocardiographic findings; LV systolic diameter [26(25-28) vs 27(25-28) p = 0.028], mitral E wave [0.67 (0.54-0.78) vs 0.69 (0.61-0.77), p = 0.009] and mitral E/e' [5.44 (4.60-7.52) vs 6.33(5.00-9.10), p= 0.005] ratio were less than before treatment. Presystolic wave [0.57 (0.51-0.64) vs 0.48 (0.42-0.64), p < 0.001] higher than before treatment. Echocardiographic findings of the patients before and after empagliflozin treatment are given in Table IV. LV-GLS [-20.0(-17.6;-20.9) vs -19.2(-17.5;-20.2), p= 0.005] and LV-GCS [-18.9(-16.0;-20.8) vs -17.1(-15.8;- 18.7), p= 0.003] were significantly higher than before treatment. LV-GRS did not change after treatment [37.0(31.0-41.6) vs 36.3(32.4-40.3), p= 0.776] (Figure 3). Intra and interobserver variability of LV myocardial strain parameters are given in Table V.

Table IV: Echocardiographic findings of the patients before and after empagliflozin treatment.

Variables	Before treatment	After treatment	p value
Heart rate, beat/min	84(74-91)	84(73-91)	0.522
LVdiastolic diameter, mm	45(43-49)	46(44-48)	0.445
LV systolic diameter, mm	27(25-28)	26(25-28)	0.028
Septum thickness, mm	11(10-12)	11(10-12)	0.248
LV posterior wall thickness, mm	10(9-11)	10(10-11)	0.243
Biplane ejection fraction (%)	64(62-66)	65(62-66)	0.667
LV diastolic volume, ml	86(75-98)	83(75-95)	0.168
LV systolic volume, ml	31(27-35)	31(27-33)	0.156
LV diastolic volume index, ml/m^2	43.37(39.18-47.97)	44.36(40.10-48.42)	0.918
LV systolic volume index, ml/m^2	15.45(13.89-18.38)	15.51(14.87-16.96)	0.909
LV mass, g	174(148-205)	170(158-182)	0.588
LV mass index g/m^2	89.71(77.27-98.29)	87.47(76.51-93.81)	0.498
LA volume, ml	41(35-45)	40(35-44)	0.271
LA volume index, ml/ m^2	20.50(17.27-22.79)	21.13(17.72-24.04)	0.667
Mitrale E wave, cm/sec	0.69(0.61-0.77)	0.67(0.54-0.78)	0.009
Mitrale A wave, cm/sec	0.85(0.73-0.96)	0.78(0.70-0.95)	0.980
Mitral E/ e'	6.33(5.00-9.10)	5.44(4.60-7.52)	0.005
Lateral e wave, cm/sec	0.11(0.08-0.15)	0.12(0.09-0.15)	0.547
Lateral a wave, cm/sec	0.12(0.10-0.14)	0.13(0.11-0.16)	0.112
Lateral Sm, cm/sec	0.09(0.07-0.11)	0.10(0.08-0.11)	0.274
Septal e wave, cm/sec	0.08(0.06-0.11)	0.09(0.06-0.11)	0.343
Septal a wave, cm/sec	0.11(0.10-0.14)	0.12(0.10-0.13)	0.245
Septal Sm, cm/sec	0.08(0.08-0.10)	0.09(0.08-0.10)	0.542
IVRT, ms	90(81-100)	87(80-97)	0.250
LV presistolic wave, cm/sec	0.48(0.42-0.64)	0.57(0.51-0.64)	<0.001

Data are expressed as median interquartile range

IVRT: Isovolumetric relaxation time, LV: Left ventricle, LA: Left atrium, Sm: Peak systolic velocity at myocardial segments.

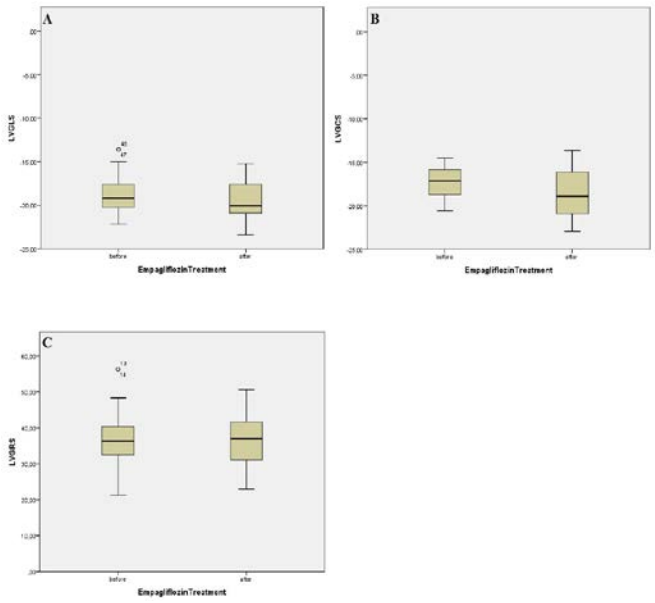

Figure 3. Comparison of before and after empagliflozin treatment in left ventricle myocardial strain parameters.

Table V: Intraobserver and interobserver agreement.

Variables	Intraobserver CoV(%)	Intraobserver agreement(ICC, 95% CI)	Interobserver CoV(%)	Interobserver agreement(ICC, 95% CI)
LV-GLS, before treatment	20.8	0.76(0.60-0.86)	21.7	0.70(0.53-0.82)
LV-GLS, after treatment	18.8	0.71(0.53-0.82)	19.5	0.67(0.48-0.80)
LV-GCS, before treatment	18.6	0.73(0.56-0.84)	18.9	0.76(0.61-0.86)
LV-GCS, after treatment	32.9	0.64(0.44-0.78)	31.3	0.71(0.52-0.83)
LV-GRS, before treatment	21.9	0.78(0.64-0.87)	22.8	0.74(0.57-0.84)
LV-GRS, after treatment	17.8	0.76(0.61-0.86)	18.6	0.73(0.56-0.84)

CI: Confidence interval, CoV: Coefficient of variation, ICC: intraclass correlation coefficients, LV-GCS: Left ventricle global circumferential strain, LV-GLS: Left ventricle global longitudinal strain, LV-GRS: Left ventricle global radial strain.

DISCUSSION

Empagliflozin is associated with beneficial cardiac outcomes in patients with HF. In our study, LV myocardial strain parameters were evaluated using 2D-STE before and after 3 months of empagliflozin treatment in patients with type-2 DM and normal LV systolic functions. To the best of our knowledge, this is the first study to evaluate LV strain parameters before and after treatment with empagliflozin in the same patient group. Our study showed that LV-GLS and LV-GCS increased after empagliflozin treatment in patients with type-2 DM.

Although it is primarily antidiabetic, empagliflozin has become popular in the treatment of HF in recent years. The mechanism by which empagliflozin improves cardiac function is not clearly understood[8], but some theories point to its extrarenal cardioprotective effects. Pre-experimental studies suggest that SGLT-2 inhibitors may improve vascular structural properties, interfering with collagen, elastin, and advanced glycation end-products[9]. Others have asserted that SGLT-2 inhibitors increase ketone bodies to facilitate myocardial energetics[10], and a study found that myocardial utilization of beta-hydroxybutyrate resulted in a significant increase in adenosine triphosphate (ATP) production concerning glucose and fatty acid oxidation and improved efficiency in a model of an isolated working heart by 25%[11]. Empagliflozin has also been shown to have direct myocardial effects, as mitochondrial Ca^{+2} in cardiomyocytes is considered one of the main activators of ATP synthesis and the antioxidant enzymatic network[12]. High cardiac cytoplasmic Na^{+} and Ca^{+2} concentrations and decreased mitochondrial Ca^{+2} concentration are characteristic factors of HF and cardiac death caused by hyperglycemia. A recent study found that empagliflozin reduces cardiac cytoplasmic Na^{+} and Ca^{+2} concentrations of cardiomyocytes and increases mitochondrial Ca^{+2} [13]. Finally, the proposal of a novel mechanism of action has suggested the hypothesis that the benefit of SGLT-2s in HF may be mediated by the sodium-hydrogen exchanger rather than by the effect on glucose reabsorption[14].

In an animal study with empagliflozin, myocardial infarction was induced in non-diabetic subjects by inflating a percutaneous intracoronary balloon into the left anterior descending coronary artery. Then, myocardial damage was examined using 3D echocardiography and cardiac magnetic resonance (CMR) imaging. The subjects were given either 10 mg/day of empagliflozin or a placebo for 2 months. In postinfarction 3D echocardiography, EF, longitudinal strain, circumferential strain, and radial strain were found to have increased in the empagliflozin group. It has also been suggested that empagliflozin ameliorates neurohumoral activation and cardiac injury[15]. In the SUGAR-DM-HF study, patients who have type-2 DM or prediabetes and reduced EF were examined. Some of these patients were given empagliflozin for 36 weeks. Initial and after treatment strain parameters were examined by CMR imaging. Left ventricular systolic and diastolic volume indices were decreased in the empagliflozin group. LVEF and LV-GLS were observed similarly[16]. In another study, diabetic patients with reduced or normal EF given empagliflozin were followed for 12 months. LV-GLS, LV-GCS, and LV-GRS were significantly increased after empagliflozin compared to baseline[17]. The EMPA-HEART study investigated whether empagliflozin reduced LV mass in patients with type-2 DM and coronary artery disease (CAD). CMR was used as the imaging method. After 6 months, a significant decrease in BSA indexed LV mass was observed [18]. In addition to their proven effect in decreasing plasma glucose levels, SGLT-2 inhibitors have been shown to have potential benefits in improving other cardiovascular risk factors, such as body weight and blood pressure, when the patient can tolerate the drug[19].

In our study, BMI and BSA decreased after empagliflozin. Systolic and diastolic blood pressures also decreased from baseline. Symptomatic hypotension was not observed in any patient and blood pressure was well tolerated in the patients. In a previous study, it was observed that empagliflozin compared to placebo did not change the cardiac index or systemic vascular resistance in patients with type-2 DM, but rapidly improved LV filling pressure. It was also found that LV mass index, left atrial (LA) area, left atrium volume index (LAVI), and LV-GLS were similar compared to treatment with placebo[20]. In our study, LV-GLS and LV-GCS increased after empagliflozin treatment, while LA area, LAVI, LV mass, and LV mass index were similar compared to baseline.

Although patients with normal LV systolic function were included in our study population, most patients had subclinical LV diastolic dysfunction. Subclinical LV diastolic dysfunction is highly prevalent in people with type-2 DM[21,22]. In this study, we found that strain parameters such as LV-GLS and LV-GCS improved after treatment, but we did not investigate the effect of empagliflozin in patients with type-2 DM without LV diastolic dysfunction. We think that clinicians should not disregard this in patients with type-2 DM.

There are several limitations to our study. First, the sample size was not sufficiently large, but the statistical significance found with this number of patients could be indicative of the magnitude of empagliflozin's effects. Second, while only patients with normal LV systolic function were included in our study, most also had LV diastolic dysfunction. This may have been due to the existence of comorbidities, such as hypertension and CAD. We do not know whether the positive echocardiographic findings of empagliflozin are seen in pure diabetic patients without comorbidities. Future studies should consider this avenue of research. Third, more than half of our study consisted of obese patients. In some obese patients, the demarcation of the ventricle and atrium boundaries was repeated several times due to

its non-echoic structure. However, we argue that this is not indicative of bias, as echocardiography analyses were performed by different specialists.

CONCLUSION

Despite the many mechanisms currently available, the impact of SGLT-2 inhibitors on cardiac structure and function remains unclear, necessitating further detailed studies. Our study found improvements in LV myocardial strain parameters and some LV diastolic parameters in patients treated with empagliflozin. These results support previous studies showing the cardioprotective effects of empagliflozin.

Ethics Committee Approval: This study was approved by Gazi Yaşargil Training and Research Hospital Ethics Committee (Protocol no: 377, date: 29.11.2019).

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