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Longitudinal Assessment of Diastolic Function and Myocardial Strain in Type 2 Diabetes: A Comparison of Empagliflozin and Linagliptin

ABSTRACT

Objective: The cardiovascular effects of sodium–glucose cotransporter-2 inhibitors and dipeptidyl peptidase-4 inhibitors have attracted increasing interest in patients with type 2 diabetes mellitus. This study aimed to compare the time-dependent effects of empagliflozin and linagliptin on left ventricular diastolic function and global longitudinal strain (GLS).

Methods: This prospective longitudinal study included 350 patients with type 2 diabetes mellitus treated with empagliflozin (n = 200) or linagliptin (n = 150). Transthoracic echocardiography and speckle-tracking strain analysis were performed at baseline, 1 month, and 6 months. Diastolic function was evaluated using septal e′ velocity, E/e′ ratio, isovolumetric relaxation time (IVRT), and mitral E-wave deceleration time. Longitudinal changes were analyzed using linear mixed-effects models including treatment group, time, and group × time interaction.

Results: Diastolic function parameters improved significantly over time in both groups (all $P < .001$). At follow-up, HbA1c levels decreased in both groups, with comparable glycemic control achieved at 6 months. Significant group × time interactions were observed for septal e′ velocity, E/e′ ratio, and IVRT (all $P < .001$). These findings remained consistent after adjustment for baseline differences. At 6 months, empagliflozin was associated with greater improvement in septal e′ velocity and IVRT, whereas linagliptin resulted in a more pronounced reduction in the E/e′ ratio. Although GLS improved in both groups, its temporal pattern differed significantly between treatments ($P < .001$).

Conclusion: Empagliflozin and linagliptin exert distinct effects on left ventricular diastolic function and myocardial deformation in type 2 diabetes mellitus. Empagliflozin appears to provide earlier improvement in diastolic relaxation and GLS, whereas linagliptin may have a greater effect on filling pressures. These findings should be interpreted cautiously and considered hypothesis-generating; confirmation in randomized controlled trials is required to determine their clinical relevance.

Keywords: Diastolic dysfunction, diabetes mellitus, echocardiography

ORIGINAL INVESTIGATION

INTRODUCTION

Type 2 diabetes (T2D) is strongly associated with heart failure (HF), subclinical myocardial dysfunction, and diastolic dysfunction, beyond microvascular complications.[1] In diabetes, early-stage left ventricular relaxation disorders, increased filling pressures, and myocardial deformation anomalies can occur; this phenotype is defined within the concept of "diabetic cardiomyopathy" and predisposes to the development of clinical HF.[2]

Sodium–glucose cotransporter-2 inhibitors (SGLT2i) have become one of the most potent classes of drugs for improving cardiovascular (CV) endpoints in T2D. Empagliflozin has demonstrated significant benefits on HF and renal endpoints; its efficacy has been demonstrated in randomized studies reporting positive effects on clinical endpoints, particularly in the Heart Failure with Reduced Ejection Fraction (HFrEF) population.[3] The fact that empagliflozin also reduces HF hospitalizations in the Heart Failure with Preserved Ejection Fraction (HFpEF) population has supported its inclusion among the essential therapies

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in the SGLT2i class of HF spectrum in current guidelines.[4,5] It is suggested that this clinical benefit is due to multiple mechanisms, including osmotic diuresis/natriuresis, reduced preload/afterload, reprogramming of cardiac energy metabolism, reduction of inflammation and oxidative stress, improved endothelial function, and effects at the microvascular level.[6,7]

In the class of dipeptidyl peptidase-4 inhibitors (DPP-4i), cardiovascular safety is generally considered neutral, although interdrug heterogeneity and different effects depending on patient phenotype are discussed.[8] Linagliptin has demonstrated a non-inferior safety profile in large-scale studies, particularly with regard to renal safety and cardiovascular endpoints.[9] However, prospective longitudinal data directly comparing the effects of DPP-4i on diastolic function and myocardial deformation with SGLT2i are limited.[10]

Classic ejection fraction (EF) measurements may be insufficient for detecting early myocardial involvement due to diabetes. Global longitudinal strain (GLS) obtained by speckle-tracking echocardiography is a sensitive indicator of subclinical systolic dysfunction and contributes to early risk stratification in the diabetic population.[11] In diastolic function assessment, parameters such as septal e′, E/e′ ratio, isovolumetric relaxation time (IVRT), and deceleration time (DT) provide complementary information about both relaxation and filling pressures.[12] Furthermore, the potential effects of different systemic stress conditions on diastolic function have been previously highlighted; for example, the potential effects of acute allergic reactions on diastolic function have been reported at the clinical level.[13]

In this context, the aim of the study is to compare the time-dependent effects of empagliflozin and linagliptin on diastolic function parameters (septal e′, E/e′, IVRT, DT) and absolute GLS in patients with T2D in a prospective longitudinal design and to reveal treatment-specific differentiating patterns through group × time interaction.[14]

HIGHLIGHTS

- Empagliflozin and linagliptin demonstrate distinct time-dependent effects on left ventricular diastolic function in type 2 diabetes.
- Empagliflozin treatment is associated with earlier and more sustained improvement in diastolic relaxation parameters and global longitudinal strain.
- Linagliptin shows a more pronounced effect on parameters reflecting left ventricular filling pressures.
- Longitudinal strain imaging enables detection of subclinical myocardial dysfunction despite preserved ejection fraction.
- Findings highlight differential cardiac response patterns between antidiabetic therapies.
- These findings are hypothesis-generating and require confirmation in randomized controlled studies.

METHODS

Study Design and Patient Population

This prospective longitudinal study included a total of 350 patients diagnosed with T2D and scheduled to begin treatment with empagliflozin or linagliptin between January 2020 and June 2024. Patients were divided into empagliflozin (n = 200) or linagliptin (n = 150) treatment groups according to clinical indications.

Treatment allocation was not randomized and was based on clinical indication and physician discretion, reflecting real-world clinical practice.

Baseline concomitant medications, particularly those potentially affecting diastolic function, were recorded and analyzed.

Ethics Statement

The study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by an institutional Clinical Research Ethics Committee on 12 September 2019 (Decision No: 2019-272). Written informed consent was obtained from all participants prior to enrollment.

Inclusion and Exclusion Criteria

The study included patients over 18 years of age with T2D who were in sinus rhythm, had preserved left ventricular EF, and completed scheduled follow-up visits.

Patients meeting any of the following criteria were excluded from the study:

- Recent acute coronary syndrome (within the past 6 months) or clinically unstable coronary artery disease,
- Clinically significant valvular disease,
- Heart failure (LVEF <50%),
- Atrial fibrillation or other persistent arrhythmias,
- Chronic renal failure (eGFR <30 mL/min/1.73 m^2),
- Active infection, systemic inflammatory, or malignant disease,
- Changes in dosage or discontinuation of existing antihypertensive or antidiabetic treatments (other than empagliflozin or linagliptin) during the study period,
- Inadequate image quality that may impair the reliability of echocardiographic measurements.

Patients with stable coronary artery disease were not excluded from the study.

Echocardiographic Evaluation

All patients underwent transthoracic echocardiography using a commercially available ultrasonography system (Philips EPIQ 7, Philips Medical Systems, Andover, MA, USA). Echocardiographic assessments were performed by experienced cardiologists, unaware of the treatment groups. The examinations were performed with the patients in the left lateral decubitus position; parasternal long and short axis and apical 2, 3, and 4-chamber views were obtained in accordance with the guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.

Left ventricular diameters, wall thicknesses, and systolic function parameters were measured using 2-dimensional and M-mode echocardiography. Left ventricular EF was calculated using the biplane Simpson method. Pulsatile wave Doppler and tissue Doppler imaging techniques were used to evaluate diastolic function; septal early diastolic mitral annulus velocity (e′), transmitral E-wave velocity, E/e′ ratio, IVRT, and mitral E-wave deceleration time (DT) were measured.

Speckle-Tracking and Global Longitudinal Strain Analysis

Global longitudinal strain analysis was performed using the speckle-tracking method obtained from apical 4, 2, and 3-cavity images. Global longitudinal strain measurements were calculated by averaging the values obtained from 3 apical planes. The analyses were performed blindly by an experienced observer. In the study, GLS values were reported as absolute values (absolute GLS) in accordance with clinical interpretation. Echocardiographic and strain assessments were repeated at baseline, at 1 month, and at 6 months of treatment.

Laboratory Evaluation

Fasting venous blood samples were taken from all patients and subjected to biochemical and hematological evaluations. Serum urea and creatinine levels, as well as total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels, were measured using automated biochemistry analyzers.

Complete blood count parameters (hemoglobin, hematocrit, leukocyte, and platelet counts) were evaluated using standard hematology analyzers. All laboratory measurements were performed in the hospital's central laboratory and in accordance with international quality control standards.

Statistical Analysis

Statistical analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are expressed as mean ± SD, and categorical variables are expressed as number and percentage. For baseline comparisons between groups, the independent samples *t*-test was used for continuous variables, and the chi-square or Fisher exact test was used for categorical variables.

Linear mixed-effects models were used to evaluate time-dependent group differences, including treatment group, time, and their interaction (group × time) as fixed effects and a random intercept for each individual. Additionally, to account for potential confounding due to baseline differences, the models were further adjusted for clinically relevant covariates including age, baseline HbA1c, smoking status, and coronary artery disease. These covariates were selected based on their clinical relevance and potential confounding effects on diastolic function. The group × time interaction term was considered the primary parameter for assessing differential temporal effects between treatment groups.

Given the non-randomized design, covariate-adjusted analyses and within-patient longitudinal comparisons were performed to mitigate the potential impact of baseline differences and selection bias.

In addition, the consistency of the findings was evaluated by comparing adjusted and unadjusted models, which yielded similar results, supporting the robustness of the analysis.

As a sensitivity analysis, repeated-measures analysis of variance (RM-ANOVA) was additionally performed for GLS, septal e′ velocity, E/e′ ratio, and IVRT. Normality was assessed using the Shapiro–Wilk test. Outliers were assessed by visual inspection of boxplots and standardized residuals. Post-hoc pairwise comparisons were adjusted using the Holm method. The consistency of RM-ANOVA findings with the primary linear mixed-effects models was evaluated to assess the robustness of the results.

RESULTS

Initial Clinical and Echocardiographic Features

The study included a total of 350 patients with T2D: 200 who started treatment with empagliflozin and 150 who started treatment with linagliptin.

The groups were similar in terms of age and gender distribution (age: 55.9 ± 6.8 vs. 54.7 ± 7.1 years; male proportion: 46% vs. 44%; $P > .05$ for both). The prevalence of hypertension and coronary artery disease did not differ significantly between the groups ($P > .05$); however, smoking was more frequent in the empagliflozin group ($P < .01$). Baseline HbA1c levels were significantly higher in the linagliptin group (7.71 ± 1.02 vs. 7.11 ± 0.97; $P < .001$).

At baseline echocardiographic evaluation, left ventricular EF was preserved in both groups but was statistically significantly higher in the empagliflozin group (61.9 ± 2.4 vs. 61.1 ± 2.5; $P = .001$). Among diastolic function parameters, IVRT and DT were longer in the empagliflozin group, whereas the E/e′ ratio was higher in the linagliptin group ($P < .01$ for all). Absolute GLS values were similar between groups at baseline (16.0 ± 1.0 vs. 16.3 ± 1.3; $P > .05$). Baseline clinical and echocardiographic characteristics are summarized in Table 1.

Changes Over Time and Intergroup Comparisons

During the follow-up period, significant changes were observed in diastolic function parameters and myocardial deformation measurements in both groups ($P < .001$ for all parameters for time effect). Overall longitudinal changes in myocardial deformation during follow-up are summarized in Figure 1. In linear mixed-effects models, the group × time interaction was significant for septal e′, E/e′ ratio, IVRT, and absolute GLS ($P < .001$ for all).

At follow-up, HbA1c levels decreased in both groups, and comparable glycemic control was achieved at 6 months, suggesting that differences in cardiac parameters were not solely attributable to glycemic effects.

In covariate-adjusted analyses including age, baseline HbA1c, smoking status, and coronary artery disease, the main findings remained robust. Detailed model outputs are provided in the Supplementary Material (Supplementary Table 1). Significant group × time interactions persisted for

Table 1. Baseline Clinical and Echocardiographic Characteristics

Variables	Empagliflozin (n = 200)	Linagliptin (n = 150)	*P*
Age (years)	55.9 ± 8.1	54.7 ± 7.9	.047
Male, n (%)	92 (46)	66 (44)	.792
Hypertension, n (%)	110 (55)	82 (55)	1.000
Smoking, n (%)	38 (19)	53 (35)	.0046
Coronary artery disease, n (%)	20 (10)	28 (19)	<.001
HbA1c (%)	7.11 ± 0.62	7.71 ± 0.68	<.001
LVEF (%)	61.9 ± 3.4	61.1 ± 3.2	.001
IVS (mm)	11.0 ± 1.2	10.8 ± 1.1	.096
LVEDD (mm)	47.6 ± 3.8	48.0 ± 3.6	.242
LVESD (mm)	28.0 ± 3.1	27.6 ± 3.0	.059
IVRT (ms)	108 ± 14	104 ± 13	.002
DT (ms)	225 ± 28	200 ± 26	<.001
Septal e′ (cm/s)	6.14 ± 1.02	6.06 ± 1.01	.616
E/e′	0.97 ± 0.21	1.18 ± 0.24	<.001
|GLS| (%)	16.0 ± 2.1	16.3 ± 2.0	.088

Data are presented as mean ± SD or number (percentage).
P values were calculated using the independent samples *t*-test for continuous variables and the chi-square test or Fisher's exact test, as appropriate, for categorical variables.
DT, deceleration time; GLS, global longitudinal strain; IVRT, isovolumetric relaxation time; HbA1c, glycated hemoglobin; LVEF, left ventricular ejection fraction; IVS, interventricular septum; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; IVRT, isovolumetric relaxation time; DT, deceleration time; septal e′, septal early diastolic mitral annular velocity; E/e′, ratio of early transmitral inflow velocity to early diastolic mitral annular velocity; GLS, global longitudinal strain.

GLS ($P < .001$), septal e′ ($P < .001$), E/e′ ratio ($P < .001$), and IVRT ($P < .001$), indicating that the observed differential temporal patterns between empagliflozin and linagliptin were independent of baseline differences.

As a sensitivity analysis, RM-ANOVA was additionally performed. The results were fully consistent with the primary linear mixed-effects models. Significant group × time interactions were observed for GLS ($F = 70.327$, $P < .001$), septal e′ velocity ($F = 84.649$, $P < .001$), E/e′ ratio ($F = 16.101$, $P < .001$), and IVRT ($F = 70.889$, $P < .001$) (Supplementary Table 2).

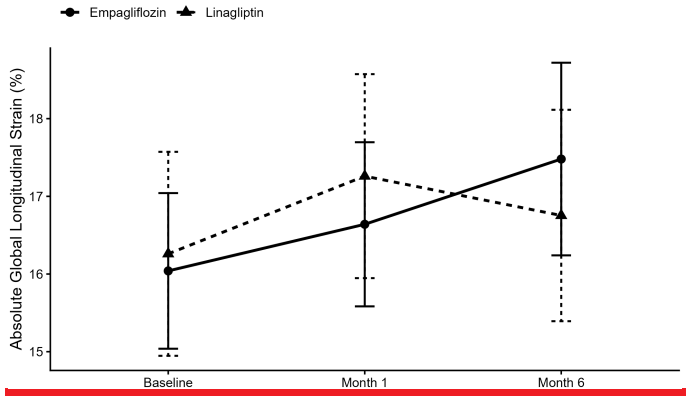

Figure 1. Temporal changes in absolute global longitudinal strain (GLS) during follow-up in patients treated with empagliflozin or linagliptin. Data are presented as mean ± SD at baseline, 1 month, and 6 months. A significant time × treatment interaction was observed, indicating differential longitudinal GLS responses between treatment groups. This interaction remained significant after adjustment for baseline differences. Higher absolute GLS values indicate better left ventricular systolic deformation.

Septal e′

In the empagliflozin group, septal e′ values increased by 0.96 ± 0.11 cm/s at 1 month and by 1.98 ± 0.11 cm/s at 6 months compared with baseline ($P < .001$ for both).

In the linagliptin group, a more limited increase was observed at month 1 (0.76 ± 0.12 cm/s; $P < .001$), while no significant change from baseline was detected at month 6 ($P > .05$). At 6 months, the difference between groups was statistically significant in favor of empagliflozin (–1.99 cm/s; $P < .001$) (Table 2, Table 3). The longitudinal changes in septal e′ velocity according to treatment group are illustrated in Figure 2A.

E/e′ Ratio

In both groups, the E/e′ ratio decreased significantly over time. This decrease was more pronounced in the linagliptin group; a reduction of −0.21 ± 0.02 was observed at 6 months compared with baseline ($P < .001$), whereas a decrease of −0.07 ± 0.02 was observed in the empagliflozin group ($P < .001$). In intergroup comparisons, the linagliptin group exhibited significantly lower E/e′ ratios at all time points ($P < .01$ for all) (Table 2). The longitudinal trends of the E/e′ ratio in both treatment groups are shown in Figure 2B.

Table 2. Between-Group Comparison of Baseline and 6-Month Changes in Echocardiographic and Metabolic Parameters

Parameters	Empagliflozin Baseline	Empagliflozin 6 months	Linagliptin Baseline	Linagliptin 6 months	*P* for group × time interaction
|GLS| (%)	16.04 ± 1.00	17.48 ± 1.08	16.26 ± 1.05	16.75 ± 1.10	<.001 *Pinteraction*
Septal e′ (cm/s)	6.14 ± 1.49	8.12 ± 1.52	6.06 ± 1.43	6.13 ± 1.46	<.001 *Pinteraction*
E/e′	0.97 ± 0.18	0.90 ± 0.17	1.18 ± 0.19	0.97 ± 0.18	<.001 *Pinteraction*
IVRT (ms)	108.5 ± 9.1	96.2 ± 10.4	104.4 ± 9.5	101.9 ± 10.1	<.001 *Pinteraction*

Data are presented as mean ± SD.
Between-group differences over time were assessed using linear mixed-effects models including fixed effects for treatment group, time, and group × time interaction, with a random intercept for each subject. *P* values represent the significance of the group × time interaction. Post-hoc pairwise comparisons were adjusted using the Holm method and were derived from estimated marginal means. All analyses were performed in 200 empagliflozin-treated and 150 linagliptin-treated patients with complete follow-up.
GLS, global longitudinal strain; IVRT, isovolumetric relaxation time.

Table 3. Within-Group Changes in Empagliflozin and Linagliptin

Parameters	Baseline	1 month	6 months	*P* (overall)
A (Empagliflozin)				
|GLS| (%)	16.04 ± 1.00	16.64 ± 1.06	17.48 ± 1.08	<.001
Septal e′ (cm/s)	6.14 ± 1.49	7.10 ± 1.38	8.12 ± 1.52	<.001
E/e′	0.97 ± 0.18	0.93 ± 0.18	0.90 ± 0.17	<.001
IVRT (ms)	108.5 ± 9.1	100.3 ± 11.5	96.2 ± 10.4	<.001
B (Linagliptin)				
|GLS| (%)	16.26 ± 1.05	17.26 ± 1.09	16.75 ± 1.10	<.001
Septal e′ (cm/s)	6.06 ± 1.43	6.82 ± 1.40	6.13 ± 1.46	<.001
E/e′	1.18 ± 0.19	1.10 ± 0.18	0.97 ± 0.18	<.001
IVRT (ms)	104.4 ± 9.5	101.0 ± 10.2	101.9 ± 10.1	<.001

Data are presented as mean ± SD.
Within-group changes over time in the empagliflozin group were assessed using linear mixed-effects models, including time as a fixed effect and a random intercept for each subject.
Post-hoc comparisons were performed using estimated marginal means with Holm adjustment for multiple comparisons.
P values represent comparisons of follow-up time points (month 1 and month 6) vs. baseline.
Within-group changes over time in the linagliptin group were evaluated using linear mixed-effects models including time as a fixed effect and a random intercept for each subject.
Post-hoc comparisons were conducted using estimated marginal means with Holm adjustment for multiple comparisons.
P values represent comparisons of follow-up time points (month 1 and month 6) versus baseline.
GLS, global longitudinal strain; IVRT, isovolumetric relaxation time.

Isovolumetric Relaxation Time and Deceleration Time

A significant reduction in IVRT and DT values was observed in the empagliflozin group. Isovolumetric relaxation time decreased by −12.3 ± 0.5 ms at 6 months compared with baseline in the empagliflozin group ($P < .001$), whereas a more limited reduction of −2.5 ± 0.6 ms was observed in the linagliptin group ($P < .01$). At 6 months, the between-group difference in IVRT was statistically significant in favor of empagliflozin ($P < .001$) (Table 2).

Global Longitudinal Strain

Absolute GLS values improved over time in both groups. In the empagliflozin group, absolute GLS increased from 16.0 ± 1.0 at baseline to 17.5 ± 1.2 at 6 months ($P < .001$). In the linagliptin group, although a more pronounced improvement was observed at 1 month (17.3 ± 1.3), this effect was partially attenuated at 6 months (16.8 ± 1.4). The pattern of GLS change over time differed significantly between groups, as reflected by a significant group × time interaction ($P < .001$) (Figure 1).

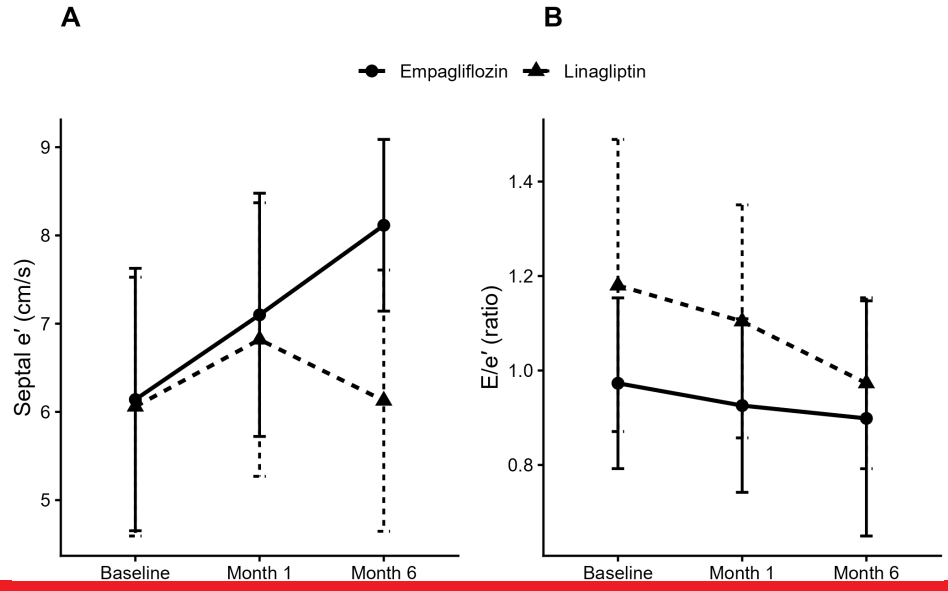

Figure 2. Longitudinal changes in diastolic function parameters during follow-up according to treatment group. (A) Septal early diastolic mitral annular velocity (septal e′). (B) Ratio of early mitral inflow velocity to septal mitral annular velocity (E/e′). Values are presented as mean ± SD at baseline, 1 month, and 6 months. Empagliflozin treatment was associated with greater improvement in septal e′, whereas a more pronounced reduction in E/e′ was observed with linagliptin, reflecting differential effects on left ventricular diastolic function over time. These findings remained consistent in covariate-adjusted analyses. e′, early diastolic mitral annular velocity; E/e′, ratio of early mitral inflow velocity to mitral annular early diastolic velocity.

Summary of Results

In summary, empagliflozin treatment was associated with a more pronounced and sustained improvement in diastolic relaxation parameters (septal e′, IVRT, and DT) and absolute GLS, whereas linagliptin treatment exerted a stronger effect on the E/e′ ratio, reflecting left ventricular filling pressures. These differential response patterns suggest treatment-specific effects on the underlying cardiac phenotype.

DISCUSSION

The findings of this study show that empagliflozin and linagliptin have time-dependent but distinct effects on left ventricular diastolic function and myocardial deformation parameters in patients with T2D. Although improvements in diastolic function parameters and GLS measurements were observed in both treatment arms during the follow-up period, the significant group × time interaction for septal e′, E/e′, IVRT, and absolute GLS suggests that these changes are not solely time-dependent and that the antidiabetic agent used is a determining factor in the direction and magnitude of the cardiac response.

Importantly, these findings remained consistent after adjustment for baseline differences, including age, HbA1c, smoking status, and coronary artery disease, supporting the robustness of the observed treatment-specific temporal patterns.

Baseline differences between groups, particularly in HbA1c levels, smoking status, and coronary artery disease prevalence, should be considered when interpreting the findings, although covariate-adjusted analyses demonstrated consistent results. Importantly, these variables were included in the adjusted mixed-effects models, and the primary findings remained robust after adjustment. Although stable coronary artery disease was included in the study population, it was incorporated as a covariate in the adjusted statistical models and did not materially affect the primary findings. Furthermore, similar results were observed in both adjusted and unadjusted analyses, further supporting the robustness of the findings.

In particular, the empagliflozin group showed a more pronounced and sustained increase in GLS along with early and progressive improvement in diastolic relaxation, while the linagliptin group featured a more significant decrease in the E/e′ ratio, reflecting filling pressures. These differing response profiles may be related to the specific and partially divergent effects of SGLT2 inhibitors and DPP-4 inhibitors on myocardial energy metabolism, preload/afterload balance, interstitial fibrosis, and microvascular function.

However, given the observational and non-randomized nature of the study, these findings should be interpreted with caution, and causal inferences cannot be definitively established.

In this context, the study observed significant changes in both diastolic function and myocardial deformation parameters in T2D patients treated with empagliflozin and linagliptin during a 6-month follow-up period. The most important finding is that the group × time interaction was significant for septal e′, E/e′, and IVRT, and the improvement pattern in absolute GLS diverged between the 2 treatment arms. These results suggest that antidiabetic treatments may affect cardiac phenotype through different mechanisms.[15]

The strong effect of SGLT2i on HF endpoints has been demonstrated with empagliflozin in the HFrEF population; one of the key explanations is that this class reduces hemodynamic overload and modulates congestion via the cardiac-renal axis.[3] The clinical benefits reported with empagliflozin in HFpEF have also made the mechanisms that may affect diastolic function and filling pressures more visible.4 In line with this clinical framework, the data showed a more pronounced increase in septal e′, particularly in the early phase, and shortening of IVRT in the empagliflozin arm, which presented a pattern consistent with improvement in the relaxation phase and an increase in relaxation rate.[16] It is suggested that SGLT2i's effects on microvascular function, intracellular sodium–calcium balance, and mitochondrial efficiency may improve diastolic relaxation and deformation parameters.[6,17]

In the linagliptin group, a more significant decrease in the E/e′ ratio was observed, which may indicate a potential advantage in terms of filling pressures. While cardiovascular safety has been well established,[9] the extent to which these echocardiographic improvements translate into meaningful clinical outcomes remains uncertain, particularly in the absence of hard clinical endpoints in the present study.

When evaluated in terms of GLS, the improvement observed in absolute GLS values in both groups is consistent with the early and modifiable nature of diabetic myocardial dysfunction.[11] However, the divergence of the change pattern over time into 2 groups suggests that the effects of empagliflozin and linagliptin on myocardial deformation cannot be reduced to the same biological pathway.

There are observational/medium-scale studies reporting improvements in deformation parameters in the short-to-medium term in SGLT2i through reduction in preload/afterload and regression of interstitial edema.[18,19] On the DPP-4i side, the data are more heterogeneous, with some studies reporting limited or neutral changes in strain parameters.[20]

In the study, the significant change in DT throughout the follow-up period and the significant signal it gave in terms of group × time interaction emphasize that diastolic filling dynamics should be considered dynamically, not only with relaxation/filling pressure indicators but also with the time components of the transmitral flow pattern.[12] This concept is consistent with recent insights highlighting that the interpretation of left ventricular diastolic function may substantially vary depending on the specific diastolic indices used, underscoring the importance of a comprehensive and methodologically nuanced echocardiographic assessment.[21] This finding is clinically significant because symptom burden and exertional dyspnea in diabetic patients may sometimes be associated with decreased diastolic reserve while EF is preserved.[22]

From a clinical perspective, these findings may suggest that different antidiabetic agents could exert heterogeneous

effects on cardiac functional profiles; however, such interpretations should be considered hypothesis-generating and require confirmation in randomized controlled trials.

In conclusion, this prospective longitudinal study demonstrated that empagliflozin and linagliptin exert time-dependent but significantly different effects on left ventricular diastolic function and myocardial deformation parameters in patients with T2D.

While empagliflozin was associated with a more pronounced and sustained improvement in markers of diastolic relaxation and myocardial deformation, and linagliptin showed a greater effect on parameters reflecting filling pressures, these observations should be interpreted within the limitations of an observational design.

Further randomized and outcome-driven studies are needed to determine the clinical relevance of these differential effects, ideally incorporating clinical endpoints and multimodal imaging approaches to better define their translational significance.

Study Limitations

This study has some limitations. First, the non-randomized design of the study introduces the possibility of selection bias and limits causal inference. Second, a single-center design can limit the generalizability of the results. Third, no invasive hemodynamic measurements were performed; diastolic function was assessed using echocardiographic parameters. Fourth, the study's primary endpoints did not include clinical events (such as hospitalization or mortality due to HF) but focused primarily on echocardiographic phenotyping.

During the follow-up period, dose adjustments or discontinuation of concomitant treatments were minimized using exclusion criteria, but could not be completely ruled out. However, the prospective longitudinal design, the evaluation with serial speckle-tracking echocardiography in the same patients, and the linear mixed-effects model approach based on group × time interaction enhance the methodological power of the study in revealing treatment-specific cardiac response patterns. Finally, although covariate-adjusted analyses were performed, residual confounding related to non-randomized treatment allocation cannot be completely excluded.

CONCLUSION

This prospective longitudinal study demonstrated that empagliflozin and linagliptin exert time-dependent but distinct effects on left ventricular diastolic function and myocardial deformation parameters in patients with T2D. Although improvements in diastolic function parameters and absolute GLS values were observed in both treatment arms, the significant group × time interaction detected for septal e′, E/e′, IVRT, and GLS suggests that this improvement is related to the specific cardiac response profiles of the antidiabetic agents used. Empagliflozin treatment was associated with a more pronounced and sustained improvement pattern, particularly in indicators of diastolic relaxation and myocardial deformation, while linagliptin treatment showed a more significant effect on parameters reflecting filling pressures.

These findings should be considered hypothesis-generating, and further randomized controlled trials with clinical endpoints are required to determine their clinical relevance.

Ethics Committee Approval: This study was approved by the Ethics Committee of Antalya Training and Research Hospital (Approval No: 2019-272, Date: 12 September 2019).

Informed Consent: Written informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – O.K.K., G.K.; Design – O.K.K., G.K.; Supervision – O.K.K.; Resources – O.K.K., G.K.; Materials – O.K.K., G.K.; Data Collection and/or Processing – O.K.K., G.K.; Analysis and/or Interpretation – O.K.K., G.K.; Literature Search – O.K.K., G.K.; Writing – O.K.K.; Critical Review – G.K.

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Supplementary Table 1. Group × Time Interaction Results from Linear Mixed-Effects Models

Outcome	Model	F value	*P*
GLS	Adjusted	70.33	<0.001
Septal e′	Adjusted	84.65	<0.001
E/e′	Adjusted	16.10	<0.001
IVRT	Adjusted	70.89	<0.001

Group × time interaction terms derived from linear mixed-effects models adjusted for age, baseline HbA1c, smoking status, and coronary artery disease. Results were consistent across adjusted and unadjusted models, supporting the robustness of the findings

Supplementary Table 2. Group × Time Interaction Results from Repeated-Measures ANOVA (Sensitivity Analysis)

Outcome	Group × Time Interaction F value	*P*
GLS	70.327	<0.001
Septal e′	84.649	<0.001
E/e′	16.101	<0.001
IVRT	70.889	<0.001

Group × time interaction terms derived from repeated-measures ANOVA models. Results were fully consistent with the primary linear mixed-effects models, supporting the robustness of the findings.