

Effects of Tenueligliptin on Left Ventricular Function in Patients with Type 2 Diabetes

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ABSTRACT

Introduction: Tenueligliptin, a cost-effective gliptin widely used in India, has shown promising effects on glycemic control, but its impact on left ventricular (LV) function remains under-explored. This study aimed to evaluate the effects of tenueligliptin on LV function in patients with type 2 diabetes (T2D). **Methods:** This prospective, single-center study enrolled 60 T2D patients with glycated hemoglobin (HbA1c) $\leq 7.5\%$, excluding those with pre-existing cardiac or severe renal/hepatic conditions. Tenueligliptin 20 mg daily was added to their existing therapy. Clinical, biochemical, and echocardiographic evaluations were conducted at baseline and after 3 months. Statistical analysis was performed using SPSS version 17.0. **Results:** Sixty patients (33 males) were able to complete the 3-month study with mean age of 48.86 ± 10.91 years. Mean HbA1c significantly reduced from $6.84 \pm 0.42\%$ to $6.22 \pm 0.29\%$ ($p < 0.01$), and mean fasting plasma glucose also reduced significantly from 116.2 ± 14.2 mg/dL to 104.2 ± 20.4 mg/dL ($p < 0.01$). Left ventricular ejection fraction improved from $58.6 \pm 4.0\%$ to $59.6 \pm 3.8\%$ ($p = 0.003$), and E-wave velocity increased slightly ($p = 0.049$). The proportion of patients with normal diastolic function increased significantly from 30% to 56% ($p < 0.02$, Wilcoxon signed-rank test). No significant changes were observed in body weight, blood pressure, or lipid parameters. A mild but significant reduction in eGFR was noted from 92.98 ± 13.7 to 90.70 ± 14.0 mL/min/1.73 m²; $p < 0.001$. A significant negative correlation was found between HbA1c and E/A ratio ($r = -0.407$, $p = 0.001$). **Conclusion:** Tenueligliptin significantly improved glycemic control and modestly enhanced LV systolic and diastolic functions in T2D patients over 3 months.

Keywords: Tenueligliptin, type 2 diabetes, diastolic dysfunction, left ventricular function, DPP-4 inhibitors, cardiovascular effects

Dipeptidyl peptidase-4 inhibitors (DPP-4is) are oral antihyperglycemic medications that inhibit activity of the DPP-4 and prevent degradation and modestly increasing endogenous glucagon-like peptide-1 (GLP-1) activity and improving glucose regulation. DPP-4is are generally well-tolerated, weight neutral and have minimal or no risk of hypoglycemia¹. Sitagliptin, linagliptin, vildagliptin, saxagliptin, tenueligliptin, alogliptin, and evogliptin are various DPP-4is

available for type 2 diabetes (T2D) treatment in India. Among them, tenueligliptin was introduced in India in year 2015 as a cheaper option when other gliptins were relatively costly. Japan was the first market where tenueligliptin received regulatory approval and was launched in Japan in year 2012 by Mitsubishi Tanabe Pharma for the treatment of T2D. It is now approved in several other countries including South Korea, Argentina, Thailand, and India. It has gained popularity in Asia and parts of South America due to its affordability and efficacy. The drug is currently in early stages of regulatory review or pre-registration in countries like China and Indonesia. However, it has not yet been approved by major western regulatory agencies such as the US Food and Drug Administration (FDA) or the European Medicines Agency, although clinical trials are ongoing in these regions².

Being available since May 2015, tenueligliptin holds a dominant position in India's gliptin market, accounting for a significant share with over ₹500 crore in annual sales, largely due to its affordability compared to other DPP-4is. It became widely popular after patent expiries

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allowed multiple brands to enter the market at low cost. Globally, however, teneligliptin's market share is more modest, estimated at around 5% between 2018 and 2021, with its growth constrained by limited regulatory approvals and increasing competition from generic versions of other gliptins like sitagliptin^{2,3}.

DPP-4is are one of important molecule in T2D management and may offer cardiovascular (CV) benefits, with increasing global research focused on incretin-based therapy and CV safety⁴. CV studies suggest no increased coronary risk but indicate a potential link between certain DPP-4is and heart failure. DPP-4 levels correlate with heart failure severity, and inhibition has shown benefits in ventricular function and remodeling in diabetic cardiomyopathy models⁵⁻⁸. However, the extent to which these effects are GLP-1-mediated remains unclear, and long-term CV safety data for DPP-4is and GLP-1 analogs are still limited. Several studies have evaluated the CV effects of DPP-4is in patients with T2D. Sitagliptin, examined in multiple studies, showed benefits such as improved diastolic function, attenuation of cardiac remodeling, and myocardial performance enhancement, with no increased CV risk in TECOS study⁹. However, saxagliptin (SAVOR-TIMI 53) was linked to higher hospitalization rates for heart failure¹⁰. It is suggested that prolonged diabetes duration (≥ 4 years) is linked to left ventricular (LV) diastolic dysfunction, independent of hypertension or coronary artery disease¹¹. Studies on linagliptin, alogliptin, and teneligliptin suggest they are generally safe from a CV standpoint. In a 6.3-year trial, the CAROLINA randomized clinical trial, of over 6,000 people with early T2D and high CV risk, linagliptin was as effective as glimepiride in preventing major CV events, with a much lower risk of hypoglycemia¹². In the EXAMINE trial, conducted among people with T2D and recent acute coronary syndrome who were on metformin and sulfonylurea, the addition of alogliptin significantly reduced glycated hemoglobin (HbA1c) and was well tolerated over 18 months. Although hospitalizations for heart failure were slightly higher, the difference was not statistically significant, and alogliptin was associated with rates of major adverse cardiovascular events comparable to placebo¹³.

Limited data exist on teneligliptin's cardiac safety, with only one study indicating potential benefits on ventricular diastolic function, warranting further research. In small studies, teneligliptin, demonstrated improvements in LV function, endothelial function, and reduction of adverse CV events. However, teneligliptin is linked to QTc prolongation, requiring caution when combined

with other QTc-prolonging drugs. In this study, we aimed to assess the effects of treatment with teneligliptin on LV function in patients with T2D.

METHODS

Study Design

This prospective, single-center study was conducted on 60 patients in the medicine and endocrine clinic of our institute in patients with T2D.

Inclusion and Exclusion Criteria

The patients having T2D with HbA1c levels $\leq 7.5\%$ were included in the study.

The exclusion criteria for the study included the use of incretin-based drugs at baseline, use of insulin therapy, chronic atrial fibrillation, recent intervention for coronary artery disease within 4 weeks or during the registration period, and symptomatic heart failure classified as New York Heart Association (NYHA) classes II, III, or IV. Additionally, patients with other endocrine and gastrointestinal disorders, those with past history of pancreatitis, severe renal dysfunction (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m²) or hepatic dysfunction (Child-Pugh score ≥ 10), active malignancy, or type 1 diabetes (T1D) were also excluded from the study.

Ethical Consideration

The study was approved by Institutional Ethics Committee (IEC/Th/15/MED-05). A written informed consent was obtained from all participants before inclusion in the study.

Study Procedure

The patients meeting inclusion criteria were enrolled in the study. The clinical and demographic profile was recorded in a pre-designed proforma. It included detailed medical history, comprehensive physical examination, anthropometric measurements, and laboratory evaluations. The biochemical investigations of each participant were recorded at baseline and at 3 months while the patients were followed on a monthly basis during the study period. Investigations included a complete blood count, urine microalbumin, HbA1c, fasting blood glucose (FPG), lipid profile, liver and renal function tests, and electrocardiogram (ECG). The eGFR was calculated using serum creatinine, age, sex, and race via Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Echocardiographic assessments were performed using Simpson's method

by single experienced cardiologist. The key parameters measured included transmitral LV inflow velocity in the apical four chamber view by using pulsed-wave Doppler, the peak velocity of early E-waves (E) and late A-waves (A), deceleration time, the mitral annulus velocity ($\dot{e}$) was visualized using pulse wave Doppler imaging, the left atrial diameter, LV diastolic diameter (LVDD), and LV systolic diameter (LVSD) were calculated in the standard manner and LV ejection fraction (LVEF) was assessed.

Statistical Analysis

Statistical analysis was conducted using SPSS software version 17.0. Descriptive statistics, including frequencies, percentages, means, and standard deviations, were calculated for various variables. To compare the means of the same parameter within a single group at two time points, a paired Student's *t*-test was used, and *p*-values were obtained to determine statistical significance. For non-normally distributed data, the Wilcoxon signed-rank test was applied, considering a *p*-value of ≤ 0.05 as significant. Additionally, the Pearson correlation coefficient was calculated for two normally distributed variables.

RESULTS

A total of 83 patients were screened and finally 60 patients were enrolled in the study. Figure 1 shows the flowchart of the study. Among them, 33 were male and 27 were female, with a mean age of 48.86 ± 10.91 years. Tenueligiptin 20 mg was added to their baseline prescription, and they were followed for 3 months. Throughout the study, patients were asked to continue their other existing medications without any changes.

Effects of Tenueligiptin on Glycemic Parameters

The mean HbA1c decreased significantly from $6.84 \pm 0.42\%$ at baseline to $6.22 \pm 0.29\%$ after 3 months of adding tenueligiptin ($p < 0.01$). Similarly, the mean FPG decreased from 116.20 ± 14.24 mg/dL at baseline to 104.16 ± 20.41 mg/dL after 3 months of tenueligiptin treatment ($p < 0.01$), demonstrating a significant antihyperglycemic effect (Table 1).

Effects of Tenueligiptin on Echocardiographic Parameters

The echocardiographic assessment showed no significant change in mean left atrial diameter, which was 31.60 ± 6.16 mm at baseline and 31.53 ± 4.33 mm after 3 months of therapy ($p = 0.916$). The mean LVSD decreased slightly from 29.14 ± 5.54 mm to 28.46 ± 5.01 mm, and

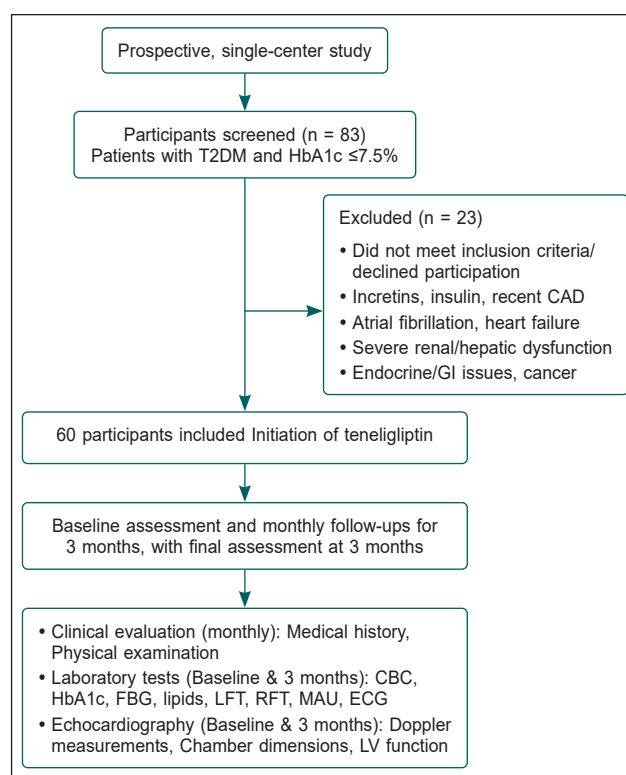


Figure 1. Flowchart of the study.

T2DM = Type 2 diabetes mellitus; HbA1c = Glycated hemoglobin; CAD = Coronary artery disease; GI = Gastrointestinal; CBC = Complete blood count; FPG = Fasting blood glucose; LFT = Liver function test; RFT = Renal function test; MAU = Microalbuminuria; ECG = Electrocardiogram; LV = Left ventricle.

the mean LVDD decreased from 44.01 ± 4.24 mm to 43.13 ± 6.97 mm after 3 months of treatment, but both changes were statistically insignificant ($p = 0.186$ and $p = 0.281$, respectively). The mean deceleration time remained unchanged, measuring 156.41 ± 32.31 ms at baseline and 156.78 ± 34.42 ms after 3 months ($p = 0.795$) (Table 1).

The mean LVEF increased significantly from $58.55 \pm 4.01\%$ at baseline to $59.55 \pm 3.80\%$ after 3 months ($p = 0.003$). The mitral inflow measurements showed a significant increase in mean E-wave velocity from 0.80 ± 0.095 m/s to 0.81 ± 0.094 m/s ($p = 0.049$). The mean A-wave velocity remained unchanged (0.78 ± 0.10 m/s, $p = 0.749$), while the E/A ratio showed a mild but statistically insignificant increase ($p = 0.436$) after 3 months (Table 1).

Diastolic function improved significantly after 3 months ($p < 0.02$, Wilcoxon signed-rank test). The proportion of patients with normal diastolic function increased from 30% (18/60) to 56% (34/60), while Grade 1 diastolic dysfunction decreased from 46% (28/60) to 28.33% (17/60) and Grade 2 diastolic dysfunction from 23% (14/60) to 15% (9/60).

Effects of Teneiglipitin on BMI, Blood Pressure, and Lipid Profile

The mean body mass index (BMI) remained unchanged after 3 months of teneiglipitin treatment (23.32 ± 1.34 to 23.29 ± 1.32 kg/m², $p = 0.537$), showing no statistically significant difference. Similarly, there was no significant change in mean systolic blood pressure (128.43 ± 12.80 mmHg to 128.40 ± 12.78 mmHg, $p = 0.321$) or diastolic blood pressure (85.60 ± 8.07 mmHg to 85.30 ± 7.29 mmHg, $p = 0.129$) from baseline after 3 months (Table 1).

Lipid profile parameters showed no significant changes after 3 months of teneiglipitin treatment. Serum high-density lipoprotein (HDL) (41.10 ± 7.59 mg/dL to 41.08 ± 7.46 mg/dL, $p = 0.837$), low-density lipoprotein

(LDL) (133.76 ± 22.23 mg/dL to 133.73 ± 22.17 mg/dL, $p = 0.659$), and triglycerides (161.76 ± 15.85 mg/dL to 161.73 ± 15.68 mg/dL, $p = 0.621$) remained statistically unchanged (Table 1).

Effects of Teneiglipitin on Renal Function

The mean eGFR showed a slight but significant decline from 92.98 ± 13.69 to 90.70 ± 14.01 mL/min^{1.73} m² ($p < 0.001$). However, the microalbumin/creatinine ratio remained unchanged from 50.08 ± 20.68 at baseline to 50.00 ± 20.75 after 3 months ($p = 0.531$) (Table 1).

Correlation Coefficient Between E/A Ratio and HbA1c

The scatter plot between E/A ratio and HbA1c showed a negative correlation. At baseline, the correlation was weak and insignificant ($r = -0.059$, $p = 0.657$) (Fig. 2a), while after 3 months, it became statistically significant ($r = -0.407$, $p = 0.001$), as shown in the graph (Fig. 2b).

Table 1. Effects of Teneiglipitin on Study Parameters

Parameter	At baseline (mean $\pm$ SD)	At 3 months (mean $\pm$ SD)	P value
HbA1c (%)	6.84 ± 0.42	6.22 ± 0.29	<0.01
FPG (mg/dL)	116.2 ± 14.24	104.16 ± 20.41	<0.01
LAD (mm)	31.6 ± 6.16	31.53 ± 4.33	0.916
LVSD (mm)	29.14 ± 5.54	28.46 ± 5.01	0.187
LVDD (mm)	44.01 ± 4.24	43.13 ± 6.97	0.281
Deceleration time (ms)	156.41 ± 32.31	156.78 ± 34.42	0.795
LVEF (%)	58.55 ± 4.01	59.55 ± 3.8	0.003
E (meter/sec)	0.8 ± 0.094	0.81 ± 0.094	0.049
A (meter/sec)	0.78 ± 0.1	0.78 ± 0.1	0.749
E/A ratio	1.03 ± 0.15	1.04 ± 0.11	0.436
SBP (mmHg)	128.43 ± 12.8	128.4 ± 12.78	0.321
DBP (mmHg)	85.6 ± 8.07	85.3 ± 7.29	0.129
HDL (mg/dL)	41.1 ± 7.59	41.08 ± 7.46	0.837
LDL (mg/dL)	133.76 ± 22.23	133.73 ± 22.17	0.659
TG (mg/dL)	161.76 ± 15.85	161.73 ± 15.68	0.621
BMI (kg/m ²)	23.32 ± 1.34	23.29 ± 1.32	0.537
eGFR (mL/min ^{1.73} m ²)	92.98 ± 13.69	90.7 ± 14.01	<0.001
Microalbumin: Creatinine ratio (mg/g)	50.08 ± 20.68	50 ± 20.75	0.531

HbA1c = Glycated hemoglobin; FPG = Fasting plasma glucose; LAD = Left atrial diameter; LVSD = Left ventricular systolic diameter; LVDD = Left ventricular diastolic diameter; LVEF = Left ventricular ejection fraction; E = Early diastolic filling velocity; A = Atrial contraction velocity; E/A ratio: Ratio of early to atrial filling velocities; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; HDL = High-density lipoprotein; LDL = Low-density lipoprotein; TG = Triglycerides; BMI = Body mass index; eGFR = Estimated glomerular filtration rate.

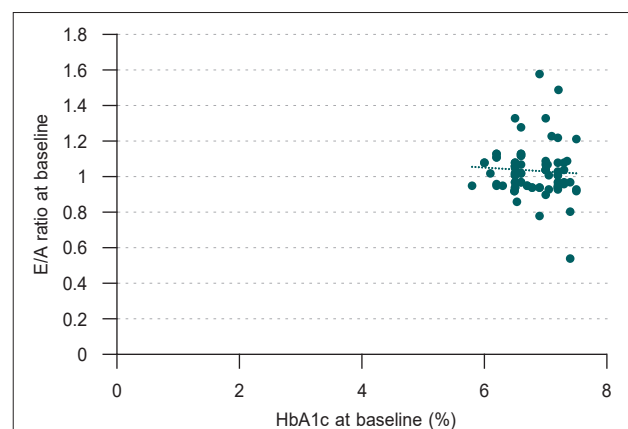


Figure 2a. Correlation coefficient between E/A ratio and HbA1c at baseline.

HbA1c = Glycated hemoglobin; E/A ratio: Ratio of early to atrial filling velocities.

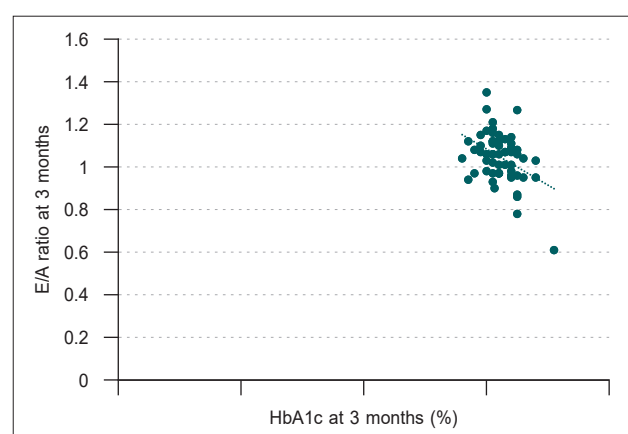


Figure 2b. Correlation coefficient between E/A ratio and HbA1c at 3 months.

HbA1c = Glycated hemoglobin; E/A ratio: Ratio of early to atrial filling velocities.

DISCUSSION

This prospective study on 60 patients with T2D assessed the effects of teneligliptin over 3 months. Significant improvements were observed in glycemic control, with reductions in HbA1c and FPG. Echocardiographic parameters showed a modest but significant improvement in LVEF and diastolic function, though most structural cardiac parameters remained unchanged. BMI, blood pressure, and lipid profile did not show significant changes, while renal function showed a slight but statistically significant decline in eGFR. A significant negative correlation was found between HbA1c and the E/A ratio after 3 months. DPP-4is, including teneligliptin, may offer cardioprotective benefits in T2D by increasing B-type natriuretic peptide (BNP) (1-32) bioavailability and incretin levels¹⁴. Teneligliptin inhibits NOD-like receptor protein 3 (NLRP3) inflammasome activation, providing anti-inflammatory effects and potential as a preventive treatment for diabetic cardiomyopathy¹⁵. Incretin-based agents, including teneligliptin, improve glycemic control, reduce inflammation, and lower CV risk with minimal hypoglycemia^{16,17}.

In a network meta-analysis of 58 studies involving over 21,000 patients conducted in 2025 found teneligliptin to provide strong glycemic control with no significant differences in serious adverse events were observed among DPP-4is, suggesting teneligliptin is both effective and safe¹⁸. Our study demonstrated modest antihyperglycemic effect of teneligliptin. After 3 months of treatment, the mean HbA1c decreased from $6.84 \pm 0.42\%$ to $6.22 \pm 0.29\%$ ($p < 0.01$), while the mean FPG levels dropped from 116.20 ± 14.24 mg/dL to 104.16 ± 20.41 mg/dL ($p < 0.01$), indicating a meaningful improvement in glycemic control. Another recent study by Ghosh et al also reported similar results, showing a significant reduction in HbA1c and FPG after 3 months of teneligliptin use, either as monotherapy or in combination with other oral antidiabetic medications, in the Indian population ($p < 0.0001$)¹⁹.

In our study, treatment with teneligliptin led to improvements in LV systolic and diastolic function. The mean LVEF increased from $58.55 \pm 4.01\%$ to $59.55 \pm 3.80\%$ after 3 months ($p = 0.003$), indicating a statistically significant improvement. Similarly, Hashikata et al observed an increase in LVEF from $62 \pm 6.5\%$ to $64.5 \pm 5.0\%$ ($p = 0.01$) in Japanese patients after 3 months of teneligliptin treatment¹⁷. Teneligliptin is known to significantly improve vascular endothelial function in T2D patients with acute coronary syndrome or high CV risk, as measured by flow-mediated dilation,

through mechanisms beyond increasing endothelial progenitor cells (EPCs), suggesting cardioprotective benefits through multiple mechanisms^{20,21}. However, despite the statistical significance, the clinical relevance of these changes remains uncertain, as the improvements in LVEF were relatively small, and echocardiographic measurements have an inherent degree of variability. These findings suggest that while teneligliptin may have a positive impact on cardiac function, further studies are needed to determine its true clinical significance in heart function improvement.

This study demonstrated that teneligliptin significantly improved LV diastolic function in T2D patients, with an increase in number of participants with normal diastolic function. In few studies, it has shown to enhance endothelial function and increased serum adiponectin levels, supporting its cardioprotective benefits. Previous studies, including those on sitagliptin (PROLOGUE study) and other DPP-4is, have shown similar improvements in diastolic function. Additionally, it may improve vascular endothelial function in high-risk patients through mechanisms beyond increasing circulating EPCs, highlighting its potential role in early-stage LV dysfunction treatment²². Our study found a negative correlation between improvement in LV diastolic dysfunction and glucose-lowering effects, as shown by the relationship between E/A and HbA1c at baseline ($r = -0.059$, $p = 0.567$) and after 3 months ($r = -0.407$, $p = 0.001$). Similar findings were reported by Hashikata et al, who observed no correlation between E/e' and HbA1c after 3 months of teneligliptin treatment. These results suggest that teneligliptin's cardioprotective effects may be independent of its glucose-lowering properties¹⁷.

This study found no statistically significant changes in systolic (128.43 ± 12.80 mmHg to 128.40 ± 12.78 mmHg, $p = 0.321$) or diastolic blood pressure (85.60 ± 8.07 mmHg to 85.30 ± 7.29 mmHg, $p = 0.129$) after 3 months of teneligliptin treatment, aligning with Zhang et al's meta-analysis, which reported no significant blood pressure changes with DPP-4is²³. Similarly, no significant changes were observed in lipid levels, including HDL (41.10 ± 7.59 mg/dL to 41.08 ± 7.46 mg/dL, $p = 0.837$), LDL (133.76 ± 22.23 mg/dL to 133.73 ± 22.17 mg/dL, $p = 0.659$), and triglycerides (161.76 ± 15.85 mg/dL to 161.73 ± 15.68 mg/dL, $p = 0.621$), consistent with findings from Hashikata et al's study. Furthermore, BMI remained unchanged (23.32 ± 1.34 kg/m² to 23.29 ± 1.32 kg/m², $p = 0.537$), suggesting teneligliptin has no significant impact on weight, which is supported by other previous studies as well¹⁷. This study observed a mild but statistically significant decrease in mean eGFR from 92.98 ± 13.69 to

90.70 ± 14.01 ($p < 0.001$) after 3 months of teneligliptin treatment. However, the microalbumin/creatinine ratio remained unchanged ($p = 0.531$). Previous research on DPP-4is have not clearly shown their such negative effect on renal function *in vivo* or *in vitro* models, making it difficult to determine the exact mechanism behind this observation⁶. Given the study's short follow-up duration and small sample size, further research is necessary to evaluate long-term renal outcomes²³.

This prospective, single-center study has several strengths, including systematic data collection, comprehensive clinical and laboratory evaluations, standardized echocardiographic techniques by a single experienced cardiologist all contributing to robust and reliable findings. However, its limitations include a small sample size, short follow-up duration, lack of a control group or randomization, and absence of cardiac biomarkers such as NT-proBNP or high-sensitivity troponins, which weaken the interpretation of modest LVEF changes, and may also restrict the generalizability of the results and the ability to draw definitive conclusions.

CONCLUSION

This study found that adding teneligliptin to existing oral antihyperglycemic medications in T2D patients significantly improved glycemic control and enhanced LV systolic and diastolic function. While eGFR showed a slight decline, other parameters, including blood pressure, lipid profile, and BMI remained unchanged. These findings suggest a potential cardioprotective role of teneligliptin in early-stage asymptomatic LV dysfunction. However, further larger multicenter studies are needed to confirm our findings.

KEY SUMMARY POINTS

Teneligliptin significantly improved glycemic control (HbA1c and fasting glucose) and modestly enhanced left ventricular systolic and diastolic function over 3 months in T2D patients without overt cardiovascular disease.

Diastolic function improved significantly, with a notable increase in patients achieving normal diastolic function (from 30% to 56%), and a negative correlation between HbA1c and E/A ratio was observed, suggesting possible cardioprotective effects beyond glycemic control.

No significant changes were found in BMI, blood pressure, or lipid profile, while eGFR declined slightly but significantly, warranting further research into renal safety with prolonged use.

Source(s) of Support: Nil.

Conflict of Interest: Nil.

Compliance with Ethics: The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Pt. BD Sharma University of Health Science, Rohtak, India (IEC/Th/15/MED-05).

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