

# Renal and Glycemic Outcomes with Linagliptin versus Vildagliptin as Add-On Therapy in Uncontrolled Type 2 Diabetes Mellitus: A Prospective Observational Study

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DOI: <https://doi.org/10.5281/zenodo.21960515>

Article Received: 21 July 2026, Accepted: 07 August 2026, Online First: 16 August 2026

## ABSTRACT

**Background:** Linagliptin and vildagliptin are commonly used dipeptidyl peptidase-4 (DPP-4) inhibitors, but direct real-world comparisons of renal and glycemic outcomes remain limited. This study compared the renal profile, glycemic response, and tolerability of these agents in adults with uncontrolled type 2 diabetes mellitus (T2DM). **Methods:** In this prospective observational cohort study, 100 adults with T2DM inadequately controlled on stable metformin monotherapy were allocated to linagliptin 5 mg once daily (n=50) or vildagliptin 50 mg twice daily (n=50), each added to metformin 500 mg twice daily. Clinical, glycemic, renal, hematological, lipid, hepatic, and adverse-event data were assessed at baseline, 2 months, and 6 months. **Results:** Baseline characteristics were comparable between groups. At 6 months, fasting plasma glucose was  $105.42 \pm 12.52$  mg/dL with linagliptin and  $108.10 \pm 10.23$  mg/dL with vildagliptin (between-group  $p=0.472$ ); postprandial glucose was  $151.25 \pm 10.25$  versus  $152.32 \pm 12.32$  mg/dL ( $p=0.289$ ); and HbA1c was  $6.01 \pm 0.21\%$  versus  $6.12 \pm 0.41\%$  ( $p=0.396$ ). Renal indices also remained similar at 6 months, including serum creatinine ( $0.89 \pm 0.38$  versus  $0.89 \pm 0.79$  mg/dL;  $p=0.685$ ) and estimated glomerular filtration rate ( $81.23 \pm 9.45$  versus  $81.36 \pm 10.23$  mL/min/1.73 m<sup>2</sup>;  $p=0.814$ ). Adverse events were mild and did not differ significantly between treatments. **Conclusions:** Linagliptin and vildagliptin produced comparable short-term glycemic improvement when added to metformin, with broadly stable renal indices and similar tolerability over 6 months. Larger controlled studies with longer follow-up are needed to define their comparative long-term renal safety.

**Keywords:** diabetes mellitus, type 2; dipeptidyl peptidase-4 inhibitors; linagliptin; vildagliptin; metformin; renal function; estimated glomerular filtration rate; glycated hemoglobin

## 1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) continues to expand worldwide. The 11th edition of the International Diabetes Federation Diabetes Atlas estimated that 589 million adults aged 20–79 years were living with diabetes in 2024 and projected an increase to 853 million by 2050 [1]. Persistent hyperglycemia increases the risk of microvascular and cardiorenal complications, making sustained but individualized glycemic treatment a central goal of care [2,3].

Metformin remains a commonly used initial therapy, but many patients require an additional agent when individualized glycemic targets are not achieved. Dipeptidyl peptidase-4 (DPP-4) inhibitors are oral

incretin-based drugs that improve glucose-dependent insulin secretion and suppress inappropriate glucagon secretion. They are generally weight neutral and have a low intrinsic risk of hypoglycemia, although contemporary guidelines place them below agents with established cardiovascular or kidney outcome benefits when such comorbidities are present [3,4].

Linagliptin and vildagliptin differ in important practical respects. Linagliptin is eliminated predominantly through nonrenal pathways and is widely used without dose adjustment across levels of kidney function, whereas vildagliptin generally requires dose consideration in moderate or severe renal impairment. This pharmacologic distinction makes

direct comparative evidence clinically relevant, particularly in settings where renal monitoring or access to specialized care may be limited [5,6].

Recent comparative and modeling studies suggest broadly similar glycemic efficacy for linagliptin and vildagliptin, with some differences according to baseline renal function, comorbidity burden, and modeling approach [5–7]. Meta-analyses of DPP-4 inhibitors indicate possible reductions in albuminuria but little consistent effect on estimated glomerular filtration rate (eGFR) or serum creatinine [8,9,11,13]. Nevertheless, head-to-head real-world evidence comparing renal indices and tolerability between linagliptin and vildagliptin remains limited. The present study therefore compared renal, glycemic, and safety outcomes over 6 months in adults with uncontrolled T2DM receiving either agent as add-on therapy to stable metformin.

## 2. MATERIALS AND METHODS

### 2.1 Study design and setting

This was a prospective observational cohort study conducted in the Department of Pharmacology in collaboration with the Department of Internal Medicine at Darbhanga Medical College and Hospital, Laheriasarai, Bihar, India. Participants were recruited from the Internal Medicine outpatient department. The overall study period encompassed protocol development, participant recruitment, data collection, evaluation, and presentation over 12 months.

### 2.2 Participants

Adults aged 18 years or older of either sex were eligible if they had T2DM, had been taking a stable dose of metformin 500 mg twice daily for at least 3 months, remained inadequately controlled on metformin alone, and had HbA1c of at least 7.5%. Diagnosis required any two of the following: fasting plasma glucose  $\geq 126$  mg/dL, HbA1c  $\geq 6.5\%$ , or 2-hour postprandial glucose  $\geq 200$  mg/dL [2].

Key exclusion criteria were type 1 diabetes; pregnancy or lactation; secondary diabetes; diabetic ketoacidosis or a hyperosmolar state during the preceding 3 months; moderate-to-severe chronic kidney disease; major cardiac, central nervous system, or gastrointestinal disease; uncontrolled major neuropsychiatric illness; alcohol or substance abuse or dependence; and acute or chronic pancreatitis.

## 3. RESULTS

### 3.1 Baseline characteristics

Of 110 planned participants, 100 completed the study and were analyzed: 50 receiving linagliptin plus metformin and 50 receiving vildagliptin plus metformin. Mean age was  $51.47 \pm 7.65$  years in the linagliptin group and  $52.14 \pm 8.21$  years in the vildagliptin group ( $p=0.789$ ). Men represented 64.0% and 60.0% of the groups, respectively ( $p=0.680$ ). Anthropometric measurements, diabetes duration, vital signs, hematological indices, baseline glycemic measures, renal indices, lipids, and liver function tests did not differ significantly between groups (Tables 1–10; Figures 1–10).

### 2.3 Sample size and treatment groups

The planned enrollment was 110 participants, allowing for an anticipated 10% dropout rate. Ten participants discontinued or were lost to follow-up, leaving 100 participants for analysis. Group A ( $n=50$ ) received linagliptin 5 mg once daily, and Group B ( $n=50$ ) received vildagliptin 50 mg twice daily. Both groups continued metformin 500 mg twice daily. Because the study was observational, treatment selection reflected routine clinical practice rather than random assignment.

### 2.4 Assessments and outcomes

Participants were evaluated at baseline, 2 months, and 6 months. The primary comparative focus was the renal profile, including blood urea, serum creatinine, eGFR, and serum uric acid. Estimated GFR was calculated using the Cockcroft–Gault formula. Secondary outcomes included fasting plasma glucose, postprandial plasma glucose, and HbA1c. Baseline evaluation also included anthropometry, clinical examination, hematological indices, lipid profile, and liver function tests. Blood urea nitrogen, electrolytes, and 24-hour urinary creatinine clearance were recorded as part of the study assessment schedule. Adverse events reported during follow-up were documented and compared between groups.

### 2.5 Statistical analysis

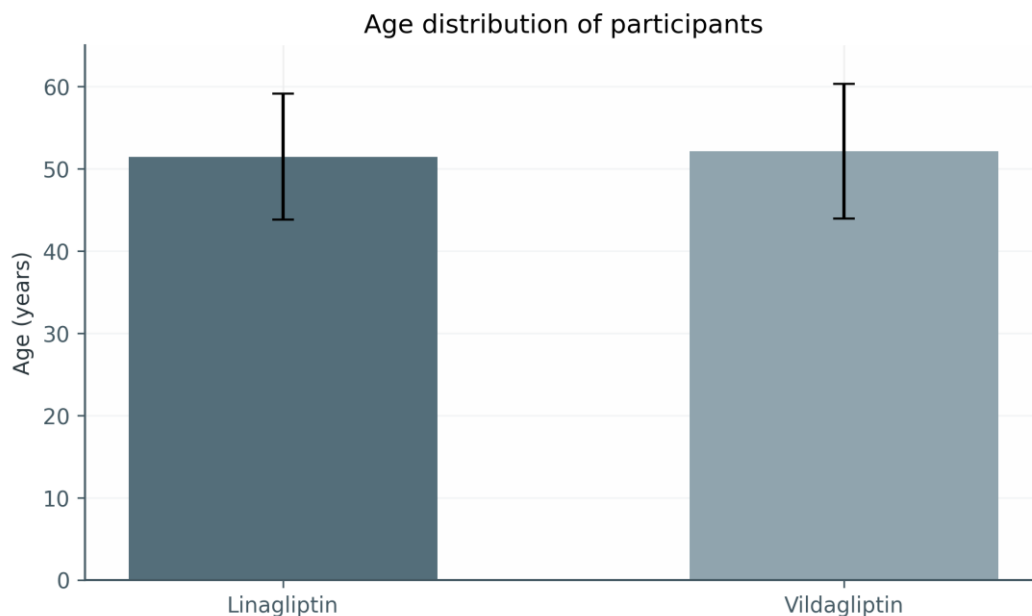
Categorical variables were compared using the chi-square test, and continuous variables were compared using Student's *t*-test. Repeated measurements over time were analyzed using repeated-measures analysis of variance or an appropriate nonparametric alternative, as applicable. A two-sided *p* value below 0.05 was considered statistically significant. Analyses were performed using SPSS version 20.

### 2.6 Ethics approval and consent

The study was approved by the Institutional Ethics Committee, Darbhanga Medical College, Laheriasarai (approval letter Ref. No. 271, dated 30 October 2023). The study was reviewed and approved at the committee meeting held on 30 October 2023. Written informed consent was obtained from all participants in Hindi or English. For participants unable to read or write, a witnessed thumb impression was used in accordance with the approved consent process.

**Table 1. Age distribution of study participants.**

| Parameter                  | Linagliptin (n=50) | Vildagliptin (n=50) | P value |
|----------------------------|--------------------|---------------------|---------|
| Age (years), mean $\pm$ SD | 51.47 $\pm$ 7.65   | 52.14 $\pm$ 8.21    | 0.789   |

**Figure 1. Age distribution of participants. Bars show mean values; error bars show SD.****Table 2. Sex distribution of study participants.**

| Sex    | Linagliptin (n=50), n (%) | Vildagliptin (n=50), n (%) | Total, n (%) |
|--------|---------------------------|----------------------------|--------------|
| Male   | 32 (64.0)                 | 30 (60.0)                  | 62 (62.0)    |
| Female | 18 (36.0)                 | 20 (40.0)                  | 38 (38.0)    |
| Total  | 50 (100.0)                | 50 (100.0)                 | 100 (100.0)  |

Note. Chi-square=0.16977;  $p=0.680$ .

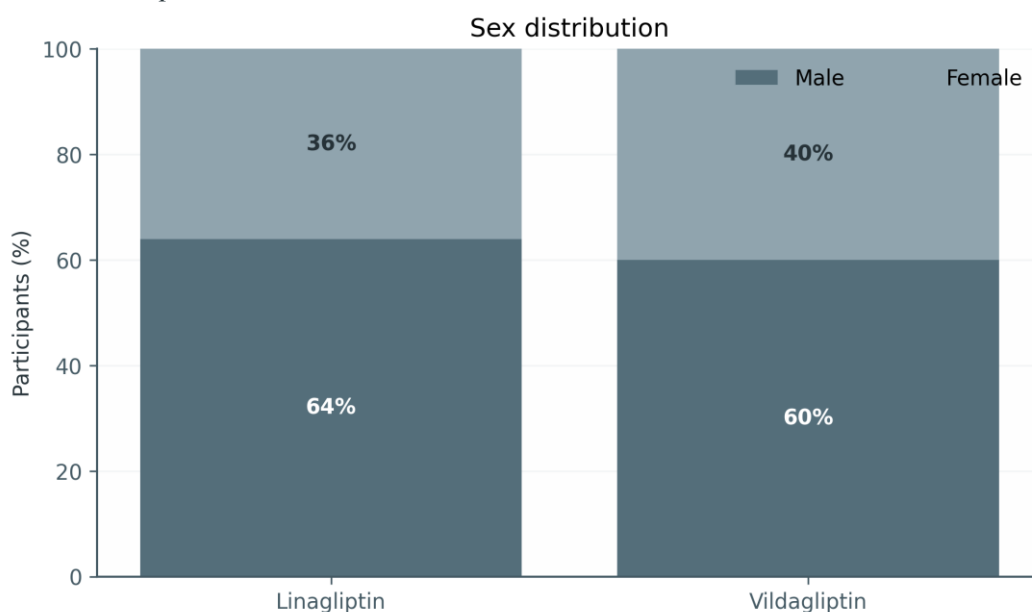
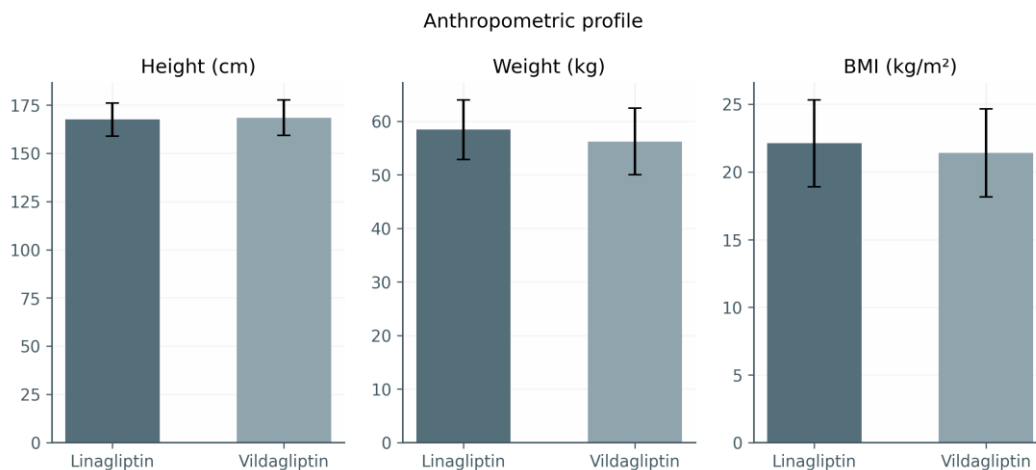
**Figure 2. Sex distribution by treatment group.**

**Table 3. Baseline anthropometric measurements.**

| Parameter                            | Linagliptin (n=50) | Vildagliptin (n=50) | P value |
|--------------------------------------|--------------------|---------------------|---------|
| Height (cm)                          | 167.45 ± 8.56      | 168.45 ± 9.22       | 0.412   |
| Weight (kg)                          | 58.45 ± 5.56       | 56.23 ± 6.22        | 0.398   |
| Body mass index (kg/m <sup>2</sup> ) | 22.12 ± 3.21       | 21.41 ± 3.25        | 0.897   |

Note. Values are mean ± SD.

**Figure 3. Baseline anthropometric measurements. Bars show mean values; error bars show SD.****Table 4. Duration of diabetes mellitus.**

| Duration  | Linagliptin (n=50), n (%) | Vildagliptin (n=50), n (%) |
|-----------|---------------------------|----------------------------|
| <1 year   | 14 (28.0)                 | 12 (24.0)                  |
| 1–5 years | 28 (56.0)                 | 31 (62.0)                  |
| >5 years  | 8 (16.0)                  | 7 (14.0)                   |

Note. Chi-square=0.37305; p=0.829.

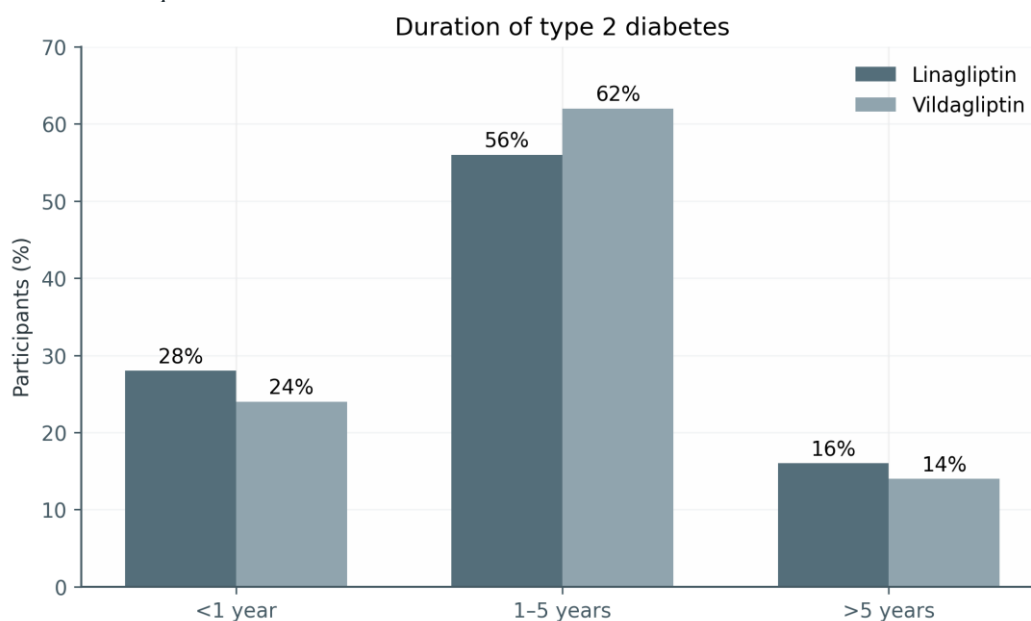
**Figure 4. Duration of type 2 diabetes by treatment group.**

**Table 5. Baseline clinical profile.**

| Parameter                       | Linagliptin (n=50) | Vildagliptin (n=50) | P value |
|---------------------------------|--------------------|---------------------|---------|
| Systolic blood pressure (mmHg)  | 129.41 ± 12.44     | 130.22 ± 10.41      | 0.345   |
| Diastolic blood pressure (mmHg) | 78.41 ± 8.74       | 78.45 ± 9.22        | 0.625   |
| Heart rate (beats/min)          | 74.22 ± 5.41       | 73.54 ± 4.36        | 0.741   |
| Respiratory rate (breaths/min)  | 17.45 ± 2.56       | 17.65 ± 3.24        | 0.521   |

*Note. Values are mean ± SD.*

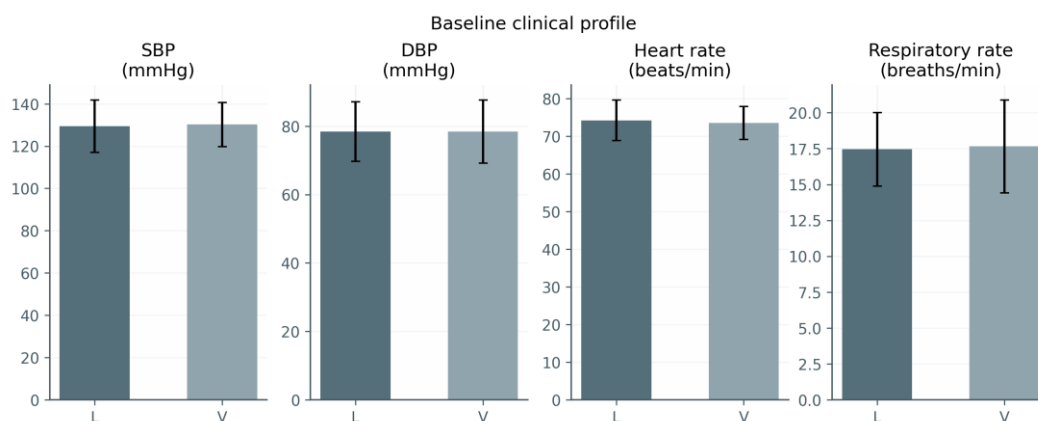


**Figure 5. Baseline clinical profile. L, linagliptin; V, vildagliptin. Bars show mean values; error bars show SD.**

**Table 6. Baseline hematological parameters.**

| Parameter                                | Linagliptin (n=50) | Vildagliptin (n=50) | P value |
|------------------------------------------|--------------------|---------------------|---------|
| Hemoglobin (g%)                          | 11.42 ± 2.34       | 11.25 ± 3.24        | 0.982   |
| Total leukocyte count (/cumm)            | 7984.25 ± 1245.23  | 7795.00 ± 1452.23   | 0.741   |
| Red blood cell count (million/cumm)      | 4.21 ± 0.48        | 4.17 ± 4.20         | 0.655   |
| Neutrophils (%)                          | 58.32 ± 7.81       | 57.45 ± 8.25        | 0.528   |
| Lymphocytes (%)                          | 34.21 ± 8.47       | 35.12 ± 8.47        | 0.636   |
| Eosinophils (%)                          | 3.78 ± 2.45        | 4.21 ± 2.88         | 0.234   |
| Monocytes (%)                            | 1.93 ± 1.14        | 1.84 ± 1.14         | 0.321   |
| Basophils (%)                            | 0.11 ± 0.31        | 0.12 ± 0.32         | 0.521   |
| Erythrocyte sedimentation rate (mm/hour) | 22.45 ± 8.45       | 21.45 ± 9.52        | 0.124   |

*Note. Values are mean ± SD. The vildagliptin RBC standard deviation is transcribed exactly as reported in the source dataset.*

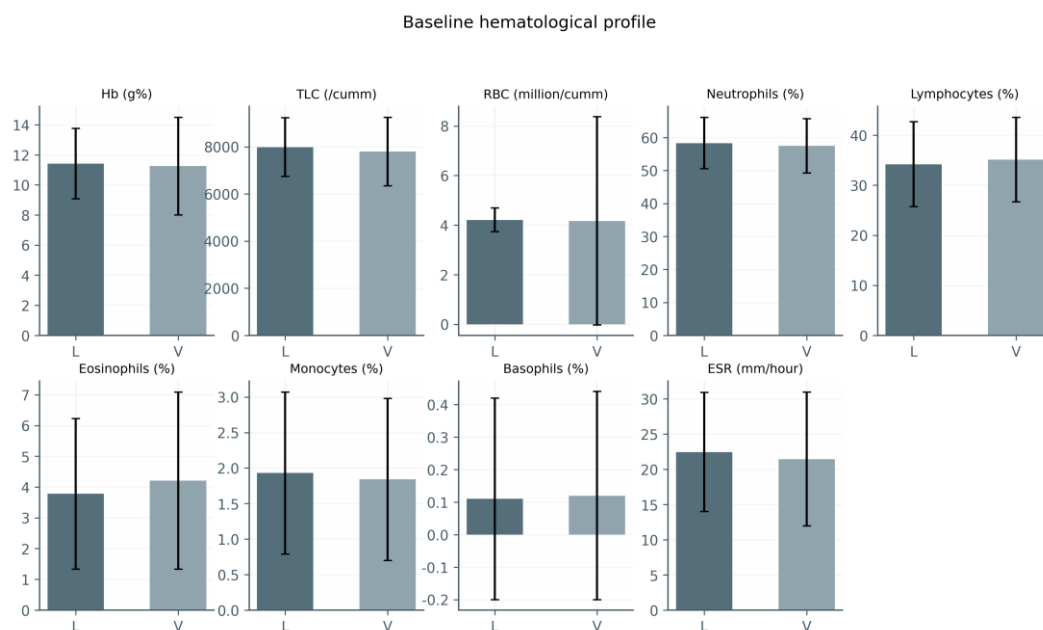


**Figure 6. Baseline hematological parameters. L, linagliptin; V, vildagliptin. Bars show mean values; error bars show SD.**

**Table 7. Baseline plasma glucose and HbA1c.**

| Parameter                           | Linagliptin (n=50) | Vildagliptin (n=50) | P value |
|-------------------------------------|--------------------|---------------------|---------|
| Fasting plasma glucose (mg/dL)      | 165.85 ± 14.21     | 166.42 ± 18.45      | 0.452   |
| Postprandial plasma glucose (mg/dL) | 245.12 ± 25.32     | 241.32 ± 21.45      | 0.094   |
| HbA1c (%)                           | 8.21 ± 1.23        | 8.01 ± 2.44         | 0.567   |

*Note. Values are mean ± SD.*

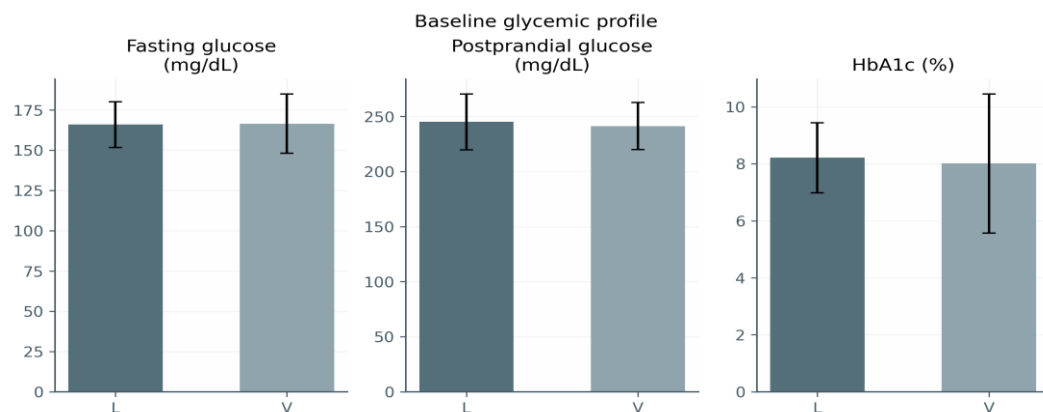


**Figure 7. Baseline glycemic profile. L, linagliptin; V, vildagliptin. Bars show mean values; error bars show SD.**

**Table 8. Baseline renal profile.**

| Parameter                                   | Linagliptin (n=50) | Vildagliptin (n=50) | P value |
|---------------------------------------------|--------------------|---------------------|---------|
| Blood urea (mg/dL)                          | 34.21 ± 7.12       | 32.45 ± 8.55        | 0.431   |
| Serum creatinine (mg/dL)                    | 0.84 ± 0.21        | 0.85 ± 0.12         | 0.741   |
| Estimated GFR (mL/min/1.73 m <sup>2</sup> ) | 82.19 ± 17.45      | 82.72 ± 18.41       | 0.674   |
| Serum uric acid (mg/dL)                     | 4.25 ± 1.27        | 4.32 ± 1.74         | 0.952   |

*Note. Values are mean ± SD.*

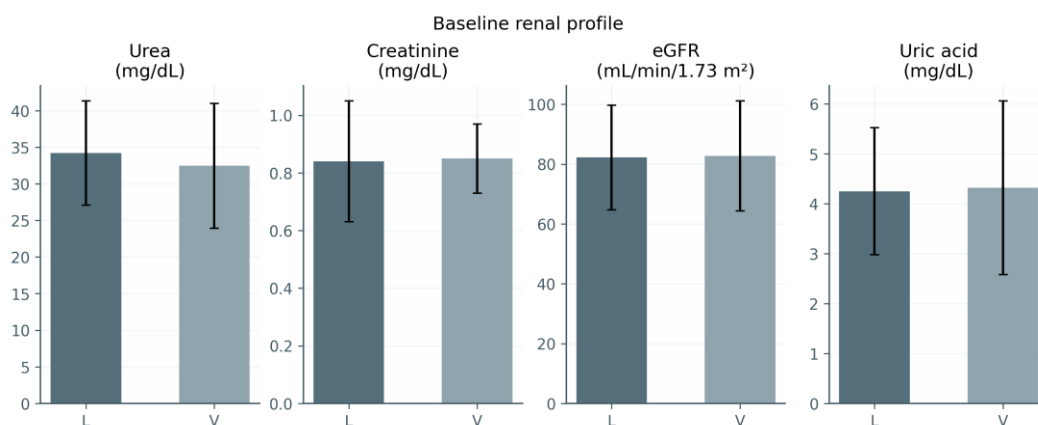


**Figure 8. Baseline renal profile.** L, linagliptin; V, vildagliptin. Bars show mean values; error bars show SD.

**Table 9. Baseline lipid profile.**

| Parameter                            | Linagliptin (n=50) | Vildagliptin (n=50) | P value |
|--------------------------------------|--------------------|---------------------|---------|
| Total cholesterol (mg/dL)            | 175.42 ± 32.45     | 176.23 ± 36.52      | 0.321   |
| Triglycerides (mg/dL)                | 148.56 ± 36.45     | 142.32 ± 32.45      | 0.415   |
| High-density lipoprotein (mg/dL)     | 52.41 ± 12.45      | 51.23 ± 13.22       | 0.369   |
| Low-density lipoprotein (mg/dL)      | 96.45 ± 31.22      | 97.45 ± 35.41       | 0.421   |
| Very-low-density lipoprotein (mg/dL) | 21.45 ± 4.12       | 22.32 ± 4.23        | 0.225   |

*Note. Values are mean ± SD.*

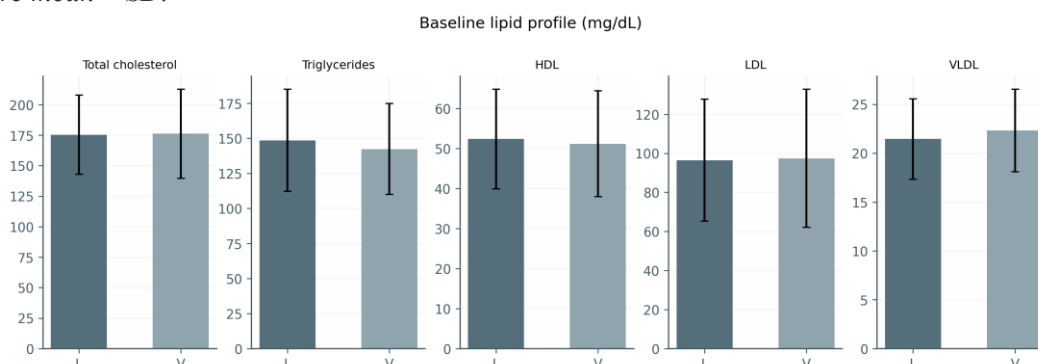


**Figure 9. Baseline lipid profile.** L, linagliptin; V, vildagliptin. Bars show mean values; error bars show SD.

**Table 10. Baseline liver function tests.**

| Parameter                  | Linagliptin (n=50) | Vildagliptin (n=50) | P value |
|----------------------------|--------------------|---------------------|---------|
| Total bilirubin (mg/dL)    | 0.81 ± 0.11        | 0.84 ± 0.14         | 0.123   |
| Direct bilirubin (mg/dL)   | 0.25 ± 0.09        | 0.22 ± 0.06         | 0.254   |
| SGPT (U/L)                 | 36.45 ± 5.23       | 37.45 ± 6.12        | 0.742   |
| SGOT (U/L)                 | 33.41 ± 4.23       | 32.65 ± 5.22        | 0.568   |
| Alkaline phosphatase (U/L) | 97.21 ± 13.45      | 98.45 ± 12.45       | 0.552   |
| Total protein (g/dL)       | 7.90 ± 1.22        | 7.80 ± 1.32         | 0.426   |
| Albumin (g/dL)             | 4.20 ± 1.14        | 4.00 ± 0.98         | 0.321   |

*Note. Values are mean ± SD.*

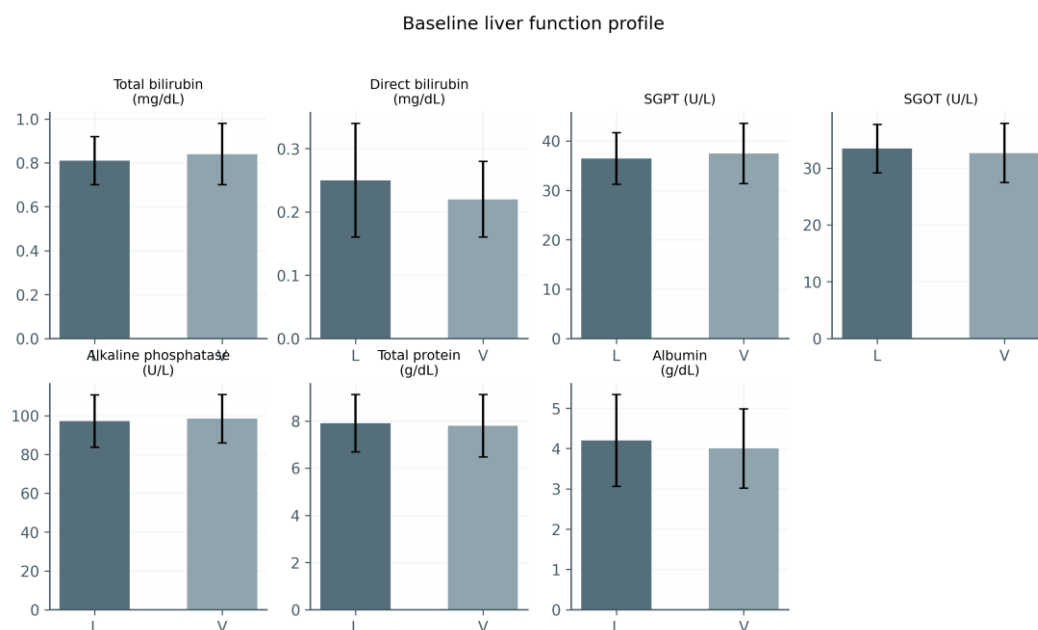


**Figure 10. Baseline liver function tests. L, linagliptin; V, vildagliptin. Bars show mean values; error bars show SD.**

### 3.2 Glycemic outcomes

Both treatments were followed by substantial within-group reductions in fasting plasma glucose, postprandial plasma glucose, and HbA1c at 2 and 6 months (all within-group  $p < 0.0001$ ). Between-group differences were not statistically significant at either follow-up. At 6 months, mean fasting glucose was  $105.42 \pm 12.52$  mg/dL with linagliptin and  $108.10 \pm 10.23$  mg/dL with vildagliptin ( $p = 0.472$ ); postprandial glucose was  $151.25 \pm 10.25$  versus  $152.32 \pm 12.32$  mg/dL ( $p = 0.289$ ); and HbA1c was  $6.01 \pm 0.21\%$  versus  $6.12 \pm 0.41\%$  ( $p = 0.396$ ) (Tables 11 and 12; Figures 11 and 12).

**Table 11. Glycemic response after 2 months.**

| Parameter                           | Linagliptin baseline | Linagliptin 2 months | Within-group P | Vildagliptin baseline | Vildagliptin 2 months | Within-group P | Between-group P |
|-------------------------------------|----------------------|----------------------|----------------|-----------------------|-----------------------|----------------|-----------------|
| Fasting plasma glucose (mg/dL)      | 165.85 ± 14.21       | 126.42 ± 19.25       | <0.0001        | 166.42 ± 18.45        | 123.45 ± 14.23        | <0.0001        | 0.891           |
| Postprandial plasma glucose (mg/dL) | 245.12 ± 25.32       | 168.25 ± 18.45       | <0.0001        | 241.32 ± 21.45        | 165.23 ± 23.45        | <0.0001        | 0.412           |
| HbA1c (%)                           | 8.21 ± 1.23          | 6.61 ± 1.12          | <0.0001        | 8.01 ± 2.44           | 6.45 ± 1.19           | <0.0001        | 0.339           |

*Note. Values are mean ± SD.*

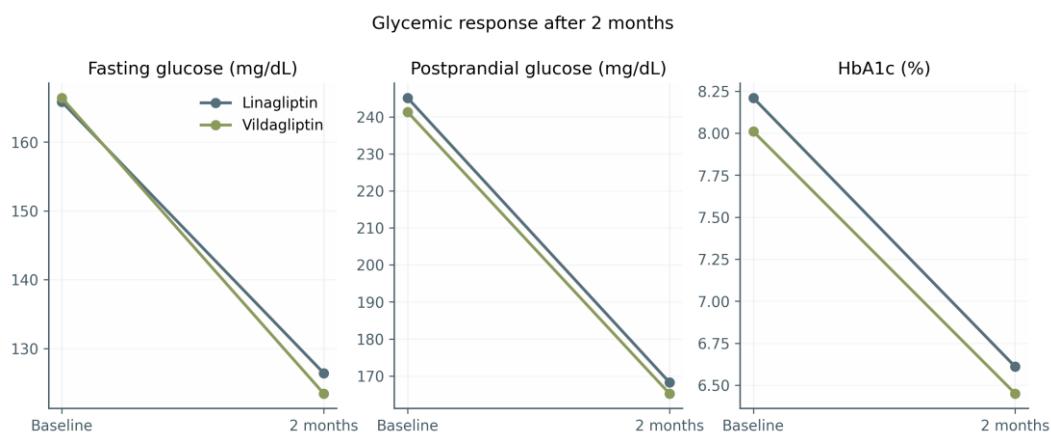


Figure 11. Glycemic response from baseline to 2 months.

Table 12. Glycemic response after 6 months.

| Parameter                           | Linagliptin baseline | Linagliptin 6 months | Within-group P | Vildagliptin baseline | Vildagliptin 6 months | Within-group P | Between-group P |
|-------------------------------------|----------------------|----------------------|----------------|-----------------------|-----------------------|----------------|-----------------|
| Fasting plasma glucose (mg/dL)      | 165.85 ± 14.21       | 105.42 ± 12.52       | <0.0001        | 166.42 ± 18.45        | 108.10 ± 10.23        | <0.0001        | 0.472           |
| Postprandial plasma glucose (mg/dL) | 245.12 ± 25.32       | 151.25 ± 10.25       | <0.0001        | 241.32 ± 21.45        | 152.32 ± 12.32        | <0.0001        | 0.289           |
| HbA1c (%)                           | 8.21 ± 1.23          | 6.01 ± 0.21          | <0.0001        | 8.01 ± 2.44           | 6.12 ± 0.41           | <0.0001        | 0.396           |

Note. Values are mean ± SD.

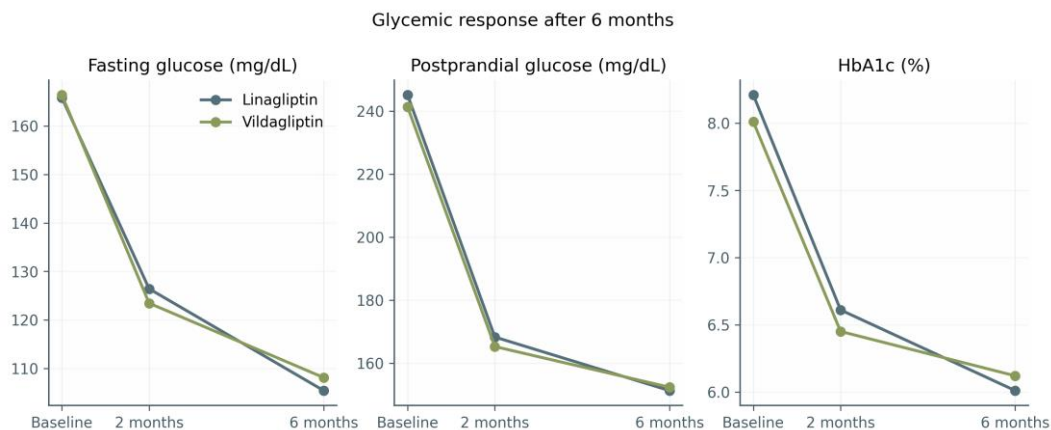


Figure 12. Glycemic response from baseline to 2 and 6 months.

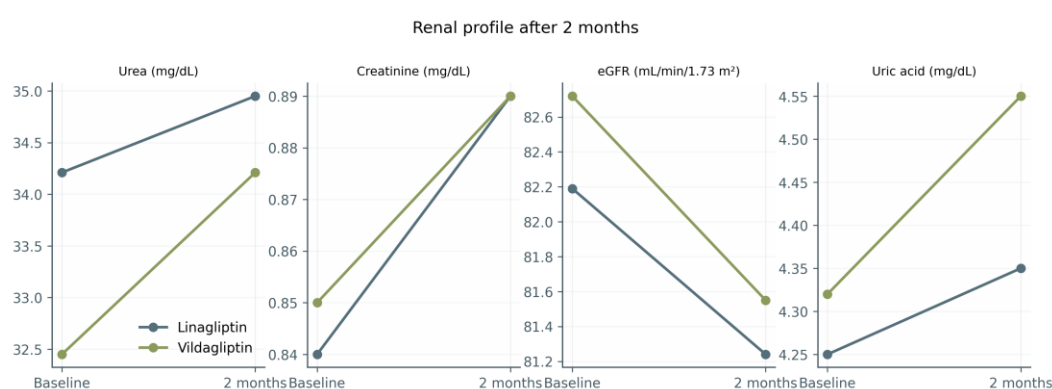
### 3.3 Renal outcomes

Blood urea, serum creatinine, eGFR, and serum uric acid remained broadly stable through 6 months. No within-group or between-group difference reached statistical significance at the prespecified threshold. At 6 months, serum creatinine was  $0.89 \pm 0.38$  mg/dL in the linagliptin group and  $0.89 \pm 0.79$  mg/dL in the vildagliptin group ( $p=0.685$ ), while eGFR was  $81.23 \pm 9.45$  versus  $81.36 \pm 10.23$  mL/min/1.73 m<sup>2</sup> ( $p=0.814$ ) (Tables 13 and 14; Figures 13 and 14).

**Table 13. Renal profile after 2 months.**

| Parameter                                   | Linagliptin baseline | Linagliptin 2 months | Within-group P | Vildagliptin baseline | Vildagliptin 2 months | Within-group P | Between-group P |
|---------------------------------------------|----------------------|----------------------|----------------|-----------------------|-----------------------|----------------|-----------------|
| Blood urea (mg/dL)                          | 34.21 ± 7.12         | 34.95 ± 6.45         | 0.652          | 32.45 ± 8.55          | 34.21 ± 8.22          | 0.085          | 0.978           |
| Serum creatinine (mg/dL)                    | 0.84 ± 0.21          | 0.89 ± 0.25          | 0.325          | 0.85 ± 0.12           | 0.89 ± 0.32           | 0.495          | 0.655           |
| Estimated GFR (mL/min/1.73 m <sup>2</sup> ) | 82.19 ± 17.45        | 81.24 ± 12.45        | 0.065          | 82.72 ± 18.41         | 81.55 ± 13.42         | 0.074          | 0.874           |
| Serum uric acid (mg/dL)                     | 4.25 ± 1.27          | 4.35 ± 1.32          | 0.654          | 4.32 ± 1.74           | 4.55 ± 1.36           | 0.412          | 0.952           |

Note. Values are mean ± SD.

**Figure 13. Renal profile from baseline to 2 months.****Table 14. Renal profile after 6 months.**

| Parameter                                   | Linagliptin baseline | Linagliptin 6 months | Within-group P | Vildagliptin baseline | Vildagliptin 6 months | Within-group P | Between-group P |
|---------------------------------------------|----------------------|----------------------|----------------|-----------------------|-----------------------|----------------|-----------------|
| Blood urea (mg/dL)                          | 34.21 ± 7.12         | 35.12 ± 5.22         | 0.498          | 32.45 ± 8.55          | 34.28 ± 9.23          | 0.078          | 0.651           |
| Serum creatinine (mg/dL)                    | 0.84 ± 0.21          | 0.89 ± 0.38          | 0.325          | 0.85 ± 0.12           | 0.89 ± 0.79           | 0.552          | 0.685           |
| Estimated GFR (mL/min/1.73 m <sup>2</sup> ) | 82.19 ± 17.45        | 81.23 ± 9.45         | 0.098          | 82.72 ± 18.41         | 81.36 ± 10.23         | 0.078          | 0.814           |
| Serum uric acid (mg/dL)                     | 4.25 ± 1.27          | 4.12 ± 1.21          | 0.654          | 4.39 ± 1.77           | 4.35 ± 1.37           | 0.274          | 0.952           |

Note. Values are mean ± SD. The vildagliptin baseline uric acid value shown here is transcribed exactly as reported in the 6-month source table; the baseline table reports 4.32 ± 1.74 mg/dL.

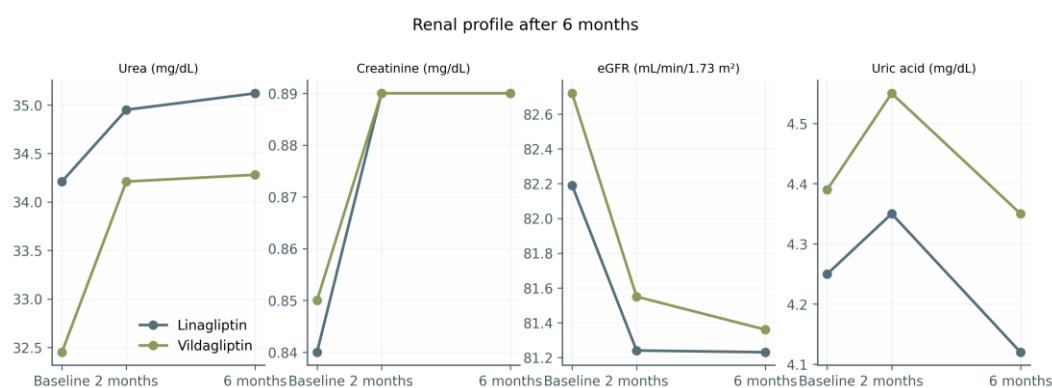


**Figure 14. Renal profile from baseline to 2 and 6 months, using the values reported in the 6-month source table.**

### 3.4 Adverse events

Adverse events were generally mild, nonspecific, and similarly distributed between groups. Nausea, loose stool, abdominal cramp, nasal stuffiness, headache, fatigue, dizziness, abdominal bloating, cough, and joint pain did not differ significantly between treatments. No serious adverse event was identified in the source study report (Table 15; Figure 15).

**Table 15. Adverse events during follow-up.**

| Adverse event      | Linagliptin (n=50), n (%) | Vildagliptin (n=50), n (%) | P value |
|--------------------|---------------------------|----------------------------|---------|
| Nausea             | 6 (12.0)                  | 4 (8.0)                    | 0.524   |
| Loose stool        | 5 (10.0)                  | 2 (4.0)                    | 0.124   |
| Abdominal cramp    | 4 (8.0)                   | 4 (8.0)                    | 0.985   |
| Nasal stuffiness   | 3 (6.0)                   | 5 (10.0)                   | 0.254   |
| Headache           | 5 (10.0)                  | 4 (8.0)                    | 0.652   |
| Fatigue            | 5 (10.0)                  | 4 (8.0)                    | 0.652   |
| Dizziness          | 6 (12.0)                  | 5 (10.0)                   | 0.621   |
| Abdominal bloating | 2 (4.0)                   | 2 (4.0)                    | 1.000   |
| Cough              | 1 (2.0)                   | 0 (0.0)                    | 0.423   |
| Joint pain         | 1 (2.0)                   | 0 (0.0)                    | 0.423   |

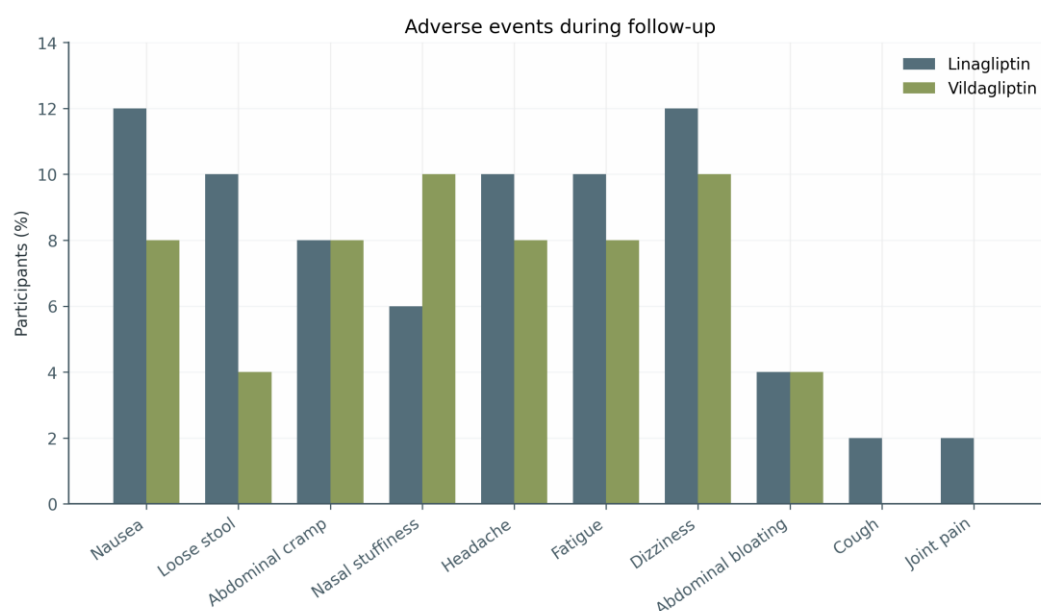


**Figure 15. Adverse events reported during follow-up.**

## 4. DISCUSSION

In this prospective observational comparison of adults with uncontrolled T2DM, linagliptin and vildagliptin each added to stable metformin were associated with marked improvement in fasting glucose, postprandial glucose, and HbA1c over 6 months. The magnitude and time course of glycemic improvement were similar between groups. Renal indices changed little during follow-up, and no statistically significant between-group difference was detected for urea, creatinine, eGFR, or uric acid. Mild gastrointestinal, neurologic, and respiratory symptoms were the most common reported adverse events, with no meaningful safety separation between treatments.

The glycemic findings align with recent direct comparative evidence. In a larger Indian observational study, Chaudhuri et al. reported similar glycemic control with linagliptin and vildagliptin added to metformin, although a higher proportion of vildagliptin recipients experienced a 20% creatinine increase after 6 months [5]. Ahmed et al. likewise found both agents effective in patients with T2DM and chronic kidney disease, with some postprandial glucose advantage for linagliptin [6]. A machine-learning analysis found that linagliptin and vildagliptin produced similar HbA1c reductions in nonimputed real-world data, while model-based estimates varied with comorbidity burden, eGFR, uric acid, and LDL cholesterol [7]. Together, these studies support the present finding that average glycemic responses are broadly comparable, while individual clinical context may guide drug selection.

The renal findings are also consistent with the wider evidence base. In CARMELINA, linagliptin demonstrated cardiovascular safety in patients at high cardiovascular and renal risk, but did not significantly improve the secondary composite kidney outcome compared with placebo [12]. Meta-analyses have reported reduced albuminuria or urinary albumin-to-creatinine ratio with DPP-4 inhibitors, while eGFR and serum creatinine generally remained unchanged [8,9,11,13]. Smaller mechanistic and clinical studies suggest possible albuminuria reduction with linagliptin in renal dysfunction [14,15]. The present cohort did not show a significant change in creatinine or eGFR over 6 months, which is compatible with these mixed results and with the relatively preserved baseline renal function of the enrolled participants.

The present findings should be interpreted within current treatment guidance. Contemporary standards emphasize person-centered selection according to glycemic need, kidney and cardiovascular status, hypoglycemia risk, weight, cost, access, and patient preference [3,4]. DPP-4 inhibitors remain useful when a well-tolerated oral agent with low hypoglycemia risk is appropriate, but agents with proven kidney or

cardiovascular outcome benefits particularly SGLT2 inhibitors or GLP-1 receptor agonists take priority in many patients with established cardiorenal disease [3,4]. Within the DPP-4 class, linagliptin's nonrenal elimination offers practical advantages when kidney function is reduced, whereas twice-daily vildagliptin may be selected when cost, availability, formulation, or clinician experience favors it.

Two source-data features warrant transparent interpretation. First, the vildagliptin RBC standard deviation in the baseline hematology table was unusually large relative to its mean and is preserved exactly as reported. Second, the vildagliptin baseline uric acid value differed between the baseline and 6-month renal tables ( $4.32 \pm 1.74$  versus  $4.39 \pm 1.77$  mg/dL). Both tables are reproduced with their original values, and the discrepancy is flagged rather than corrected retrospectively.

### Strengths of the Study

The present study has several strengths. First, it prospectively evaluated two commonly used DPP-4 inhibitors, linagliptin and vildagliptin, under real-world clinical conditions in patients with inadequately controlled type 2 diabetes mellitus receiving stable metformin therapy. Second, the study included both glycemic and renal outcomes, allowing assessment of treatment response beyond glycemic control alone. Third, participants were evaluated at baseline, 2 months, and 6 months, providing longitudinal information on the trajectory of treatment response. Fourth, multiple clinically relevant parameters, including fasting and postprandial plasma glucose, HbA1c, blood urea, serum creatinine, eGFR, serum uric acid, hematological indices, lipid profile, liver function tests, and adverse events, were assessed. Fifth, baseline characteristics were broadly comparable between the two treatment groups, reducing the likelihood that major baseline differences accounted for the observed findings. Finally, the study was conducted in a routine clinical setting, which enhances the practical relevance of the findings for patients receiving DPP-4 inhibitor therapy in similar healthcare settings.

### Future Recommendations

Future studies should include larger, multicenter cohorts with longer follow-up to determine whether the comparable short-term renal and glycemic findings observed in the present study persist over time. Randomized controlled trials would be valuable to minimize confounding and provide stronger comparative evidence between linagliptin and vildagliptin. Future research should also include patients with different stages of chronic kidney disease, particularly moderate-to-severe renal

impairment, because renal function may influence treatment selection and clinical outcomes. Assessment of urinary albumin-to-creatinine ratio and other markers of albuminuria should be incorporated to provide a more comprehensive evaluation of renal effects. Longer-term studies should additionally evaluate major cardiovascular and renal outcomes, treatment adherence, quality of life, hypoglycemia, healthcare costs, and treatment persistence. Stratified analyses according to baseline eGFR, diabetes duration, age, comorbidities, and concomitant medications may further identify patient subgroups that derive greater benefit from either treatment. Comparative pharmacoeconomic studies may also help determine the most appropriate DPP-4 inhibitor in resource-limited clinical settings.

## 5. Limitations

This was a single-center observational study with a modest sample size and 6-month follow-up. Treatment allocation was not randomized, so confounding by indication cannot be excluded. Albuminuria, urinary albumin-to-creatinine ratio, medication adherence, dietary intake, physical activity, and socioeconomic factors were not analyzed as primary outcomes. Participants with moderate-to-severe chronic kidney disease were excluded, limiting applicability to populations in whom differences in DPP-4 inhibitor handling may be most clinically important. The study was not powered to detect small differences in renal decline, uncommon adverse events, or hard clinical outcomes.

## 6. CONCLUSION

Linagliptin 5 mg once daily and vildagliptin 50 mg twice daily, each added to stable metformin, produced comparable improvement in glycemic indices over 6 months in adults with uncontrolled T2DM. Renal indices remained broadly stable, and tolerability was similar between groups. These data support either agent as a short-term add-on option when a DPP-4 inhibitor is clinically appropriate, while emphasizing that longer and larger controlled studies are required to establish comparative renal safety, particularly in patients with impaired kidney function.

## Declarations

### Ethics approval and consent to participate

The study was approved by the Institutional Ethics Committee, Darbhanga Medical College, Laheriasarai (Ref. No. 271, dated 30 October 2023). Written informed consent was obtained in Hindi or English; witnessed thumb impression consent was used for participants unable to read or write.

## Funding

No external funding source was reported in the source document.

## Competing interests

No competing interests were reported in the source document.

## Acknowledgement

The authors thank the technical staff of the Department of Pharmacology, DMCH, and the participating patients for their cooperation.

## Authors' Contributions

All authors contributed to the conception and design of the study, data collection, analysis and interpretation of the results, and preparation of the manuscript. All authors critically reviewed the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

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