



## Baseline Profile and Adverse Drug Reaction Pattern of Dipeptidyl Peptidase-4 Inhibitors in Patients with Type 2 Diabetes Mellitus: A 12-Month Prospective Observational Study from a Tertiary Care Teaching Hospital in Kalaburagi

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**Abstract:** Background: Dipeptidyl peptidase-4 (DPP-4) inhibitors are established oral glucose-lowering agents used in the management of type 2 diabetes mellitus (T2DM). Although their safety has been extensively evaluated in randomized clinical trials, prospective real-world data describing the spectrum and severity of adverse drug reactions (ADRs) among individual DPP-4 inhibitors remain limited in routine-care settings in India. Objectives: To describe the baseline demographic characteristics of patients with T2DM receiving DPP-4 inhibitors and to document the frequency, spectrum and severity of reported ADRs during 12 months of routine clinical follow-up, including an agent-wise description of sitagliptin, vildagliptin, linagliptin and saxagliptin. Methods: A prospective, non-randomized observational cohort study was conducted in the Department of General Medicine, Basaveshwar Teaching and General Hospital, Kalaburagi, from June 2025 to July 2026. Adults aged  $\geq 35$  years with T2DM and baseline HbA1c  $>6.5\%$  who were receiving physician-prescribed DPP-4 inhibitor therapy were followed at baseline and at 3, 6, 9 and 12 months. The complete-case DPP-4 cohort comprised 250 participants. Data were analysed using IBM SPSS Statistics version 32.0 and summarized using frequencies, percentages and mean  $\pm$  standard deviation. Results: Among 250 participants, 128 (51.2%) were male and 122 (48.8%) were female. The mean age was  $56.62 \pm 6.23$  years, with 119 (47.6%) participants belonging to the 56-65-year age group. Reported ADRs occurred in 38 participants (15.2%), whereas 212 (84.8%) had no recorded ADR. Of the 38 participants with ADRs, 31 (12.4% of the total cohort) experienced mild reactions and 7 (2.8%) experienced moderate reactions; no severe reaction was recorded. The largest number of recorded ADR cases occurred among participants receiving saxagliptin (12; 4.8%), followed by sitagliptin (10; 4.0%), vildagliptin (9; 3.6%) and linagliptin (7; 2.8%). Headache was the most frequently recorded reaction (11; 4.4%), followed by upper respiratory tract infection (7; 2.8%). Four cases of hypoglycaemia (1.6%) were recorded, all among participants receiving saxagliptin. Conclusion: In this single-centre prospective observational cohort, reported ADRs among patients receiving DPP-4 inhibitors occurred in 15.2% of participants and were predominantly mild, with no severe reactions recorded. Headache and upper respiratory tract infection were the most frequently documented reactions. Drug -wise counts showed the greatest number of recorded ADR cases among saxagliptin users; however, these descriptive frequencies should not be interpreted as

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comparative drug-specific risk because individual-agent denominators and formal comparative analyses were not available. Continued pharmacovigilance and larger multicentre studies with standardized ADR ascertainment and formal causality assessment are warranted.

**Keywords:** type 2 diabetes mellitus, DPP-4 inhibitors, sitagliptin, vildagliptin, linagliptin, saxagliptin, adverse drug reactions, pharmacovigilance, real-world evidence, India

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## **INTRODUCTION**

Type 2 diabetes mellitus (T2DM) is a chronic and progressive metabolic disorder that frequently requires long-term pharmacological treatment to achieve and maintain individualized glycaemic targets. Contemporary diabetes management emphasizes individualized selection of glucose-lowering therapy according to glycaemic efficacy, comorbidities, hypoglycaemia risk, adverse-effect profile, treatment burden and patient-related considerations.<sup>1</sup>

Dipeptidyl peptidase-4 (DPP-4) inhibitors are an established class of oral glucose-lowering agents used in the treatment of T2DM. By inhibiting the enzymatic degradation of endogenous incretin hormones, principally glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, they enhance glucose-dependent insulin secretion and reduce inappropriate glucagon secretion.<sup>2</sup> Sitagliptin, vildagliptin, linagliptin and saxagliptin are among the DPP-4 inhibitors used in clinical practice, and their efficacy and safety have been evaluated in pooled analyses of randomized trials of incretin-based therapy.<sup>3</sup>

DPP-4 inhibitors have generally demonstrated a favourable tolerability profile, particularly with respect to hypoglycaemia when used without concomitant therapies that independently increase hypoglycaemic risk. Nevertheless, safety cannot be assumed to be identical across all members of a class. Differences in molecular characteristics, pharmacokinetics, renal elimination, concomitant treatment and patient characteristics may influence the safety profile of individual agents.<sup>4</sup>

Large cardiovascular outcome trials illustrate the importance of considering individual DPP-4 inhibitors separately. Sitagliptin (TECOS) was non-inferior to placebo for major cardiovascular outcomes and did not increase hospitalization for heart failure.<sup>5</sup> Saxagliptin (SAVOR-TIMI 53) did not increase the primary composite endpoint but was associated with more hospitalization for heart failure.<sup>6</sup> Linagliptin (CARMELINA) showed cardiovascular non-inferiority in patients at high cardiovascular and renal risk.<sup>7</sup> A meta-analysis of randomized trials similarly did not suggest increased cardiovascular risk with the class as a whole.<sup>8</sup> Current guidance accordingly describes DPP-4 inhibitors as having intermediate glucose-lowering efficacy and neutral effects on weight and cardiovascular outcomes, with a heart-failure concern specifically associated with saxagliptin.<sup>1</sup>

Although randomized controlled trials provide important evidence on efficacy and safety, routine clinical practice includes patients with heterogeneous demographics, comorbidities, concomitant medications and treatment histories. Prospective observational studies can therefore provide complementary information on the adverse events encountered during routine medication use.

Pharmacovigilance is particularly important in chronic diseases such as T2DM, where patients receive multiple medications over prolonged periods. The World Health Organization defines pharmacovigilance as the science and activities concerned with the detection, assessment, understanding and prevention of adverse effects or other possible drug-related problems.<sup>9</sup> Systematic documentation of adverse drug reactions (ADRs) therefore contributes to evaluating medication safety beyond the controlled environment of clinical trials.

Indian real-world evidence is also important because treatment patterns, patient characteristics and healthcare practices may differ from those in international trials. A recent Indian phase 4 study of a fixed-dose combination of dapagliflozin and saxagliptin reported adverse events that were predominantly mild, demonstrating the value of prospective safety surveillance in an Indian population.<sup>10</sup> However, that study evaluated a fixed-dose combination rather than describing four individual DPP-4 inhibitors. Prospective single-centre data on the ADR spectrum of individual DPP-4 inhibitors in routine care in northern Karnataka remain limited. Therefore, this study was undertaken to describe the baseline demographic characteristics of patients with T2DM receiving DPP-4 inhibitors and to document the frequency, spectrum and severity of reported ADRs over 12 months of prospective follow-up, with an agent-wise description of sitagliptin, vildagliptin, linagliptin and saxagliptin.

## **MATERIALS AND METHODS**

### **Study Design and Setting**

A prospective, non-randomized, observational cohort study was conducted in the Department of General Medicine, Basaveshwar Teaching and General Hospital, Kalaburagi, Karnataka, India, from June 2025 to July 2026. The study was designed to describe the real-world demographic and ADR profile of patients with T2DM receiving DPP-4 inhibitor therapy. Participants were evaluated at baseline and subsequently at 3, 6, 9 and 12 months. The study was observational and non-interventional. The treating physician independently selected the antidiabetic agent, dose and dosing frequency according to routine clinical practice. No randomization, allocation concealment or investigator-directed modification of pharmacotherapy was performed.

### **Ethical Considerations**

The study protocol was reviewed on 23 February 2024 and approved on 12 March 2024 by the Institutional Ethics Committee (Registration No. EC/NEW/INST/2022/KA/0194). Written informed consent was obtained from all participants before enrolment. All study procedures were conducted in accordance with applicable ethical requirements for research involving human participants.

### **Study Population**

Adults aged  $\geq 35$  years with established T2DM who were receiving physician-prescribed adjunctive DPP-4 inhibitor therapy were considered eligible.

**Inclusion Criteria**

1. Age  $\geq 35$  years.
2. Confirmed diagnosis of T2DM.
3. Baseline HbA1c  $>6.5\%$ .
4. Clinical history and medication records available for at least 3 months before recruitment.
5. Current physician-prescribed adjunctive DPP-4 inhibitor therapy.
6. Provision of written informed consent.
7. Ability to attend scheduled follow-up evaluations.

**Exclusion Criteria**

1. Type 1 diabetes mellitus.
2. Physical dependency or circumstances preventing valid informed consent.
3. Pregnancy or breastfeeding.
4. Chronic kidney disease or another clinically significant renal abnormality that could confound interpretation of the study variables.
5. Concurrent medications with a substantial potential to alter the relevant biochemical parameters.
6. Concurrent use of homeopathic or Unani preparations.
7. Inadequate previous clinical documentation or absence of baseline laboratory data.

**Enrolment and Follow-up**

In the parent observational cohort, 763 potentially eligible individuals were screened, of whom 684 provided informed consent and were enrolled. The enrolled population comprised 342 patients receiving SGLT-2 inhibitors and 342 receiving DPP-4 inhibitors according to their existing treatment. Participants who did not complete the protocol-specified follow-up were excluded from the complete-case analysis. The complete-case analytical population consisted of 500 participants, including 250 patients in each treatment class. The present manuscript is restricted to the DPP-4 inhibitor cohort comprising 250 participants.

**Drug Exposure**

DPP-4 inhibitor exposure was determined from the treating physician's prescription records and categorized according to the active molecule. The agents evaluated were:

- Sitagliptin
- Vildagliptin
- Linagliptin

- Saxagliptin

Treatment selection and dose adjustment remained under the responsibility of the treating clinician and were not influenced by the study investigators.

### Outcome Measures

The study outcomes included:

- baseline demographic characteristics;
- overall frequency of reported ADRs;
- type and frequency of reported ADRs;
- Drug -wise distribution of recorded ADRs; and
- severity distribution of reported ADRs.

ADRs were recorded during scheduled follow-up visits over the 12-month observation period.

### Statistical Analysis

Data were analysed using IBM SPSS Statistics version 32.0. Categorical variables were expressed as frequencies and percentages. Continuous variables were summarized as mean  $\pm$  standard deviation. Because treatment allocation and individual-agent prescribing were determined by routine clinical practice, agent-specific ADR observations were interpreted descriptively. No inferential comparison of ADR risk between individual DPP-4 inhibitors was performed. Where inferential analyses were applicable, a two-sided p-value  $<0.05$  was considered statistically significant.

## **RESULTS**

### **Baseline Demographic Characteristics**

The complete-case DPP-4 inhibitor cohort comprised 250 participants. Of these, 128 (51.2%) were male and 122 (48.8%) were female. The mean age of the cohort was  $56.62 \pm 6.23$  years. The mean age among male participants was  $55.28 \pm 6.09$  years, whereas the mean age among female participants was  $58.03 \pm 6.09$  years. The largest age category was 56-65 years, comprising 119 participants (47.6%), followed by 46-55 years with 108 participants (43.2%). Twenty participants (8.0%) were aged 66-70 years, while 3 participants (1.2%) were aged 42-45 years.

**Table 1: Gender distribution of the DPP-4 inhibitor cohort (n=250)**

| Gender | n   | %    |
|--------|-----|------|
| Male   | 128 | 51.2 |
| Female | 122 | 48.8 |
| Total  | 250 | 100  |

**Table 2: Baseline Distribution of Mean Age According to Sex Among Patients Treated with DPP-4 Inhibitors**

| Sex     | Mean $\pm$ SD, years |
|---------|----------------------|
| Male    | 55.28 $\pm$ 6.09     |
| Female  | 58.03 $\pm$ 6.09     |
| Overall | 56.62 $\pm$ 6.23     |

**Table 3: Age-group distribution of the DPP-4 inhibitor cohort (n=250)**

| Age group (years) | n   | %    |
|-------------------|-----|------|
| 42-45             | 3   | 1.2  |
| 46-55             | 108 | 43.2 |
| 56-65             | 119 | 47.6 |
| 66-70             | 20  | 8    |
| Total             | 250 | 100  |

**Overall Incidence and Severity of Adverse Drug Reactions**

During the 12-month follow-up period, reported ADRs occurred in 38 of 250 participants (15.2%), while 212 participants (84.8%) had no recorded ADR. Among the total cohort, 31 participants (12.4%) experienced mild reactions and 7 participants (2.8%) experienced moderate reactions. No severe ADR was recorded. Among participants who experienced ADRs, mild reactions constituted 81.6% and moderate reactions constituted 18.4%.

**Table 4: Overall frequency and severity of reported ADRs in the DPP-4 inhibitor cohort**

| Parameter   | n   | % of cohort | % of ADRs |
|-------------|-----|-------------|-----------|
| ADR present | 38  | 15.2        | 100       |
| No ADR      | 212 | 84.8        | —         |
| Mild        | 31  | 12.4        | 81.6      |
| Moderate    | 7   | 2.8         | 18.4      |
| Severe      | 0   | 0           | 0         |

**Drug -wise Pattern of Reported Adverse Drug Reactions**

The largest number of recorded ADR cases occurred among participants receiving saxagliptin (12; 4.8%), followed by sitagliptin (10; 4.0%), vildagliptin (9; 3.6%) and linagliptin (7; 2.8%). The most frequently recorded ADR overall was headache, reported in 11 participants (4.4%), followed by upper respiratory tract infection in 7 participants (2.8%). Among sitagliptin users, upper respiratory tract infection was recorded in 4 participants (1.6%), headache in 3 (1.2%) and arthralgia in 3 (1.2%). The arthralgia cases were classified as moderate. Among vildagliptin users, nasopharyngitis, headache and dizziness were each recorded in 3 participants (1.2%). These reactions were classified as mild. Among linagliptin users, gastrointestinal disturbances and upper respiratory tract infection were each recorded in 3 participants (1.2%), while rash was recorded in 1 participant (0.4%). These reactions were classified as mild. Among saxagliptin users, headache was recorded in 5 participants (2.0%), hypoglycaemia in 4 (1.6%) and skin rash in 3 (1.2%). Hypoglycaemia was classified as moderate, while headache and skin rash were classified as mild.

**Table 5: Drug -wise distribution of reported ADRs**

| DPP-4 inhibitor | Reported ADR                      | n  | % of total cohort | Severity |
|-----------------|-----------------------------------|----|-------------------|----------|
| Sitagliptin     | Upper respiratory tract infection | 4  | 1.6               | Mild     |
|                 | Headache                          | 3  | 1.2               | Mild     |
|                 | Arthralgia                        | 3  | 1.2               | Moderate |
|                 | Drug total                        | 10 | 4                 | —        |
| Vildagliptin    | Nasopharyngitis                   | 3  | 1.2               | Mild     |
|                 | Headache                          | 3  | 1.2               | Mild     |
|                 | Dizziness                         | 3  | 1.2               | Mild     |
|                 | Drug total                        | 9  | 3.6               | —        |
| Linagliptin     | Gastrointestinal disturbances     | 3  | 1.2               | Mild     |
|                 | Upper respiratory tract infection | 3  | 1.2               | Mild     |
|                 | Rash                              | 1  | 0.4               | Mild     |
|                 | Drug total                        | 7  | 2.8               | —        |
| Saxagliptin     | Headache                          | 5  | 2                 | Mild     |
|                 | Hypoglycaemia                     | 4  | 1.6               | Moderate |
|                 | Skin rash                         | 3  | 1.2               | Mild     |
|                 | Drug total                        | 12 | 4.8               | —        |
| Total           | All reported ADRs                 | 38 | 15.2              | —        |

## **DISCUSSION**

### **Overall ADR Frequency and Severity**

ADRs were reported in 38 of 250 participants (15.2%) receiving DPP-4 inhibitors over 12 months. Thirty-one participants (81.6% of those with ADRs) had mild reactions, seven (18.4%) had moderate reactions, and no severe ADR was recorded. This mild-to-moderate pattern is consistent with the established tolerability profile of DPP-4 inhibitors, although agent-specific profiles vary with the drug, patient characteristics and treatment context.<sup>4</sup> As an observational routine-care cohort, the study includes heterogeneous patients with differing comorbidities and concomitant medications, unlike randomized trials.

### **Comparison with Indian Evidence**

An Indian phase 4 study of a dapagliflozin-saxagliptin fixed-dose combination reported adverse events in 22 of 196 participants (11.2%), mostly mild, with nasopharyngitis in 3 (1.5%) and hypoglycaemia in 1 (0.5%).<sup>10</sup> The ADR frequency here (15.2%) was numerically higher, but the difference should not be read as a difference in drug toxicity. The studies differed in design, population, follow-up, exposure and method of adverse-event ascertainment. In addition, that study evaluated a combination containing an SGLT-2 inhibitor, whereas the present study describes four individual DPP-4 inhibitors, so the comparison is exploratory.

### **Spectrum of Adverse Drug Reactions**

Headache was the most frequent reaction (11 participants, 4.4%), followed by upper respiratory tract infection (7 participants, 2.8%). A meta-analysis of randomized trials likewise reported higher risks of headache, nasopharyngitis and urinary tract infection with

DPP-4 inhibitors than with control, so this spectrum is directionally in line with trial evidence.<sup>3</sup> Because this is descriptive pharmacovigilance, an event occurring during treatment is not proof that the drug caused it. Concomitant medications, underlying disease and intercurrent illness may contribute, and causality tools such as the Naranjo algorithm estimate probability rather than establish causation.<sup>11</sup>

### Hypoglycaemia

Four cases of hypoglycaemia (1.6% of the cohort) were recorded, all moderate and all among saxagliptin users. DPP-4 inhibitors carry a low intrinsic hypoglycaemia risk because their effect depends on ambient glucose, but hypoglycaemia may occur with concomitant agents that independently cause it.<sup>1</sup> These four events are of clinical interest, but they do not show that saxagliptin carries a higher hypoglycaemia risk than the other agents, because the analysis has no exposure denominators or adjusted estimates. SAVOR-TIMI 53, a much larger randomized trial, identified a heart-failure hospitalization signal with saxagliptin rather than a comparative hypoglycaemia signal of the type suggested here.<sup>6</sup>

### Drug-wise ADR Pattern

The most ADR cases occurred among saxagliptin users (12; 4.8%), followed by sitagliptin (10; 4.0%), vildagliptin (9; 3.6%) and linagliptin (7; 2.8%). These percentages in Table 5 use the whole cohort of 250 as the denominator, so they are not drug-specific incidence rates. More ADR cases in one group could simply reflect more patients on that drug. The study therefore does not establish that saxagliptin has the highest ADR risk. It describes observed safety patterns in routine care rather than comparative drug safety.

### Evidence from Cardiovascular Outcome Trials

Safety findings differ between individual DPP-4 inhibitors in large randomized trials. In TECOS (14,671 patients with T2DM and established cardiovascular disease), sitagliptin was non-inferior to placebo for the primary composite outcome (hazard ratio 0.98; 95% CI 0.89-1.08), and heart-failure hospitalization did not differ (hazard ratio 1.00; 95% CI 0.83-1.20).<sup>5</sup> In SAVOR-TIMI 53 (16,492 patients), saxagliptin did not alter the primary endpoint (hazard ratio 1.00; 95% CI 0.89-1.12), but heart-failure hospitalization was more frequent with saxagliptin than placebo (3.5% vs 2.8%; hazard ratio 1.27; 95% CI 1.07-1.51).<sup>6</sup> In CARMELINA (6979 patients at high cardiovascular and renal risk), linagliptin was non-inferior to placebo (hazard ratio 1.02; 95% CI 0.89-1.17), with no increase in heart-failure hospitalization (hazard ratio 0.90; 95% CI 0.74-1.08).<sup>7</sup> These findings, together with current guidance,<sup>1</sup> show why DPP-4 inhibitors should not be considered interchangeable from a safety perspective. They cannot be extrapolated directly to this small observational cohort, whose population, outcomes and design differ.

### Pharmacovigilance Significance

This study provides prospective routine-care ADR data from a tertiary-care teaching hospital in Kalaburagi. Pharmacovigilance extends beyond severe reactions: systematic

documentation of common mild and moderate events improves understanding of tolerability and can generate hypotheses for further study.<sup>9</sup> Prospective monitoring therefore remains relevant even for medicines with established safety profiles, and these findings add local observational evidence to complement larger randomized and pharmacovigilance datasets.

### **LIMITATIONS**

The study has several limitations. First, it was conducted at a single tertiary-care teaching hospital; therefore, the findings may not be generalizable to other geographical regions, healthcare settings or patient populations. Second, treatment allocation was not randomized. The choice of individual DPP-4 inhibitor was determined by treating physicians, introducing the possibility of differences in baseline characteristics, comorbidities and concomitant therapy between individual treatment groups. Third, the analysis used a complete-case cohort of 250 participants. Participants who did not complete the required follow-up were excluded, and differential loss to follow-up may have resulted in under- or over-estimation of the observed ADR frequency. Fourth, the individual DPP-4 inhibitor denominators are not presented in the current dataset. Therefore, agent-specific values should be regarded as descriptive numbers of recorded events rather than comparative incidence rates. Fifth, the study was not powered to compare individual DPP-4 inhibitors statistically. Sixth, concomitant medications and underlying clinical conditions may have contributed to some observed events. Therefore, temporal association between drug exposure and an event should not be interpreted as definitive causality. Seventh, the final manuscript should explicitly report the ADR ascertainment method, causality assessment instrument and severity classification system actually used during the study. If no validated causality instrument was applied, this should be acknowledged. Finally, the study provides observational pharmacovigilance data and cannot establish causal relationships or comparative drug safety.

### **CONCLUSION**

In this 12-month prospective observational cohort of 250 patients with T2DM receiving DPP-4 inhibitor therapy, reported ADRs occurred in 15.2% of participants. Most reported reactions were mild, while 2.8% of the total cohort experienced moderate reactions, and no severe ADR was recorded. Headache was the most frequently documented reaction, followed by upper respiratory tract infection. Saxagliptin accounted for the largest number of recorded ADR cases, followed by sitagliptin, vildagliptin and linagliptin. Four cases of hypoglycaemia were recorded among saxagliptin users. However, these agent-wise observations should not be interpreted as evidence of comparative drug-specific risk because individual-agent denominators and formal comparative analyses were not available. The study highlights the importance of continued prospective pharmacovigilance in patients receiving long-term antidiabetic therapy. Larger multicentre observational studies incorporating standardized ADR definitions, individual-drug exposure denominators, validated causality assessment, standardized severity grading and adjustment for relevant patient and treatment characteristics are required to further characterize agent-specific safety patterns.

## **ACKNOWLEDGEMENTS**

The authors acknowledge the Department of General Medicine, Basaveshwar Teaching and General Hospital, Kalaburagi, for facilitating the conduct of the study and are grateful to all participants for their cooperation and continued participation throughout the study period.

**Funding:** The authors declare that **no external funding was received** for the conduct of this study.

**Conflict of Interest:** The authors declare that **there are no conflicts of interest** regarding the publication of this study.

**Informed Consent:** Written informed consent was obtained from all participants before inclusion in the study, as applicable.

**Data Availability Statement:** The data supporting the findings of this study are available from the corresponding author upon reasonable request, subject to applicable.

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