International Journal of Basic & Clinical Pharmacology
Nimavat ZR et al. Int J Basic Clin Pharmacol. 2025 Sep;14(5):843-849
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20252377

Systematic Review

Comparison of safety profiles of DPP-4 inhibitors with SGLT-2 inhibitors in type 2 diabetes mellitus: a systematic review

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Received: 10 July 2025
Revised: 23 July 2025
Accepted: 24 July 2025

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ABSTRACT

In type 2 diabetes mellitus (T2DM), add-on therapy to metformin is often required. Both sodium-glucose cotransporter-2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors are widely used, but differ in their safety profiles due to distinct mechanisms of action. This study aimed to systematically review and compare the safety outcomes of SGLT2 versus DPP-4 inhibitors in patients receiving background metformin therapy. A systematic literature search was conducted in PubMed for studies published from 2006 onward. Randomized controlled trials and observational studies evaluating safety outcomes of SGLT2 inhibitors (empagliflozin, dapagliflozin, canagliflozin) and DPP-4 inhibitors (sitagliptin, teneligliptin, vildagliptin) as add-on to metformin were included. Data on adverse events (AEs), serious adverse events (SAEs), and drug-related adverse events (DRAEs) were extracted and analyzed. Twenty studies met the inclusion criteria: 8 studies on SGLT2 inhibitors (n=946) and 12 on DPP-4 inhibitors (n=1903). The overall incidence of AEs was higher with DPP-4 inhibitors (66%) compared to SGLT2 inhibitors (34%), while DRAEs were comparable (12% vs. 11%). SGLT2 inhibitors were more often associated with genital and urinary tract infections, whereas DPP-4 inhibitors had higher rates of gastrointestinal disturbances and hypoglycemia. Rare events included dehydration and atrial flutter (SGLT2) and dyspepsia and hypertension (DPP-4). Notably, adverse events varied across individual agents within each class. Both SGLT2 and DPP-4 inhibitors demonstrate acceptable safety as add-on therapy to metformin. Given drug-specific adverse events, individualized therapy based on patient characteristics is essential. Further large-scale safety-focused studies are warranted.

Keywords: DPP4 inhibitors, SGLT2 inhibitors, Adverse events, Safety comparison, Type II diabetes mellitus

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder that can lead to various microvascular and macrovascular complications. It results from either inadequate insulin secretion or insulin resistance.[1] According to the 10th edition of the International Diabetes Federation (IDF) Diabetes Atlas, T2DM remains one of the most urgent global health concerns of the 21st century.[2] The primary therapeutic goal in T2DM is to prevent complications by maintaining optimal blood glucose levels.[3] This is achieved through a combination of non-pharmacological measures such as regular exercise and dietary modifications and pharmacological interventions. Metformin remains the first-line drug due to its proven efficacy, safety profile, tolerability, and cost-effectiveness.[4] However, its glycemic control diminishes over time, often necessitating dose escalation or the addition of a second antidiabetic agent. Common add-on therapies include dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose cotransporter-2 (SGLT2) inhibitors. DPP-4 inhibitors, such as sitagliptin and saxagliptin, are generally well tolerated but require close monitoring for adverse effects, including nasopharyngitis,

headaches, joint pain, and rare instances of heart failure hospitalization (particularly with saxagliptin).[5–8] In contrast, SGLT2 inhibitors (e.g., empagliflozin, dapagliflozin, canagliflozin) are associated with genital mycotic infections, urinary tract infections, and mild dehydration due to their mechanism of promoting glycosuria. These infections are usually mild and manageable but require caution in patients with reduced urinary output.[9–12] Although both drug classes are effective in glycemic control, the safety data remain mixed. Some studies suggest DPP-4 inhibitors are safer and better tolerated, while others report comparable safety profiles. Therefore, the present review aims to systematically evaluate and compare the safety of DPP-4 inhibitors and SGLT2 inhibitors, focusing exclusively on adverse events (AEs) and drug-related adverse events (DRAEs).

METHODS

Study design

This systematic review is part of a larger project, but the current analysis focuses exclusively on safety outcomes. The review was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions.[13]

Data sources and search strategy

A comprehensive literature search was conducted using the MEDLINE database via PubMed (www.pubmed.gov). The search strategy was designed based on PICO components: Search terms included: [(Metformin) AND (SGLT 2 inhibitors or sodium glucose cotransporter inhibitors or empagliflozin or canagliflozin or dapagliflozin or DPP4 inhibitors or dipeptidyl peptidase IV inhibitors or sitagliptin or linagliptin or teneligliptin or vildagliptin) and (diabetes mellitus type II or diabetes mellitus type 2)].

The inclusion criteria for this review were: studies published in English from 2006 onward, available in full-text, designed as randomized controlled trials or observational studies, involving patients with Type 2 Diabetes Mellitus receiving either DPP-4 or SGLT2 inhibitors as add-on therapy to metformin, with a minimum treatment duration of 12 weeks, and reporting safety outcomes such as adverse events and drug-related adverse events. Exclusion criteria included non-English publications, abstracts without full text, studies involving antidiabetic drugs other than DPP-4 or SGLT2 inhibitors, and studies retrieved from databases other than PubMed (e.g., Scopus, Web of Science).

Study selection and data extraction

A total of 2,860 studies were initially screened. Following the application of predefined inclusion and exclusion criteria, 20 studies were selected for final review. All authors independently reviewed and cross-verified the data to ensure accuracy. The extracted data included study characteristics such as author name, year of publication, and country of origin; participant characteristics including sample size; drug-related details such as the name of the drug, dose, and duration of therapy; and safety outcomes, which encompassed total adverse events (AEs), serious adverse events (SAEs), drug-related adverse events (DRAEs), as well as specific adverse events like hypoglycemia, genital infections, urinary tract infections, and gastrointestinal side effects.

RESULTS

A total of 20 studies were included in the safety analysis, covering both SGLT2 inhibitors and DPP4 inhibitors. Eight studies evaluated SGLT2 inhibitors primarily dapagliflozin, empagliflozin, and canagliflozin while eleven studies assessed DPP4 inhibitors such as sitagliptin, vildagliptin, and teneligliptin. The treatment duration across studies ranged from 12 to 52 weeks. The daily doses varied depending on the drug and study protocol, with dapagliflozin given at 5 to 10 mg/day, empagliflozin at 10 to 25 mg/day, canagliflozin at 100 mg/day, sitagliptin at 50 to 100 mg/day, vildagliptin at 100 mg/day, and teneligliptin at 20 mg/day. The sample size in the post-treatment population ranged from 24 to 382 participants, and the mean age of participants across studies ranged from 49.4±9.7 years to 63±7 years. Study done by *Ayako* Fuchigami et al included parallel treatment arms comparing SGLT2 inhibitors with DPP4 inhibitors within the same study population.[18] For these trials, demographic data such as sample size and participant characteristics were shared between the arms, while safety outcomes were reported separately for each drug group (Table 1).

Safety analysis of DPP4 inhibitors

A summary of safety data for DPP-4 inhibitors is presented in Table 2 from 12 studies examining adverse events. Across a total sample size of 1,903 participants, 1,259 AEs were reported, representing 66% of the study population. Only 9 studies have specified the data of drug related AE hence the subtotal population is 1573. For this population the AEs reported were 1162 which represents 73% of the subtotal population and 172 drug related AEs which represents 11% of the subtotal population.

Safety analysis of SGLT2 inhibitors

Table 3 summarizes data from eight studies evaluating the safety of SGLT2 inhibitors (Empagliflozin, Dapagliflozin, and Canagliflozin) based on adverse events (AEs), serious adverse events (SAEs) and adverse events related to drugs. The combined sample size across all studies is 946 participants, with 319 AEs reported, representing 34% of the total population. Only 6 studies have specified the data of drug related AE hence the subtotal population is 741. For this population the AEs reported were 272 which represents 37% of the subtotal population and 87 drug related AEs which represents 12% of the subtotal population.

Table 1: Demographic details of the included studies.

S. no.	Study name	Drug	Dose	Treatment duration	Country	Sample size	Age (mean±SD)
1	Häring et al[14]	Empagliflozin	25 mg	24 weeks	Multinational	213	55.6 ± 10.2
2	Shigiyama et al[15]	Dapagliflozin	5 mg	16 weeks	Japan	37	57.9 ± 8.3
3	van Bommel et al[16]	Dapagliflozin	10 mg	12 weeks	Netherlands	24	63 ± 7
4	Rosenstock et al[17]	Dapagliflozin	5 mg	24 weeks	Multinational	289	55.9 ± 10.9
5	Fuchigami et al[18]	Dapagliflozin	5–10 mg	24 weeks	Japan	168	58.3 ± 12.4
6	Khan et al[19]	Empagliflozin	10–20 mg	24 weeks	Pakistan	53	-
7	Hao et al[20]	Canagliflozin	100 mg	12 weeks	China	69	57.3 ± 9.8
8	Han et al[21]	Dapagliflozin	10 mg	24 weeks	Korea	93	60.35 ± 10.62
9	Nauck et al[22]	Sitagliptin	100 mg	52 weeks	Multinational	382	56.8 ± 9.3
10	Charbonnel et al[23]	Sitagliptin	100 mg	26 weeks	USA	275	56.9 ± 10.0
11	Chawla et al[24]	Sitagliptin	100 mg	16 weeks	India	25	49.48 ± 9.71
12	Kim et al[25]	Teneligliptin	20 mg	16 weeks	Korea	119	55.7 ± 8.7
13	Al Omari et al[26]	Vildagliptin	100 mg	12 weeks	Jordan	58	52.6 ± 7.8
14	Goldenberg et al[27]	Sitagliptin	100 mg	24 weeks	Canada	292	58 ± 10
15	Hong et al[28]	Sitagliptin	100 mg	24 weeks	Korea	100	57.3 ± 9.3
16	Gadde et al[29]	Sitagliptin	100 mg	28 weeks	USA	109	54.3 ± 9
17	Frias et al[30]	Sitagliptin	100 mg	20 weeks	USA	229	55.6 ± 10.5
18	Fuchigami et al[18]	Sitagliptin	50–100 mg	24 weeks	Japan	163	57.9 ± 12.1
19	Ji et al[31]	Teneligliptin	20 mg	24 weeks	China	99	56 ± 9.8
20	Kitazawa et al[32]	Sitagliptin	50 mg	52 weeks	Japan	52	58.4 ± 12.5

Table 2: Details of adverse events reported for safety of DPP4 inhibitors.

S. no.	Study name	Drug	Sample size	AE	SAE	Drug related AE
1	Nauck et al[22]	Sitagliptin	382	419	43	85
2	Charbonnel et al[23]	Sitagliptin	275	326	17	40
3	Chawla et al[24]	Sitagliptin	89	3	0	3
4	Kim et al[25]	Teneligliptin	119	56	4	5
5	Al Omari et al[26]	Vildagliptin	58	16		
6	Goldenberg et al[27]	Sitagliptin	292	130	9	12
7	Hong et al[28]	Sitagliptin	100	43	6	4
8	Gadde et al[29]	Sitagliptin	109	40		
9	Frias et al[30]	Sitagliptin	229	101	3	3
10	Fuchigami et al[18]	Sitagliptin	163	41		
11	Ji et al[31]	Teneligliptin	99	73	4	22
12	Kitazawa et al[32]	Sitagliptin	18	11	3	1
Sub total (%)			1573	1162 (73)	89 (6)	172 (11)
Total (%)			1903	1259 (66)	89 (7)	172 (14)

Table 3: Details of adverse events reported for safety of SGLT2 inhibitors.

S. no.	Study name	Drug	Sample size	AE	SAE	Drug related AE
1	Häring et al[14]	Empagliflozin	213	106	5	27
2	Shigiyama et al[15]	Dapagliflozin	37	6		
3	van Bommel et al[16]	Dapagliflozin	24	9		9
4	Rosenstock et al[17]	Dapagliflozin	289	123	8	32
5	Fuchigami et al[18]	Dapagliflozin	168	41		
6	Khan et al[19]	Empagliflozin	53	6		6
7	Hao et al[20]	Canagliflozin	69	6		6
8	Han et al[21]	Dapagliflozin	93	22	1	7
Sub total (%)			741	272 (37)	-	87 (12)
Total (%)			946	319 (34)	14 (1)	87 (9)

Table 4: Comparison of safety between SGLT2 inhibitors and DPP4 inhibitors.

Drug Group	Sample Size	AE (%)	Drug related AE (%)
SGLT2 inhibitors	741	272 (37)	87 (12)
DPP4 inhibitors	1573	1162 (73)	172 (11)

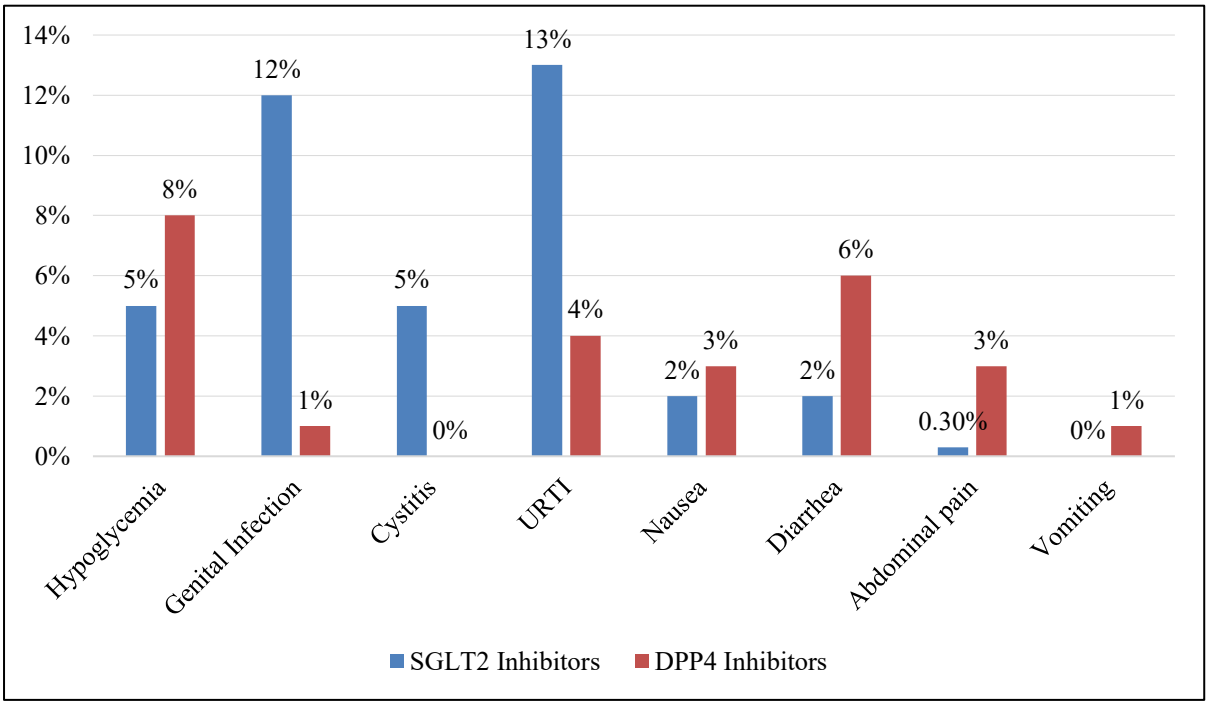

Figure 1: Specific AEs comparison.

Comparison of safety between SGLT2 inhibitors and DPP4 inhibitors

Table 4 shows comparison between SGLT2 inhibitors (Empagliflozin, Dapagliflozin, and Canagliflozin) and DPP-4 inhibitors (Sitagliptin, Teneligliptin, and Vildagliptin) differences in safety profiles based on adverse events (AEs) and drug-related AEs across their respective studies. SGLT2 inhibitors were studied in 6 studies with a total sample size of 741, reporting 272 AEs (37%) and 87 drug-related AEs (12%). In contrast, DPP-4 inhibitors were evaluated in 9 studies with a larger sample size of 1573, showing 1162 AEs (73%) and 172 drug-related AEs (11%). While DPP-4 inhibitors had a higher overall AE percentage, both groups reported a similar proportion of drug-related AEs.

Specific AEs

Figure 1 compares specific adverse drug reactions (AEs) between SGLT2 inhibitors and DPP-4 inhibitors, highlighting distinct safety profiles. The occurrence of genital infections, cystitis, and upper respiratory tract infections (URTIs) is notably higher in patients using SGLT2 inhibitors, with URTIs being the most frequently reported adverse drug reaction. In contrast, DPP-4 inhibitors show a higher incidence of abdominal pain, diarrhea, and vomiting, with a slightly greater occurrence of hypoglycemia compared to SGLT2 inhibitors. Both drug classes have low and comparable rates of nausea. These differences reflect due to their distinct pharmacological action and side effect profiles of the two drug classes, with SGLT2 inhibitors showing a predisposition toward infections and DPP-4 inhibitors exhibiting gastrointestinal-related AEs. Rare AEs reported with SGLT2 Inhibitors are dehydration, dizziness, backpain, anorexia, atrial flutter, urinary incontinence, polyuria, BPH and Prostate Cancer. Rare ADRs reported with DPP4 Inhibitors dyspepsia, headache, backpain, hypertension and constipation.

DISCUSSION

This systematic review focused exclusively on the safety profiles of SGLT2 inhibitors (empagliflozin, dapagliflozin, canagliflozin) and DPP4 inhibitors (sitagliptin, teneligliptin, vildagliptin) when used alongside metformin in type II diabetes mellitus patients. Both classes are widely prescribed as add-on therapies after metformin, but their safety concerns differ due to distinct pharmacological actions. Our analysis revealed that the overall incidence of adverse events (AEs) was significantly higher in the DPP4 inhibitor group (66%) compared to the SGLT2 inhibitor group (34%). When focusing on drug-related AEs specifically, both groups showed similar rates, with SGLT2 inhibitors causing drug-related AEs in 12% of patients and DPP4 inhibitors in 11%. This indicates that

although DPP4 inhibitors are associated with a higher rate of general adverse events, their drug-specific adverse event profile is not substantially worse compared to SGLT2 inhibitors. These findings align partially with existing literature. A meta-analysis by Kawalec et al concluded that both SGLT2 and DPP4 inhibitors have acceptable safety profiles and are generally well-tolerated in combination with metformin.[33] However, our study identified a notable difference in the frequency of total AEs between the two classes, which may reflect variations in study populations, treatment durations, or regional prescribing practices.

For the specific adverse events, SGLT2 inhibitors were predominantly associated with genital mycotic infections, urinary tract infections (UTIs), and upper respiratory tract infections (URTIs). These infections, although typically mild, are well-documented side effects due to the glucosuria-promoting mechanism of SGLT2 inhibitors. This aligned with the study done by Biyabani et al which also found that risk of genital infections is higher in SGLT2 inhibitors as compared to the DPP4 inhibitors due to its mechanism of action.[34] DPP4 inhibitors, on the other hand, exhibited a higher incidence of gastrointestinal side effects, including abdominal pain, diarrhea, and vomiting, as well as a slightly increased occurrence of hypoglycemia, particularly when used alongside other antihyperglycemic agents. A systematic review on DPP-4/metformin combinations observed that while DPP-4 inhibitors alone rarely cause hypoglycemia, such events were noted when used in combination with other antidiabetic drugs.[35] Rare adverse events reported in the SGLT2 inhibitor group included dehydration, dizziness, back pain, anorexia, atrial flutter, urinary incontinence, polyuria, benign prostatic hyperplasia (BPH), and prostate cancer. For DPP4 inhibitors, rare AEs included dyspepsia, headache, back pain, hypertension, and constipation.

Limitations

This review has several limitations that warrant consideration. The included studies varied in design, sample size, geographic region, and treatment duration, introducing potential heterogeneity that could influence the interpretation of safety outcomes. Additionally, this analysis focused solely on adverse events, without evaluating efficacy parameters, which limits the overall assessment of clinical benefit versus risk. Another important limitation is that not all studies consistently reported serious adverse events or classified adverse events by severity, making it difficult to perform detailed subgroup analyses. Furthermore, adverse event data were often reported at the drug class level (SGLT2 inhibitors or DPP-4 inhibitors), while individual drugs within each class may differ significantly in their safety profiles. For example, the risk of genital infections is more pronounced with certain SGLT2 inhibitors, while heart failure risk has been linked more specifically to saxagliptin among DPP-4 inhibitors. Therefore, the findings of this review should not be generalized to all agents within each drug class. Moreover, several studies did not clearly differentiate between drug-related adverse events and unrelated adverse events, potentially leading to misclassification. Finally, the review was restricted to studies published in English and sourced only from the PubMed database, raising the possibility of selection bias and incomplete retrieval of relevant data. Publication bias cannot be excluded, as studies reporting unfavorable safety outcomes may be underrepresented.

CONCLUSION

In conclusion, SGLT2 inhibitors demonstrated a lower incidence of overall adverse events compared to DPP4 inhibitors, but the rate of drug-related adverse events was similar between the groups. The specific side effect profiles of each drug class should guide personalized treatment decisions. Further large-scale randomized controlled trials focusing exclusively on safety outcomes are warranted to validate these findings and support individualized therapy in type II diabetes management.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Nimavat ZR, Patel AN, Gor AP, Ganguly B. Comparison of safety profiles of DPP-4 inhibitors with SGLT-2 inhibitors in type 2 diabetes mellitus: a systematic review. Int J Basic Clin Pharmacol 2025;14:843-9.