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Original Research Article

Comparative Evaluation of Adverse Drug Reactions Associated with Sodium–Glucose Cotransporter-2 Inhibitors and Dipeptidyl Peptidase-4 Inhibitors in Patients with Type 2 Diabetes Mellitus: A Prospective Observational Study

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Conflict of interest: Nil

Abstract:

Background: Sodium–glucose cotransporter-2 inhibitors (SGLT2is) and dipeptidyl peptidase-4 inhibitors (DPP-4is) have transformed the pharmacological treatment of Type 2 Diabetes Mellitus (T2DM) as second-line drugs to be added to metformin. Their different physiological pathways, however, expose patients to different organ-specific adverse drug reactions (ADRs), thus requiring real-world comparative pharmacovigilance data.

Methods: A 12-month prospective observational cohort study of 420 patients with T2DM who were newly treated with either SGLT2i (n=210) or DPP-4i (n=210) as an add-on to metformin. Patients were followed at baseline, 4, 12, 24, 36 and 52 weeks. Suspected ADRs were assessed using the Naranjo ADR Probability Scale for causality, Modified Hartwig and Siegel Scale for severity and Modified Schumock and Thornton Criteria for preventability. Independent t-tests and Chi-square tests were used for statistical comparisons.

Results: The mean age of the study population was 56.4±9.8 years in the SGLT2i group and 57.1±10.2 years in the DPP-4i group (p=0.473). The cumulative patient-level ADR incidence was significantly higher in the SGLT2i group (26.67%, 56 patients with 71 ADR events) than in the DPP-4i group (16.19%, 34 patients with 41 ADR events; p=0.009) during the 52-week follow-up period. Urogenital tract events were most commonly associated with SGLT2i therapy, such as genital mycotic infections (11.90% vs. 0.95%, p=0.0001), urinary tract infections (7.62% vs. 2.38%, p=0.014), and osmotic volume depletion (5.24% vs. 0.48%, p=0.003). Conversely, DPP-4i therapy demonstrated higher rates of nasopharyngitis (4.76% vs. 0.95%, p=0.019) and arthralgia (3.81% vs. 0.48%, p=0.018). Sixty-three percent (63.38%) of SGLT2i events and 53.66% of DPP-4i events were classified as "probable" in the Naranjo causality assessment. The majority of ADRs were mild to moderate (97.32%), although 32.39% were definitely or probably preventable with SGLT2i, compared to 14.63% with DPP-4i (p=0.038).

Conclusion: Both classes have good overall tolerability, but urogenital and hypovolemic ADRs are much more common with SGLT2is, whereas upper respiratory, musculoskeletal and cutaneous events are the most common with DPP-4is. Preventable reactions to SGLT2i can be significantly reduced through proactive patient education on perineal care and hydration.

Keywords: Adverse drug reactions, Dipeptidyl peptidase-4 inhibitors, Hartwig and Siegel scale, Naranjo algorithm, Pharmacovigilance, Sodium–glucose cotransporter-2 inhibitors, Type 2 diabetes mellitus.

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Introduction

Type 2 Diabetes Mellitus (T2DM) is one of the most critical public health crises in the twenty first century, as a result of the increasing rates of rapid urbanization, sedentary lifestyle and the increasing aging population profile [1] . Diabetes mellitus has quadrupled in prevalence worldwide over the last 30 years and about 90% of all cases are due to T2DM [1]. Maintaining glycemic control and cardiorenal protection are the main goals of clinical management in T2DM, which is inextricably linked to debilitating microvascular and macrovascular complications [1, 2]. Metformin is the universally accepted first-line pharmacotherapy, but as beta-cell function progresses, second-line oral

antihyperglycemic agents are required [3, 4]. Sodium–glucose cotransporter-2 inhibitors (SGLT2is) and dipeptidyl peptidase-4 inhibitors (DPP-4is) are the most commonly prescribed oral medications in the modern therapeutic classes recommended for dual therapy in the world [3] .

The widespread clinical use of SGLT2is (empagliflozin, dapagliflozin, canagliflozin) is largely due to their insulin-independent mechanism of action [5] . These agents inhibit SGLT2 proteins selectively in the S1 segment of the proximal renal convoluted tubule, which decreases the reabsorption of glucose by the kidney, lowers the renal threshold for glucose, and increases the excretion of glucose in the urine [5, 6]. In addition to reducing glycated hemoglobin (HbA1c) and causing modest weight loss, landmark trials and meta-analyses have demonstrated that SGLT2is provide significant reductions in heart failure hospitalization, cardiovascular mortality, and renal disease progression [2, 7, 8] . On the other hand, DPP-4is (sitagliptin, vildagliptin, teneligliptin, and linagliptin) act on the incretin pathway to produce antihyperglycemic effects [3, 9] . These drugs competitively inhibit the DPP-4 enzyme, which slows the rapid proteolytic degradation of endogenous glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), thus increasing glucose-dependent insulin secretion and reducing the release of glucagon after a meal [3, 4]. The DPP-4is are clinically preferred for their weight neutrality, low risk of intrinsic hypoglycemia and wide tolerability in various patient populations such as older adults and renal impairment [4, 9].

Although they have been shown to be effective in treating diabetes, the different modes of action of SGLT2is and DPP-4is mean that they have different adverse drug reactions (ADRs) profiles. Pharmacologically induced glucosuria with SGLT2i therapy is a persistent condition that creates a nutrient-rich microenvironment in the urogenital tract that promotes fungal colonization, especially by Candida species, which increases the risk of genital mycotic infections and urinary tract infections (UTIs) significantly [5, 10, 11]. In addition, SGLT2is have natriuretic and osmotic diuretic effects that can lead to intravascular volume depletion, orthostatic hypotension, and acute kidney injury particularly in elderly patients or those receiving concomitant loop diuretics [2, 12]. Worse yet, SGLT2is change the insulin:glucagon ratio and promote ketogenesis, which can lead to euglycemic diabetic ketoacidosis (eDKA), a rare but life-threatening metabolic emergency [13, 14].

The safety issues with DPP-4is are in contrast related to the widespread expression of the DPP-4 enzyme (CD26) on T-lymphocytes, endothelial cells, and epithelial tissues, where it cleaves a variety of off-target substrates such as bradykinin, substance P and neuropeptide Y [15] . As a result, nasopharyngitis, upper respiratory tract infections, hypersensitivity and severe disabling arthralgia have been associated with DPP-4 inhibition [15, 16, 17]. However, post-marketing surveillance and meta-analyses have also identified an association with DPP-4i therapy and acute pancreatitis [18, 19] and a spectrum of cutaneous reactions, including generalized pruritus, fixed drug eruptions, and autoimmune bullous pemphigoid [15, 20, 21]. Furthermore, some individuals in the class have been reviewed for possible signals of exacerbation of heart failure in pharmacovigilance databases [22].

Although large-scale randomized controlled trials (RCTs) have provided the baseline safety parameters for both classes of drugs, RCTs are performed in a highly selective patient population that often excludes patients with multiple comorbidities, polypharmacy, or suboptimal hygiene practices [23, 24]. Therefore, the actual incidence and range of ADRs in the real world are likely to be higher than what is observed in clinical trials [24, 25] . Moreover, there is a clear lack of head-to-head prospective observational studies that assess and compare the causality, severity, and preventability of ADRs for SGLT2is and DPP-4is using standardized pharmacovigilance algorithms in routine clinical practice. This research gap is critical to provide clinicians with evidence to guide second-line treatment and maximize treatment adherence. The purpose of the present study was to perform a prospective, comparative observational study of the incidence, clinical characteristics, causality, severity and preventability of ADRs associated with SGLT2is and DPP-4is in patients with T2DM.

Materials and Methods

Study Design and Setting: This was a prospective, parallel group, observational cohort study over a 12-month period at the Outpatient Department of Endocrinology and Internal Medicine of a tertiary care teaching hospital.

Sample Size Calculation: Sample size was determined based on a pilot hospital pharmacovigilance surveillance data, which estimated an overall ADR incidence of 25% in patients treated with SGLT2is and 13% in patients treated with DPP-4is, using the two-proportion hypothesis testing formula. The minimum sample size per cohort was calculated to be 191 patients with a two-sided alpha (α) error of 0.05 and a statistical power (1-β) of 85%. Considering a 10% attrition or loss to follow-up over the 52-week observational period, the recruitment target was determined to be 210 patients in each treatment arm, resulting in a total of 420 patients.

Study Population and Eligibility Criteria: Patients were screened for eligibility if they were adult outpatients with T2DM as defined by the American Diabetes Association criteria who had suboptimal glycemic control (HbA1c 7.0–10.0%), and had been treated with stable monotherapy with metformin (1000 mg/day or more) for at least 12 weeks. Patients were consecutively enrolled and stratified according to the treating physician's independent clinical judgment to start add-on therapy with an oral SGLT2i (dapagliflozin 10" mg/day", empagliflozin 10" or " 25" mg/day" or canagliflozin 100" mg/day") or an oral DPP-4i (sitagliptin 100" mg/day", vildagliptin 50" mg twice daily, teneligliptin 20" mg/day" or linagliptin 5" mg/day").

Inclusion Criteria:

- Patients with T2DM aged 18-75 years, both male and female, who have been diagnosed.
- Patients who were newly started on an SGLT2i or a DPP-4i as a second-line drug in addition to their existing metformin treatment.
- Patients who are willing to sign a written informed consent and follow-up as an outpatient for 52 weeks.

Exclusion Criteria:

- Type 1 Diabetes Mellitus, gestational diabetes or secondary diabetes.
- Patients who are taking insulin, sulfonylureas, thiazolidinediones, or GLP-1 receptor agonists at the same time (to avoid confounding of ADR attribution).
- Severe renal impairment (estimated glomerular filtration rate ("eGFR") less than 45 " mL/min/1.73 m" 〗^2 (calculated using the CKD-EPI equation) or severe hepatic dysfunction (serum transaminases more than 3 times the upper limit of normal).
- Patients with a history of recurrent complicated UTIs, abnormal urinary tract, chronic pancreatitis, or severe immunocompromise.
- Women who are pregnant or breastfeeding.

The data collection tools and study procedures are explained. Explanation of data collection tools and study procedures.

A structured, pre-validated Case Record Form (CRF) was used to collect demographic information (age, sex, body mass index [BMI], smoking and alcohol history), clinical characteristics (duration of T2DM, comorbidities, concomitant medications for hypertension or dyslipidemia), and baseline laboratory parameters (fasting plasma glucose [FPG], HbA1c, serum creatinine, eGFR, lipid profile, and routine urinalysis).

All enrolled participants were followed up prospectively for 52 weeks, with scheduled clinical evaluations at Week 4, Week 12, Week 24, Week 36, and Week 52. In between visits, patients were asked to report any new or adverse clinical symptoms to the study pharmacovigilance coordinator through a dedicated 24-hour telephone helpline. At each subsequent visit, active surveillance was carried out by structured patient interviews, physical examination (including orthostatic blood pressure measurement and skin examination), and laboratory log review.

Evaluation of the adverse drug reactions: All the unintended and undesirable reactions reported at normal therapeutic doses of the newly introduced SGLT2i and DPP-4i were captured on the national pharmacovigilance program's standardized Suspected ADR Reporting Form. All identified ADRs were Classified by physiological system using the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) terminology and assessed by an independent adjudication committee consisting of a senior endocrinologist and two clinical pharmacologists, who used three validated instruments:

Causality Assessment: Performed on the Naranjo ADR Probability Scale, a 10 item questionnaire that assigns weighted numerical scores from -4 to +13. The total score was used to classify ADRs as Definite (scores ≥9), Probable (scores 5"-" 8), Possible (scores 1"-" 4), or Doubtful (scores ≤0). The final comparative analysis only included events rated as Definite, Probable, or Possible.

Severity Assessment: Assessed using the Modified Hartwig and Siegel Scale which categorises ADRs into seven levels, later summarised into three main categories: Mild (Levels 1 and 2: no change in therapy or only temporary withholding without antidote), Moderate (Levels 3 and 4: drug discontinuation, specific medical treatment, or hospitalization or prolonged stay of at least 1 day), Severe (Levels 5, 6, and 7: intensive medical care, permanent disability, or direct or indirect death).

Preventability Assessment: Based on Modified Schumock and Thornton Criteria, which classifies ADRs as Definitely Preventable (e.g., history of previous reaction or inappropriate dose/route for patient's clinical condition), Probably Preventable (e.g., lack of necessary preventative measures or inadequate therapeutic monitoring), and Not Preventable (unavoidable idiosyncratic or intrinsic pharmacological reactions despite optimal clinical care).

Statistical Analysis: Data were coded and analyzed with IBM SPSS Statistics software (Version 28.0; IBM Corp., Armonk, NY, USA). Continuous variables were tested for normal distribution by Shapiro–Wilk test, and are presented as mean ± SD. Categorical variables were presented as frequencies

and percentages (n, %). Demographic and clinical differences between the SGLT2i and DPP-4i groups were compared by the independent samples Student's t-test for continuous variables and Pearson's Chi-square (χ^2) test or Fisher's exact test for categorical variables. The distributions of incidence rates, causality, severity, and preventability were compared by Chi-square tests, and relative risks (RR) and 95% confidence intervals (CI) were computed when appropriate. All analyses were considered statistically significant at a 2-tailed p-value < 0.05.

Results

Baseline Demographic and Clinical Characteristics: A total of 420 patients with T2DM were enrolled and completed the 52-week follow-up across the two study cohorts (n = 210 in the SGLT2i group; n = 210 in the DPP-4i group). Within the SGLT2i cohort, dapagliflozin was the most frequently prescribed agent (48.57%, n = 102), followed by empagliflozin (36.19%, n = 76) and canagliflozin (15.24%, n = 32). Within the DPP-4i cohort, sitagliptin accounted for 41.90% (n = 88) of prescriptions, followed by teneligliptin (26.67%, n = 56), vildagliptin (19.05%, n = 40), and linagliptin (12.38%, n = 26).

As detailed in Table 1, the two cohorts were well balanced at baseline with no statistically significant differences in age, sex distribution, duration of diabetes, glycemic indices, or renal function. The mean age of participants in the SGLT2i cohort was 56.4 ± 9.8 years compared to 57.1 ± 10.2 years in the DPP-4i cohort (p = 0.473). Males constituted 56.19% (n = 118) of the SGLT2i group and 53.81% (n = 113) of the DPP-4i group (p = 0.624). Patients assigned to SGLT2i therapy exhibited a marginally higher baseline BMI (28.4 ± 3.9 kg/m^2) compared to those prescribed a DPP-4i (27.8 ± 3.6 kg/m^2), though this difference did not reach statistical significance (p = 0.102). Concomitant hypertension and dyslipidemia were present in over half of the study population across both arms (p > 0.05).

Table 1: Baseline Demographic and Clinical Characteristics of the Study Cohorts (N = 420)

Parameter	SGLT2i Group (n=210)	DPP-4i Group (n=210)	p-value
Age (years), Mean ± SD	56.4 ± 9.8	57.1 ± 10.2	0.473
Sex: Male, n (%)	118 (56.19%)	113 (53.81%)	0.624
Sex: Female, n (%)	92 (43.81%)	97 (46.19%)	0.624
Body Mass Index (kg/m^2), Mean ± SD	28.4 ± 3.9	27.8 ± 3.6	0.102
Duration of T2DM (years), Mean ± SD	6.8 ± 3.4	6.5 ± 3.7	0.387
Baseline HbA1c (%), Mean ± SD	8.3 ± 0.8	8.2 ± 0.7	0.174
Fasting Plasma Glucose (mg/dL), Mean ± SD	168.5 ± 28.4	164.2 ± 26.9	0.112
Baseline eGFR (mL/min/1.73 m^2), Mean ± SD	78.6 ± 14.2	76.9 ± 15.1	0.235
Metformin Dose (mg/day), Mean ± SD	1485.7 ± 412.5	1460.0 ± 425.8	0.530
Comorbid Hypertension, n (%)	134 (63.81%)	128 (60.95%)	0.545
Comorbid Dyslipidemia, n (%)	142 (67.62%)	139 (66.19%)	0.756
Concomitant Diuretic Therapy, n (%)	38 (18.10%)	33 (15.71%)	0.515
Concomitant ACEi/ARB Therapy, n (%)	112 (53.33%)	106 (50.48%)	0.558

Note: SD = Standard Deviation; T2DM = Type 2 Diabetes Mellitus; HbA1c = Glycated Hemoglobin; eGFR = Estimated Glomerular Filtration Rate; ACEi = Angiotensin-Converting Enzyme Inhibitor; ARB = Angiotensin Receptor Blocker.

Overall Incidence and Clinical Spectrum of Adverse Drug Reactions: Over the 12-month follow-up period, a total of 112 distinct ADR events were documented among 90 patients across the entire study population, yielding an overall patient-level ADR incidence of 21.43%. When stratified by treatment class, the cumulative patient-level incidence of ADRs was significantly higher in the SGLT2i cohort, where 56 patients (26.67%) experienced a total of 71 ADR events, compared to the DPP-4i cohort, where 34 patients (16.19%) experienced a total of 41 ADR events (χ^2 = 6.84, p = 0.009). Multiple ADRs (two or more distinct events in the same individual) were recorded in 13 patients (6.19%) in the SGLT2i group and 6 patients (2.86%) in the DPP-4i group (p = 0.100). The mean latency period from drug initiation to the onset of the first ADR was significantly shorter in the SGLT2i cohort (42.8 ± 24.5 days) than in the DPP-4i cohort (68.4 ± 35.2 days, p = 0.0001).

As shown in Table 2, the organ-system distribution of ADRs differed markedly between the two pharmacological classes. In the SGLT2i cohort, reproductive and urogenital disorders predominated. Genital mycotic infections (vulvovaginal candidiasis in females and mycotic balanitis in males) were the single most frequent ADR in the SGLT2i arm, affecting 11.90% (n = 25) of patients compared to 0.95% (n = 2) in the DPP-4i arm (p = 0.0001). Notably, among the 25 SGLT2i-associated genital mycotic infections, 18 occurred in females

(19.57% of SGLT2i-treated females) and 7 occurred in males (5.93% of SGLT2i-treated males; $p = 0.002$). Urinary tract infections were similarly elevated in the SGLT2i group (7.62%, $n = 16$) compared to the DPP-4i group (2.38%, $n = 5$; $p = 0.014$). Furthermore, volume depletion-related events—manifesting as postural dizziness, orthostatic hypotension, and dehydration—occurred in 5.24% ($n = 11$) of SGLT2i users versus 0.48% ($n = 1$) of DPP-4i users ($p = 0.003$). A subgroup analysis revealed that 7 of the 11 SGLT2i patients experiencing volume depletion were aged ≥ 65 years and receiving concomitant diuretic therapy. Two cases (0.95%) of euglycemic diabetic ketoacidosis (eDKA) were confirmed in the SGLT2i group (both precipitated by acute febrile gastroenteritis with reduced oral intake), whereas no cases occurred in the DPP-4i group ($p = 0.499$).

Conversely, the ADR profile of the DPP-4i cohort was characterized by respiratory, musculoskeletal, gastrointestinal, and dermatological manifestations (Table 2). Nasopharyngitis and upper respiratory tract symptoms were observed in 4.76% ($n = 10$) of DPP-4i patients compared to 0.95% ($n = 2$) of SGLT2i patients ($p = 0.019$). Musculoskeletal complaints, specifically moderate-to-severe arthralgia and joint stiffness, were significantly more prevalent in the DPP-4i group (3.81%, $n = 8$) than in the SGLT2i group (0.48%, $n = 1$; $p = 0.018$). Cutaneous hypersensitivity reactions—including generalized pruritus, maculopapular rash, and one confirmed case of mild angioedema in a patient taking a concomitant angiotensin-converting enzyme inhibitor (ACEi)—were higher in the DPP-4i cohort (3.33%, $n = 7$) than in the SGLT2i cohort (0.95%, $n = 2$), though this trend was borderline non-significant ($p = 0.092$). One patient (0.48%) receiving sitagliptin developed mild acute pancreatitis at Week 28, presenting with epigastric pain and elevated serum lipase (385 U/L), which resolved promptly following drug withdrawal and conservative inpatient management.

Table 2: Comparative Spectrum and Incidence of Specific Adverse Drug Reactions (N = 420)

System Organ Class / Specific ADR	SGLT2i Group (n=210) n (%)	DPP-4i Group (n=210) n (%)	p-value
Urogenital and Renal Disorders			
Genital mycotic infections (Candidiasis/Balanitis)	25 (11.90%)	2 (0.95%)	0.0001*
Urinary tract infections (Dysuria/Cystitis)	16 (7.62%)	5 (2.38%)	0.014*
Osmotic polyuria / Nocturia	9 (4.29%)	1 (0.48%)	0.010*
Vascular and Volume Depletion Disorders			
Hypovolemia / Orthostatic hypotension / Dizziness	11 (5.24%)	1 (0.48%)	0.003*
Metabolic and Nutritional Disorders			
Euglycemic diabetic ketoacidosis (eDKA)	2 (0.95%)	0 (0.00%)	0.499
Mild symptomatic hypoglycemia	2 (0.95%)	3 (1.43%)	0.653
Respiratory, Thoracic, and Mediastinal Disorders			
Nasopharyngitis / Upper respiratory infection	2 (0.95%)	10 (4.76%)	0.019*
Musculoskeletal and Connective Tissue Disorders			
Arthralgia / Severe joint pain	1 (0.48%)	8 (3.81%)	0.018*
Skin and Subcutaneous Tissue Disorders			
Pruritus / Maculopapular rash / Angioedema	2 (0.95%)	7 (3.33%)	0.092
Gastrointestinal and Hepatobiliary Disorders			
Dyspepsia / Nausea / Abdominal discomfort	1 (0.48%)	3 (1.43%)	0.315
Acute pancreatitis	0 (0.00%)	1 (0.48%)	0.999
Total ADR Events Recorded	71 Events	41 Events	—
Total Patients With ≥ 1 ADR	56 (26.67%)	34 (16.19%)	0.009*

Note: Percentages are calculated using the cohort size ($n = 210$) as the denominator. Some patients experienced more than one ADR event. $$ indicates statistical significance at $p < 0.05$.*

Causality, Severity, Preventability, and Clinical Outcomes of ADRs: All 112 documented ADR events (71 in the SGLT2i cohort and 41 in the DPP-4i cohort) were subjected to formal pharmacovigilance scaling (Table 3). According to the Naranjo ADR Probability Scale, the majority of events in both groups were classified as "Probable" (63.38% in the SGLT2i group vs. 53.66% in the DPP-4i group) or "Possible" (32.39% vs. 43.90%). Only 3 events (4.23%) in the SGLT2i arm (recurrent genital candidiasis that resolved upon drug withdrawal and recurred upon rechallenge) and 1 event (2.44%) in the DPP-4i arm (pruritic rash confirmed on accidental re-exposure) met the criteria for "Definite" causality. There was no statistically significant difference in the overall causality distribution between the two drug classes ($p = 0.518$).

Evaluation of clinical severity using the Modified Hartwig and Siegel Scale revealed that 71.83%

(n = 51) of SGLT2i-related ADRs and 75.61% (n = 31) of DPP-4i-related ADRs were "Mild" (Levels 1–2), requiring no alteration of the antidiabetic regimen (Table 3). "Moderate" severity events (Levels 3–4)—which required targeted medical intervention (such as topical/oral fluconazole for candidiasis, oral antibiotics for UTIs, or analgesics/drug switching for arthralgia)—accounted for 25.35% (n = 18) of SGLT2i events and 21.95% (n = 9) of DPP-4i events. Only 3 events across the entire study were classified as "Severe" (Level 5, requiring hospitalization): the 2 cases of eDKA in the SGLT2i group (2.82%) and the 1 case of acute pancreatitis in the DPP-4i group (2.44%). None of the ADRs resulted in permanent disability or mortality (p = 0.908).

In contrast, preventability analysis via the Modified Schumock and Thornton Criteria demonstrated a statistically significant divergence between the cohorts (p = 0.038; Table 3). Within the SGLT2i group, 32.39% (n = 23) of ADR events were adjudicated as either "Definitely Preventable" (8.45%, n = 6) or "Probably Preventable" (23.94%, n = 17), primarily encompassing hypovolemic events in patients on unadjusted loop diuretics and recurrent urogenital infections linked to inadequate baseline counseling on perineal hygiene and water intake. Conversely, 85.37% (n = 35) of ADRs in the DPP-4i cohort were classified as "Not Preventable," reflecting the largely idiosyncratic nature of nasopharyngitis, arthralgia, and cutaneous hypersensitivity reactions. Permanent discontinuation of the offending study medication due to intolerable or severe ADRs was required in 9 patients (4.29%) in the SGLT2i group and 6 patients (2.86%) in the DPP-4i group (p = 0.430).

Table 3: Causality, Severity, Preventability, and Management Outcomes of Reported ADRs (N = 112 Events)

Assessment Scale / Category	SGLT2i ADRs (n=71 Events) n (%)	DPP-4i ADRs (n=41 Events) n (%)	p-value
Naranjo Causality Scale			0.518
Definite (Score ≥ 9)	3 (4.23%)	1 (2.44%)	
Probable (Score 5–8)	45 (63.38%)	22 (53.66%)	
Possible (Score 1–4)	23 (32.39%)	18 (43.90%)	
Hartwig and Siegel Severity Scale			0.908
Mild (Levels 1–2)	51 (71.83%)	31 (75.61%)	
Moderate (Levels 3–4)	18 (25.35%)	9 (21.95%)	
Severe (Levels 5–7)	2 (2.82%)	1 (2.44%)	
Schumock and Thornton Preventability			0.038*
Definitely Preventable	6 (8.45%)	1 (2.44%)	
Probably Preventable	17 (23.94%)	5 (12.20%)	
Not Preventable	48 (67.61%)	35 (85.37%)	
Clinical Action Taken			0.684
Drug continued without dose modification	53 (74.65%)	32 (78.05%)	
Drug temporarily withheld / Dose reduced	9 (12.68%)	3 (7.32%)	
Drug permanently discontinued and switched	9 (12.68%)	6 (14.63%)	

Note: Percentages are calculated using the total number of ADR events in each cohort (n = 71 for SGLT2i; n = 41 for DPP-4i) as the denominator. $$ indicates statistical significance at p < 0.05.*

Glycemic and Anthropometric Outcomes at 52 Weeks: Although safety was the primary endpoint, secondary efficacy parameters were tracked at Week 52 to contextualize risk-benefit profiles. Both cohorts achieved significant reductions in HbA1c from baseline (p < 0.001). At Week 52, the mean HbA1c reduction was slightly greater in the SGLT2i cohort ($-0.94 \pm 0.42\%$) than in the DPP-4i cohort ($-0.86 \pm 0.39\%$, p = 0.044). Furthermore, patients in the SGLT2i group experienced a significant reduction in body weight (-2.6 ± 1.4 kg) over 52 weeks, whereas patients in the DPP-4i group remained weight-neutral (-0.2 ± 0.9 kg, p = 0.0001).

Discussion

Choosing the best second-line antihyperglycemic agent after metformin alone is a delicate balance between glycemic durability, cardiorenal benefit and medication safety [1, 3] . We assessed and compared the real-world ADR profiles of SGLT2is and DPP-4is in 420 ambulatory patients with T2DM in this 52-week prospective observational study. Our main finding shows that both drug classes were generally safe and had mostly mild to moderate adverse drug reactions, but SGLT2i therapy had an increased cumulative patient-level incidence of ADRs compared to DPP-4i therapy (26.67% vs. 16.19%, p=0.009). Furthermore, the two classes had organ

toxicity patterns that were mutually exclusive and mechanism-driven: SGLT2is were strongly associated with urogenital infections and intravascular volume depletion, while DPP-4is were associated with upper respiratory tract inflammation, arthralgia and cutaneous hypersensitivity reactions.

The high prevalence of urogenital tract infections (UTIs) in our SGLT2i cohort (genital mycotic infections 11.90% and bacterial UTIs 7.62%) is consistent with the pathophysiological mechanisms and previous clinical studies [5, 6, 10] . SGLT2is inhibit glucose reabsorption in the renal tubules, leading to a sustained urinary glucose excretion of 50" to " 80" g/day" which directly promotes adherence and proliferation of Candida albicans on the vulvovaginal and balanopreputial mucosa. The higher prevalence of genital mycotic infections in female patients as compared to male patients (19.57% vs. 5.93%, p=0.002) was confirmed by Scheen [5] and Opingari et al. [6]. who reported that anatomical factors and moist mucosal surfaces make women with diabetes more susceptible to fungal colonization. Moreover, the relatively short mean time to onset of ADR in our SGLT2i cohort (42.8±24.5" days"") is similar to the population-based cohort study by Lega et al. [10] that showed that the risk of genital mycotic infections is highest in the first 30 days of SGLT2i use in older adults. Interestingly, a meta-analysis by Bapir et al. [11] showed that SGLT2is triple the risk of genital infections even in non-diabetic cohorts, indicating that pharmacological glucosuria is the main mechanism underlying this ADR. The association between SGLT2is and bacterial UTIs was less consistent in large cardiovascular trials [2, 8]; however, in our real-world cohort, there was a significant difference in the UTI rate between the SGLT2i arm (7.62%) and the non-SGLT2i arm (2.38%) (p=0.014). Infections of the urogenital organs were mostly mild to moderate, however, and responded quickly to standard antifungal or antibiotic therapy, and rarely required withdrawal of the drug.

The second large group of events we investigated in our study were hemodynamic ADRs, such as osmotic polyuria (4.29%) and symptomatic volume depletion or orthostatic hypotension (5.24%). SGLT2 inhibition causes transient natriuresis and osmotic diuresis, which leads to a decrease in plasma volume and interstitial fluid [2, 7]. This hemodynamic unloading is beneficial for heart failure protection [8, 12] but can cause orthostatic dizziness and hypotension in susceptible individuals [2]. In our cohort, almost two-thirds of those who developed symptomatic hypovolemia were elderly (≥65" years") and were not receiving concomitant thiazide or loop diuretics with dose reduction. Two cases (0.95%) of eDKA were also observed in the SGLT2i group, both associated with acute intercurrent gastrointestinal illness and starvation. In addition to lowering plasma glucose and insulin levels, SGLT2is increase glucagon secretion from pancreatic alpha-cells and decrease renal clearance of ketone bodies, resulting in a delicate metabolic balance that can easily lead to ketoacidosis when the body is stressed or dehydrated, even with near-normal blood glucose levels, as described by Taylor et al. [13] and Wang and Isom [14]. Our results are also consistent with the real-world comparative safety study by Dawwas et al. [25], which found that there was a significantly higher hazard of DKA in new users of SGLT2is than in new users of DPP-4i.

By contrast, the DPP-4i group had a lower overall incidence of ADRs (16.19%), which aligns with recent network meta-analyses that have shown the favourable tolerability profile of incretin enhancers. However, DPP-4i treatment had unique immunomodulatory and off-target enzymatic effects. The rates of nasopharyngitis (4.76%) and disabling arthralgia (3.81%) were significantly higher in the DPP-4i group than in the SGLT2i group. Inhibition of DPP-4/CD26 can lead to local inflammation in the nasopharynx and synovial joints, as it is involved in the costimulation of T-cells and degradation of pro-inflammatory chemokines like stromal cell-derived factor-1 (SDF-1) [15, 16]. Our incidence of arthralgia (3.81%) is consistent with the systematic review and meta-analysis by Men et al. [16], which found a significant class-wide association between DPP-4is and joint pain, and the population-based study by Wang et al. [17], which reported that the risk of arthralgia was highest in the first few months of treatment. In our study, three patients with severe DPP-4i-induced arthralgia had complete resolution of symptoms within 3 weeks of switching to an SGLT2i, which further supports the reversible, drug-induced nature of the arthralgia.

Other events that required clinical attention in the DPP-4i arm included cutaneous reactions (3.33%) and acute pancreatitis (0.48%). As summarized by Zaresharifi et al. [15] DPP-4 inhibitors increase the half-life of substance P and bradykinin, which can lead to pruritus, exanthematous eruptions, and angioedema, including the latter in one of our patients when combined with ACEis. We didn't see bullous pemphigoid in our 52-week follow-up period, which may have been due to the small number of patients and the long latency period associated with autoimmune blistering diseases; however, clinicians should be vigilant for persistent itching in older DPP-4i users. In addition, the single case of acute pancreatitis in a patient taking sitagliptin is consistent with the findings of the updated meta-analysis of randomized trials and real-world pharmacovigilance databases by Singh et al. [18] and Muhammed et al. [19], who reported a small but statistically significant risk of acute

pancreatitis with DPP-4is, which is due to the sustained stimulation of GLP-1 receptors in the ducts and acini. Notably, we did not observe any cases of exacerbation of heart failure in the DPP-4i group, which is consistent with the current cautiousness of prescribing and with the pharmacovigilance analyses performed by Fadini et al. [22].

The application of the Naranjo, Hartwig and Siegel scale and Schumock and Thornton scale, which are crucial for converting raw ADR counts into meaningful clinical information, was structured in a unique way in our study [23, 24]. More than 50% of the ADRs in both cohorts were classified as "Probable" on the Naranjo scale, which is comparable with the Naranjo causality distribution reported in ambulatory antidiabetic pharmacovigilance studies by Desai et al. [23] and Elangwe et al. [24]. Most importantly, our preventability assessment showed that almost one-third (32.39%) of ADRs in the SGLT2i group were definitely or probably preventable, whereas only 14.63% of ADRs in the DPP-4i group were definitely or probably preventable (p=0.038). This finding has major implications for clinical practice: whereas DPP-4i reactions (such as arthralgia or rash) are largely idiosyncratic, the vast majority of SGLT2i complications can be actively prevented through structured patient education on routine perineal hygiene after urination, adequate daily fluid intake, empirical reduction of concomitant diuretic doses in normovolemic elderly patients, and strict adherence to "sick-day rules" (temporarily withholding SGLT2is during acute febrile illness, vomiting, or surgical fasting) to avert eDKA [6, 13, 25].

There are a number of limitations to this study that should be noted. First, the non-randomized, observational study design may have led to channeling bias, as physicians may have been more inclined to prescribe SGLT2is to slightly younger or heavier patients and DPP-4is to older patients, but there were no statistically significant differences between the groups at baseline. Second, the ethical concerns of routinely rechallenging drugs in most patients meant that few ADRs could be given a "Definite" score on the Naranjo algorithm. Third, the 52-week follow-up period and sample size of 420 patients were adequate for common adverse drug reactions but were not large enough to detect ultra-rare or long-latency adverse drug reactions like bullous pemphigoid, Fournier's gangrene or pancreatic carcinoma. Additional multicenter registries with longer follow-up are warranted to assess these uncommon safety signals.

Conclusion

This prospective observational study shows that SGLT2 inhibitors and DPP-4 inhibitors have similar overall safety profiles when used as second-line add-on therapy to metformin in patients with T2DM, with more than 97% of the ADRs reported being mild to moderate. SGLT2 inhibitors, however, have a much greater incidence of overall ADRs, mainly due to genital mycotic infections, urinary tract infections and osmotic volume depletion in the first 2 months of treatment. In contrast, DPP-4 inhibitors have a lower overall ADR burden, but have specific risks of nasopharyngitis, disabling arthralgia, cutaneous hypersensitivity and rare acute pancreatitis. Importantly, almost a third of the ADRs linked to SGLT2i are preventable in the clinic. Therapeutic selection between these two classes should be individualized based on baseline patient risk factors and the introduction of SGLT2 inhibitors should be systematically coordinated with proactive pharmacovigilance counseling on urogenital hygiene, hydration status, diuretic dose adjustment, and sick-day medication management to optimize treatment adherence and patient safety.

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