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Disproportionality analysis of infection associated with antidiabetic drug use patterns

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While various antidiabetic drug classes are associated with differing infection risks, comprehensive evidence on infection risk across multidrug regimens remains limited. Therefore, this study aims to investigate the pharmacovigilance signal between antidiabetic drug use and infection risk, considering the number and patterns of drug use. This study evaluated the pharmacovigilance signal between antidiabetic drug use and infection utilizing the global pharmacovigilance database. To account for adverse events from multiple drug use, we restructured the database at the individual level using a unique demographic identifier, allowing assessment of infection risk by drug combination and count. Antidiabetic drugs include metformin, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), sodium-glucose cotransporter-2 (SGLT2) inhibitors, thiazolidinediones, alpha-glucosidase inhibitors, and insulin, with infections categorized by the system. The pharmacovigilance signal of adverse drug reactions was estimated using adjusted reporting odds ratios (aRORs) with 95% confidence intervals (CIs) through multivariable logistic regression. SGLT2 inhibitor users reported the highest frequency of infections (*n* = 13,570), followed by insulin (*n* = 11,322) and GLP-1 RAs (*n* = 5966). When analyzing only monotherapy, excluding combination use, urinary tract infections were significantly linked solely to SGLT2 inhibitors (aROR, 10.41 [95% CI, 9.76–11.09]), while hepatobiliary and pancreatic infections were associated with DPP-4 inhibitors (aROR, 1.72 [95% CI, 1.28–2.31]), with no significant pharmacovigilance signal observed for other drug classes. Compared to monotherapy, combination therapy with two drugs (aROR, 1.24 [95% CI, 1.20–1.29]) or three or more drugs (aROR, 1.42 [95% CI, 1.13–1.79]) was associated with infection. Although the results from disproportionality analysis did not indicate causal relationship, our findings indicate that infection types vary between monotherapy and combination therapy, highlighting the need for further investigation into these pharmacovigilance signal due to the increased susceptibility of individuals with diabetes.

Keywords Adverse drug reaction, Antidiabetic medications, Combination, Diabetes, Infection

Diabetes is estimated to affect 6.1% of the global population, with prevalence continuing to rise[1]. As a disease associated with numerous complications and serving as a significant risk factor for various conditions, diabetes garnered substantial attention, leading to the continuous development of diverse antidiabetic therapies[2]. Improvements in antidiabetic therapies have led to marked increases in both medication usage and healthcare

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expenditures. For instance, in Denmark, the prescription of antidiabetic drugs increased 3.4-fold, and related expenditures increased by nearly fivefold from 1996 to 2017[3].

While previous studies indicate an increased risk of sepsis due to infections among individuals using antidiabetic drugs, attributing this elevated risk solely to the medications is challenging, given that diabetes itself is a known risk factor for infections[4]. Emerging evidence suggests that the risk of specific infections may vary depending on antidiabetic drug class. For example, sodium-glucose cotransporter 2 (SGLT2) inhibitors have been associated with a higher risk of genital infections, while dipeptidyl peptidase-4 (DPP-4) inhibitors may increase the risk of upper respiratory tract infections[5]. Moreover, antidiabetic drugs are frequently prescribed in combination regimens rather than as monotherapy, tailored to disease severity and comorbidities[6]. These combination regimens may interact in ways that influence infection risk, underscoring the need for a comprehensive assessment of this association.

To address this gap, we analyzed data from the World Health Organization's (WHO) global pharmacovigilance database to examine the pharmacovigilance signal between antidiabetic drug use and the occurrence of infections as adverse drug reactions. Our study investigated the association between infections and both individual drug components and commonly used combination regimens. By leveraging data from diverse populations, this study aims to provide a thorough evaluation of infection risk associated with antidiabetic medications, contributing to inform clinical practice and identifying areas for further research.

Methods

Database

This pharmacovigilance study was conducted using VigiBase, the global database for individual case safety reports of adverse drug reactions, developed and maintained by the Uppsala Monitoring Centre (WHO Collaborating Centre, Uppsala, Sweden)[7]. Since its establishment in 1968, VigiBase has compiled more than 35 million reports from over 140 countries as of 2024. This database serves as a key resource for assessing potential causal relationships between specific drugs and adverse reactions on a global scale. All data in our analysis were fully anonymized to protect patient confidentiality. Approval for the use of this database was granted by the Institutional Review Boards of Kyung Hee University. This study was conducted in accordance with relevant ethical guidelines and regulations.

Case selection

Given the potential infection risks associated with antidiabetic medications, adverse drug reactions in this database were classified into system-based infection categories: (1) genital, (2) respiratory, (3) urinary tract, (4) gastrointestinal, (5) hepatobiliary and pancreatic, (6) musculoskeletal, (7) nervous system, and (8) cardiac infections. Each report included drug information, details of adverse events, and patient characteristics, with adverse events classified using the Medical Dictionary for Regulatory Activities (MedDRA; version 26.0). The MedDRA terms for the infections included in the analysis are available in Table S1.

Drug classification was conducted using the WHO Drug Global Dictionary, where each drug is assigned a unique six-character drug record number designated by the WHO. This standardization ensures consistency across drug formulations and enables a comprehensive analysis of adverse drug reactions[8]. Based on drug record numbers, this study analyzed the following antidiabetic drug classes: metformin, sulfonylureas, DPP-4 inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), SGLT2 inhibitors, thiazolidinediones (TZDs), alpha-glucosidase inhibitors (AGIs), and insulin. Only reports classified as suspected or interacting, according to WHO causality assessment guidelines, were considered significant[9].

We also extracted supplementary information from each report, including sex, age, reporting year, reporting region (African region, Region of the Americas, Southeast Asia region, European region, Eastern Mediterranean region, and Western Pacific region), outcome (mild and moderate to severe), reporter qualification (health professional and non-health professional), and time to onset.

Outcomes were classified as moderate to severe if reported as fatal or resulting in death due to the adverse drug reaction; otherwise, they were classified as mild. Time to onset is the interval between drug administration and the onset of an adverse event. The minimum is derived from the latest possible drug start date and the earliest possible reaction start date, while the maximum is based on the earliest drug start date and the latest reaction start date. The average of the minimum and maximum values was used, following VigiBase guidelines to ensure consistency and reliability in the analysis. Missing values for covariates were classified into an unknown category for each covariate[10].

Restructuring data for individual-level case consolidation

Traditional pharmacovigilance studies often analyze adverse drug reactions at the individual case report level, which may lead to duplication and overrepresentation[11]. When a single patient on multiple medications experiences an adverse event, attributing the event to a specific drug can be challenging, resulting in multiple reports for the same incident. This issue is particularly relevant for studies involving antidiabetic drugs, which frequently use combination regimens.

To minimize this bias, we restructured the data at the individual level rather than the report level. Each individual experiencing an adverse drug reaction was assigned a unique identifier, enabling the consolidation of multiple reports into individual-level records. This restructuring transformed the compiled dataset from report-bsed records into an individual-level, thereby facilitating a clearer evaluation of drug exposure patterns and their associations with infection risk[12]. Based on this restructured database, we conducted additional analyses distinguishing between instances when specific antidiabetic drugs were used alone and in various combination regimens. We also examined changes in adverse drug reactions based on the number of antidiabetic medications used.

Statistical analysis

The restructured database consists of individuals who have reported experiencing adverse drug reactions at least once. To explore the pharmacovigilance signal patterns between antidiabetic drug classes and infections in greater depth, we restricted the study population to those who have experienced adverse drug reactions related to antidiabetic drugs. This approach enabled us to indirectly conduct a case-control study within patients with diabetes. In this group, individuals reporting infections as adverse events formed the case group, while those not reporting infections served as the control group. This methodology has been utilized in a previous pharmacovigilance study[13].

We evaluated the pharmacovigilance signal of infection based on antidiabetic drug use patterns using multivariable logistic regression. Adjusted reporting odds ratios (aRORs) with 95% confidence intervals (CIs) were calculated to control for potential confounders. The analysis was adjusted for age, sex, reporting region, report qualification, and reporting year. The ROR evaluates the association between drug use and adverse event occurrence based on a contingency table. An aROR with a lower bound of the 95% CI exceeding 1.00 was considered indicative of a significant pharmacovigilance signal of adverse drug reaction[14,15]. A two-tailed p-value of <0.05 was considered statistically significant. We analyzed the distribution of valid time-to-onset values for each antidiabetic drug class and according to the number of antidiabetic drugs used, presenting the results graphically. Time-to-onset distributions are reported as the median and interquartile range (IQR) in days. All statistical analyses were conducted using Python (version 3.12) and SAS software (version 9.4).

Results

Overview of antidiabetic drug-associated infections

We identified individuals reporting infections associated with antidiabetic drugs (Table 1). SGLT2 inhibitors had the largest number of individuals reporting infection ($n=13{,}570$), followed by insulin ($n=11{,}322$), GLP-1 RAs ($n=5966$), and metformin ($n=4451$), with AGIs users reporting the fewest ($n=61$). Infection reports were more common in females than males across all drug classes, particularly with GLP-1 RAs (66.16%). Most infection reports came from individuals aged 45–64 and those over 65. The majority of reports originated from the Americas and Europe, with GLP-1 RAs (81.58%) and TZDs (83.41%) more prevalent in the Americas.

While many reported infection outcomes were mild, TZD was associated with a higher incidence of moderate to severe outcomes (8.62%). Upper and lower respiratory infections were frequently reported across drug classes. SGLT2 inhibitor users predominantly reported urinary tract infections ($n=3362$, 24.78%), musculoskeletal infection, ($n=4163$, 30.68%), and genital infections ($n=3630$, 26.75%). Metformin users also reported urinary tract infections ($n=719$, 16.15%), musculoskeletal infections ($n=566$, 12.72%), and genital infections ($n=515$, 11.57%). Gastrointestinal infections were prevalent among GLP-1 RA users ($n=722$, 12.10%), while TZD users showed a higher incidence of hepatobiliary and pancreatic infections ($n=70$, 5.64%).

Figure 1 presents the proportion of patients reporting various infections and the distribution of time to onset for each antidiabetic drug class. The highest number of infections was among insulin users ($n=9818$), followed by SGLT2 inhibitors ($n=7786$), and GLP-1 RAs ($n=4956$). In patients using two or more antidiabetic drugs, the combination of metformin and DPP-4 inhibitors had the highest infection reports ($n=950$), followed by metformin and SGLT2 inhibitors ($n=917$).

Insulin (median, 122 days [IQR, 39–595]) and metformin (median, 128 days [IQR, 31–465]), the most commonly used antidiabetic treatments, showed the longest time to onset for infections. In contrast, GLP-1 RAs (median, 67 days [IQR, 20–242]) and SGLT2 inhibitors (median, 74 days [IQR, 19–244]) were associated with a significantly shorter time to onset. Additionally, compared to monotherapy (median, 91 days [IQR, 27–310]), dual therapies (median, 122 days [IQR, 31–421]) and triple or more therapies (median, 148 days [IQR, 39–451]) showed an increased time to onset for infections with a greater number of drugs used.

Pharmacovigilance signal for antidiabetic drug-associated infections

Table 2 examines the associations between each antidiabetic drug class and reported infections by infection type. SGLT2 inhibitors showed significant pharmacovigilance signal with several infection types, notably urinary tract infections (aROR, 14.40 [95% CI, 13.06–15.88]), musculoskeletal infection (aROR, 31.94 [95% CI, 27.62–36.95]), and genital infections. Notably, most reported musculoskeletal infections associated with SGLT2 inhibitors were identified as Fournier's gangrene. Significant pharmacovigilance signals were also observed for gastrointestinal infections (aROR, 2.15 [95% CI, 1.83–2.52]), lower respiratory infection (aROR, 1.91 [95% CI, 1.76–2.08]), and cardiac infection (aROR, 3.47 [95% CI, 1.34–9.01]).

For insulin, significant signals were found with urinary tract infections (aROR, 1.23 [95% CI, 1.10–1.38]), all respiratory infections, and hepatobiliary and pancreatic infections (aROR, 1.50 [95% CI, 1.07–2.09]). GLP-1 RAs showed significant signals with gastrointestinal infection (aROR, 2.07 [95% CI, 1.76–2.44]), some respiratory infections, and hepatobiliary and pancreatic infections (aROR, 1.46 [95% CI, 1.03–2.07]). DPP-4 inhibitors had significant signal with urinary tract infections (aROR, 1.20 [95% CI, 1.07–1.34]), gastrointestinal infection (aROR, 1.55 [95% CI, 1.31–1.83]), all respiratory infections, and hepatobiliary and pancreatic infection (aROR, 2.47 [95% CI, 1.79–3.42]). Metformin (aROR, 1.37 [95% CI, 1.19–1.57]) and AGi (aROR, 1.82 [95% CI, 1.09–3.04]) showed significant pharmacovigilance signals only with gastrointestinal infections. TZD was significantly associated only with cardiac infections (aROR, 4.78 [95% CI, 1.86–12.29]), while sulfonylureas showed no signal with any infections. Table S2 presents the results of the assessment of associations between specific components of GLP-1 RAs, SGLT2 inhibitors, and DPP-4 infections with infections.

Association between combination use of antidiabetic drugs and infections

Considering the frequent use in combination of various antidiabetic drugs, we conducted an additional analysis to assess the infection associated with these combinations. Table 3 evaluates the associations with infections for

Characteristic	Participants, *n* (%)							
	SGLT2	Insulin	GLP1 RA	Metformin	DPP4	TZD	SU	AGI
	(*n* = 13,570)	(*n* = 11,322)	(*n* = 5966)	(*n* = 4451)	(*n* = 3786)	(*n* = 1242)	(*n* = 885)	(*n* = 61)
Sex, ***n (%)***								
Male	6101 (44.96)	4234 (37.40)	1851 (31.03)	1850 (41.56)	1611 (42.55)	559 (45.01)	377 (42.60)	22 (36.07)
Female	7077 (52.15)	6867 (60.65)	3947 (66.16)	2482 (55.76)	2041 (53.91)	637 (51.29)	472 (53.33)	37 (60.66)
Unknown	392 (2.89)	221 (1.95)	168 (2.82)	119 (2.67)	134 (3.54)	46 (3.70)	36 (4.07)	2 (3.28)
Age, **years**, ***n (%)***								
0–17	10 (0.07)	252 (2.23)	20 (0.34)	8 (0.18)	2 (0.05)	2 (0.16)	0 (0.00)	1 (1.64)
18–44	1039 (7.66)	772 (6.82)	397 (6.65)	366 (8.22)	192 (5.07)	65 (5.23)	72 (8.14)	2 (3.28)
45–64	5670 (41.78)	3021 (26.68)	1779 (29.82)	1789 (40.19)	1086 (28.68)	455 (36.63)	249 (28.14)	21 (34.43)
≥65	3733 (27.51)	3469 (30.64)	1319 (22.11)	1350 (30.33)	1395 (36.85)	457 (36.80)	334 (37.74)	34 (55.74)
Unknown	3118 (22.98)	3808 (33.63)	2451 (41.08)	938 (21.07)	1111 (29.34)	263 (21.18)	230 (25.99)	3 (4.92)
Reporting year, ***n (%)***								
1968–1989	0 (0.00)	15 (0.13)	0 (0.00)	2 (0.04)	0 (0.00)	0 (0.00)	30 (3.39)	0 (0.00)
1990–1999	0 (0.00)	32 (0.28)	0 (0.00)	32 (0.72)	0 (0.00)	5 (0.40)	29 (3.28)	3 (4.92)
2000–2009	0 (0.00)	555 (4.90)	292 (4.89)	187 (4.20)	183 (4.83)	513 (41.30)	148 (16.72)	2 (3.28)
2010–2019	6966 (51.33)	6009 (53.07)	2318 (38.85)	2299 (51.65)	2381 (62.89)	642 (51.69)	507 (57.29)	44 (72.13)
2020–2024	6604 (48.67)	4711 (41.61)	3356 (56.25)	1931 (43.38)	1222 (32.28)	82 (6.60)	171 (19.32)	12 (19.67)
Region reporting, ***n (%)***								
African region	59 (0.43)	426 (3.76)	12 (0.20)	27 (0.61)	12 (0.32)	2 (0.16)	7 (0.79)	0 (0.00)
Region of the Americas	6849 (50.47)	7910 (69.86)	4867 (81.58)	2496 (56.08)	2011 (53.12)	1036 (83.41)	555 (62.71)	8 (13.11)
Southeast Asia region	351 (2.59)	402 (3.55)	11 (0.18)	292 (6.56)	316 (8.35)	4 (0.32)	11 (1.24)	8 (13.11)
European region	5191 (38.25)	1258 (11.11)	753 (12.62)	1185 (26.62)	451 (11.91)	87 (7.00)	146 (16.50)	8 (13.11)
Eastern Mediterranean region	70 (0.52)	349 (3.08)	83 (1.39)	25 (0.56)	18 (0.48)	2 (0.16)	7 (0.79)	0 (0.00)
Western Pacific region	1050 (7.74)	977 (8.63)	240 (4.02)	426 (9.57)	978 (25.83)	111 (8.94)	159 (17.97)	37 (60.66)
Fatal outcomes, ***n (%)***								
Mild	6525 (48.08)	5476 (48.37)	3063 (51.34)	2229 (50.08)	2038 (53.83)	299 (24.07)	379 (42.82)	40 (65.57)
Moderate to severe	235 (1.73)	571 (5.04)	97 (1.63)	178 (4.00)	252 (6.66)	107 (8.62)	39 (4.41)	4 (6.56)
Unknown	6810 (50.18)	5275 (46.59)	2806 (47.03)	2044 (45.92)	1496 (39.51)	836 (67.31)	467 (52.77)	17 (27.87)
Reporter qualification, ***n (%)***								
Health professional	5272 (38.85)	8751 (77.29)	4377 (73.37)	1733 (38.94)	1430 (37.77)	396 (31.88)	285 (32.20)	11 (18.03)
Non-health professional	8011 (59.03)	2230 (19.70)	1349 (22.61)	2527 (56.77)	2225 (58.77)	621 (50.00)	461 (52.09)	42 (68.85)
Unknown	287 (2.11)	341 (3.01)	240 (4.02)	191 (4.29)	131 (3.46)	225 (18.12)	139 (15.71)	8 (13.11)
Type of infection, ***n (%)***								
Urinary tract infection	3362 (24.78)	943 (8.33)	528 (8.85)	719 (16.15)	415 (10.96)	133 (10.71)	111 (12.54)	4 (6.56)
Cardiac infection	11 (0.08)	22 (0.19)	7 (0.12)	7 (0.16)	6 (0.16)	21 (1.69)	2 (0.23)	0 (0.00)
Gastrointestinal infection	373 (2.75)	502 (4.43)	722 (12.10)	391 (8.78)	235 (6.21)	43 (3.46)	73 (8.25)	16 (26.23)
Upper Respiratory infection	656 (4.83)	4077 (36.01)	2078 (34.83)	871 (19.57)	1263 (33.36)	330 (26.57)	234 (26.44)	11 (18.03)
Lower Respiratory infection	1247 (9.19)	4589 (40.53)	2104 (35.27)	1219 (27.39)	1377 (36.37)	566 (45.57)	317 (35.82)	25 (40.98)
Respiratory infection	54 (0.40)	187 (1.65)	85 (1.42)	60 (1.35)	77 (2.03)	16 (1.29)	12 (1.36)	0 (0.00)
Hepatobiliary & Pancreatic infection	36 (0.27)	230 (2.03)	130 (2.18)	69 (1.55)	90 (2.38)	70 (5.64)	29 (3.28)	2 (3.28)
Musculoskeletal infection	4163 (30.68)	463 (4.09)	141 (2.36)	566 (12.72)	125 (3.30)	32 (2.58)	53 (5.99)	2 (3.28)
Nervous system infection	38 (0.28)	159 (1.40)	41 (0.69)	34 (0.76)	27 (0.71)	9 (0.72)	14 (1.58)	1 (1.64)
Genital infection	3630 (26.75)	150 (1.32)	130 (2.18)	515 (11.57)	171 (4.52)	22 (1.77)	40 (4.52)	0 (0.00)

Table 1. Baseline characteristics of individuals reporting infections associated with antidiabetic drugs. Abbreviation: AGI, alpha-glucosidase inhibitors; DPP4i, dipeptidyl peptidase-4 inhibitors; GLP1RA, glucagon-like peptide-1 receptor agonists; SGLT2i, sodium-glucose cotransporter 2 inhibitors; TZD, thiazolidinediones.

five commonly used antidiabetic drug classes—SGLT2 inhibitors, insulin, GLP-1 RAs, metformin, and DPP-4 inhibitors—when used alone. SGLT2 inhibitors (82.83%, 85,064/102,700), insulin (95.62%, 328,100/343,137), and GLP-1 receptor agonists (94.95%, 203,267/214,070) were predominantly used alone, while metformin (52.36%, 86,541/165,276) and DPP-4 inhibitors (54.43%, 50,550/92,868) had fewer reports of single use.

Notably, the pharmacovigilance signal strengths with infections varied among specific drug classes. Urinary tract infections were significantly associated only with SGLT2 inhibitors (aROR, 10.41 [95% CI, 9.76–11.09]), and hepatobiliary and pancreatic infections were associated only with DPP-4 inhibitors (aROR, 1.72 [95% CI, 1.28–2.31]). In contrast, insulin use alone was significantly associated with nervous system infections (aROR, 3.26 [95% CI, 2.25–4.72]).

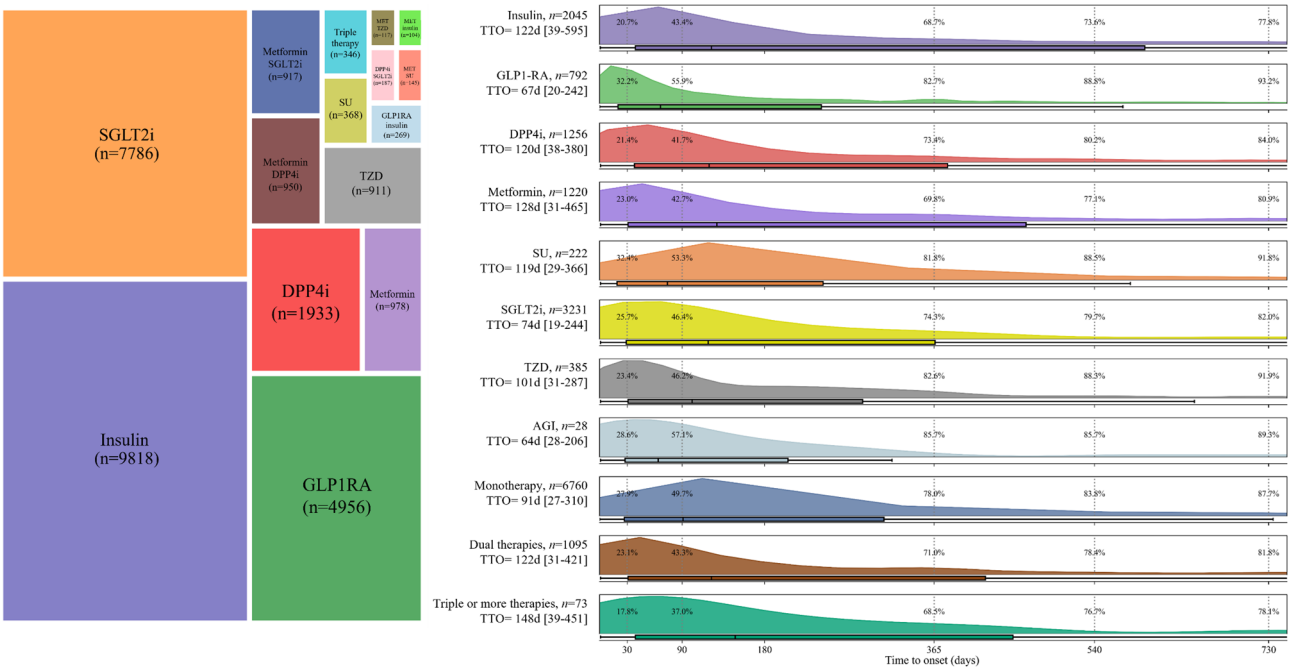


Fig. 1. Distribution of frequency in individuals reporting infections associated with antidiabetic drug regimens and time to onset of infections associated with antidiabetic drug usage patterns. TTO was defined as the time (in days) from antidiabetic drug initiation to the reported onset of infection. "n" denotes the number of infection cases with available TTO data. Boxplots display the median time to onset, interquartile range (IQR) [25th–75th percentile], and 1.5 × IQR (whiskers). The proportion of patients developing infections over time is shown along the x-axis, with reference lines at 1 month, 3 months, 1 year, and 1.5 years for each drug class. Abbreviation: DPP-4, dipeptidyl peptidase-4 inhibitors; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; SGLT2, sodium-glucose cotransporter2; SU, sulfonylureas; TZDs, Thiazolidinediones.

Figure 2 indicates significant differences in the association between various combinations of antidiabetic drugs and infection compared to the use of individual drug classes. The combination of metformin with other antidiabetic medications was associated with stronger signal for infection, particularly when combined with SGLT2 inhibitors (aROR, 14.05 [95% CI, 12.92–15.28]). Furthermore, the data indicate that using dual therapies (aROR, 1.24 [95% CI, 1.20–1.29]) or triple or more therapies (aROR, 1.42 [95% CI, 1.13–1.79]) significantly exhibited stronger signal for infection compared to monotherapy.

Discussion

Key findings

This study comprehensively investigated the pharmacovigilance signals between antidiabetic drugs and infections using a global pharmacovigilance database. We identified various infection types with differing signals by drug class. Notably, SGLT2 inhibitors were significantly associated with urinary tract infections, musculoskeletal infections, and genital infections. We also examined infection patterns associated with combinations of antidiabetic drugs. In analyses limited to single-agent use, urinary tract infections were significantly associated only with SGLT2 inhibitors, while hepatobiliary and pancreatic infections were associated solely with DPP-4 inhibitors, with no significant signals for other drug classes. Conversely, insulin use alone indicated a significant pharmacovigilance signal with nervous system infections. This indicates a pattern of pharmacovigilance signals that differs from conventional methods of assessing adverse drug reactions, which do not consider the concomitant use of other antidiabetic medications. In comparisons to single-agent metformin use, the combination of GLP-1 RAs, SGLT2 inhibitors, DPP-4 inhibitors, and insulin was associated with a higher likelihood of infections, particularly when SGLT2 inhibitors were included. Additionally, a greater number of medications correlated with an increased risk of infections.

Underlying plausible mechanism

Patients with diabetes have 2- to 4-fold increased risk of hospitalization due to infections compared to the general population, irrespective of infection type[4]. Moreover, infection-related outcomes are often worse in individuals with diabetes[16]. Both diabetes and hyperglycemia can signify a chronic inflammatory state[17], which impairs antigen-presenting cell function and diminishes adaptive immune responses, thereby heightening infection risk[18].

SGLT2 inhibitors regulate blood glucose levels by inhibiting glucose reabsorption in the renal tubules, promoting glucosuria[19]. This mechanism has raised concerns about an increased risk of urinary tract infections

	SGLT2 inhibitors (*n* = 100,700)		Insulin (*n* = 343,137)		GLP-1 RA (*n* = 214,070)		Metformin (*n* = 165,276)		DPP-4 inhibitors (*n* = 92,868)		TZDs (*n* = 118,369)		Sulfonylurea (*n* = 57,532)		AGi (*n* = 8498)	
	n	aROR[a]	n	aROR[a]	n	aROR[a]	n	aROR[a]	n	aROR[a]	n	aROR[a]	n	aROR[a]	n	aROR[a]
Type of infection																
Urinary tract infection	3362	**14.40 (13.06 to 15.88)**	943	**1.23 (1.10 to 1.38)**	528	1.09 (0.96 to 1.23)	719	0.81 (0.74 to 0.88)	415	**1.20 (1.07 to 1.34)**	133	0.68 (0.56 to 0.83)	111	0.56 (0.46 to 0.69)	4	0.15 (0.06 to 0.40)
Cardiac infection	11	**3.47 (1.34 to 9.01)**	22	2.34 (0.92 to 5.96)	7	1.13 (0.38 to 3.33)	7	0.67 (0.29 to 1.56)	6	2.04 (0.74 to 5.64)	21	**4.78 (1.86 to 12.29)**	2	0.79 (0.19 to 3.40)	0	NA
Gastrointestinal infection	373	**2.15 (1.83 to 2.52)**	502	0.90 (0.76 to 1.07)	722	**2.07 (1.76 to 2.44)**	391	**1.37 (1.19 to 1.57)**	235	**1.55 (1.31 to 1.83)**	43	0.22 (0.16 to 0.31)	73	0.80 (0.62 to 1.02)	16	**1.82 (1.09 to 3.04)**
Upper Respiratory infection	656	1.10 (0.99 to 1.22)	4077	**1.62 (1.48 to 1.78)**	2078	**1.33 (1.21 to 1.46)**	871	0.71 (0.66 to 0.78)	1263	**2.70 (2.47 to 2.95)**	330	0.48 (0.42 to 0.55)	234	0.78 (0.68 to 0.89)	11	0.22 (0.12 to 0.40)
Lower Respiratory infection	1247	**1.91 (1.76 to 2.08)**	4589	**1.93 (1.79 to 2.09)**	2104	**1.38 (1.27 to 1.49)**	1219	0.93 (0.87 to 1.00)	1377	**2.53 (2.34 to 2.73)**	566	0.71 (0.64 to 0.79)	317	0.90 (0.80 to 1.01)	25	0.60 (0.40 to 0.90)
Respiratory infection	54	1.39 (0.92 to 2.10)	187	**1.48 (1.01 to 2.19)**	85	1.07 (0.71 to 1.61)	60	0.79 (0.57 to 1.10)	77	**2.79 (1.94 to 4.02)**	16	0.46 (0.25 to 0.84)	12	0.67 (0.36 to 1.23)	0	NA
Hepatobiliary& Pancreatic infection	36	0.79 (0.52 to 1.21)	230	**1.50 (1.07 to 2.09)**	130	**1.46 (1.03 to 2.07)**	69	0.65 (0.48 to 0.86)	90	**2.47 (1.79 to 3.42)**	70	1.33 (0.92 to 1.95)	29	0.99 (0.65 to 1.51)	2	0.49 (0.12 to 2.02)
Musculoskeletal infection	4163	**31.94 (27.62 to 36.95)**	463	0.73 (0.62 to 0.86)	141	0.27 (0.22 to 0.33)	566	0.80 (0.73 to 0.88)	125	0.50 (0.41 to 0.60)	32	0.13 (0.09 to 0.18)	53	0.67 (0.50 to 0.89)	2	0.50 (0.12 to 2.03)
Nervous system infection	38	1.12 (0.63 to 1.96)	159	1.27 (0.74 to 2.17)	41	0.51 (0.28 to 0.91)	34	0.66 (0.41 to 1.07)	27	1.08 (0.63 to 1.86)	9	1.12 (0.63 to 1.96)	14	0.88 (0.45 to 1.70)	1	0.58 (0.08 to 4.40)
Genital infection																
Both	1889	**99.44 (72.42 to 136.54)**	111	0.31 (0.20 to 0.50)	88	0.55 (0.37 to 0.81)	303	0.72 (0.62 to 0.83)	107	0.90 (0.70 to 1.17)	14	0.64 (0.31 to 1.30)	39	0.27 (0.11 to 0.66)	0	NA
Male	725	**41.73 (29.30 to 59.44)**	28	0.57 (0.36 to 0.92)	27	0.82 (0.52 to 1.28)	118	1.02 (0.84 to 1.26)	33	1.01 (0.69 to 1.46)	4	0.28 (0.10 to 0.79)	0	NA	0	NA
Female	1016	**65.46 (54.01 to 79.33)**	11	0.92 (0.73 to 1.18)	15	0.86 (0.66 to 1.10)	94	0.99 (0.87 to 1.12)	31	1.11 (0.90 to 1.37)	4	0.62 (0.36 to 1.07)	1	1.09 (0.78 to 1.53)	0	NA

Table 2. Association between antidiabetic drugs and infections by drug class. Abbreviation: AGi, alpha-glucosidase inhibitors; aROR, adjusted reporting odds ratio; DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonists; SGLT2, sodium-glucose cotransporter 2; TZD, thiazolidinediones. [a] Includes possible prior infections, not limited to monotherapy cases, but encompassing all instances where the respective drug was part of the reported regimen. [b] Adjusted for age (0–17, 18–44, 45–64, and ≥ 65 years); sex (male and female); region of report (African, Americas, Southeast Asia, Europe, Eastern Mediterranean, and Western Pacific); and reporter qualification (health professional, non-health professional, and unknown). Bolded values indicate statistical significance, as they represent ROR lower 95% confidence intervals exceeding 1.00.

	SGLT2 inhibitor only (*n* = 85,064)		Insulin only (*n* = 328,100)		GLP-1 RA only (*n* = 203,267)		Metformin only (*n* = 86,541)		DPP-4 inhibitor only (*n* = 50,550)	
	n	aROR[a]	n	aROR[a]	n	aROR[a]	n	aROR[a]	n	aROR[a]
Type of infection, *n (%)*										
Urinary tract infection	2882	**10.41 (9.76 to 11.09)**	860	0.77 (0.70 to 0.85)	465	0.79 (0.71 to 0.88)	140	0.39 (0.32 to 0.46)	202	1.09 (0.94 to 1.26)
Cardiac infection	11	1.69 (0.86 to 3.32)	19	0.70 (0.37 to 1.33)	5	0.35 (0.14 to 0.88)	2	0.27 (0.07 to 1.14)	5	1.32 (0.51 to 3.39)
Gastrointestinal infection	295	**2.46 (2.14 to 2.82)**	459	0.90 (0.78 to 1.04)	663	**2.22 (2.00 to 2.47)**	181	**1.44 (1.22 to 1.70)**	116	**1.81 (1.48 to 2.20)**
Upper Respiratory infection	488	0.80 (0.72 to 0.87)	3901	**1.81 (1.69 to 1.94)**	1917	0.96 (0.91 to 1.01)	263	0.45 (0.40 to 0.51)	834	**2.25 (2.08 to 2.43)**
Lower Respiratory infection	991	**1.23 (1.15 to 1.32)**	4287	**1.51 (1.42 to 1.60)**	1881	0.81 (0.77 to 0.85)	405	0.55 (0.50 to 0.61)	753	**1.59 (1.47 to 1.72)**
Respiratory infection	39	1.00 (0.71 to 1.42)	179	**1.55 (1.16 to 2.07)**	76	0.79 (0.61 to 1.03)	22	0.63 (0.41 to 0.99)	50	**2.55 (1.86 to 3.48)**
Hepatobiliary & Pancreatic infection	28	0.55 (0.37 to 0.82)	221	1.19 (0.95 to 1.49)	120	1.01 (0.82 to 1.25)	24	0.43 (0.28 to 0.65)	53	**1.72 (1.28 to 2.31)**
Musculoskeletal infection	3607	**28.90 (26.91 to 31.05)**	397	0.42 (0.37 to 0.48)	101	0.24 (0.20 to 0.29)	48	0.52 (0.39 to 0.69)	37	0.70 (0.50 to 0.97)
Nervous system infection	31	1.21 (0.82 to 1.77)	158	**3.26 (2.25 to 4.72)**	38	0.54 (0.38 to 0.76)	18	0.74 (0.45 to 1.22)	19	1.39 (0.86 to 2.25)
Genital infection										
Both	1561	**31.81 (27.81 to 36.38)**	89	0.04 (0.02 to 0.06)	59	0.25 (0.17 to 0.37)	19	0.09 (0.04 to 0.22)	24	0.37 (0.19 to 0.69)
Male	598	**16.78 (13.97 to 20.14)**	26	0.16 (0.10 to 0.24)	22	0.43 (0.28 to 0.68)	1	0.03 (0.01 to 0.23)	12	0.77 (0.42 to 1.38)
Female	796	**19.11 (17.12 to 21.32)**	7	0.14 (0.11 to 0.18)	13	0.26 (0.19 to 0.34)	2	0.16 (0.10 to 0.25)	6	0.47 (0.31 to 0.73)

Table 3. Association between antidiabetic drugs and infections with single antidiabetic drug use. Abbreviation: aROR, adjusted reporting odds ratio; DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonists; SGLT2, sodium-glucose cotransporter 2. [a] Adjusted for age (0–17, 18–44, 45–64, and ≥ 65 years); sex (male and female); region of report (African, Americas, Southeast Asia, Europe, Eastern Mediterranean, and Western Pacific); and reporter qualification (health professional, non-health professional, and unknown). Bolded values indicate statistical significance, as they represent ROR lower 95% confidence intervals exceeding 1.

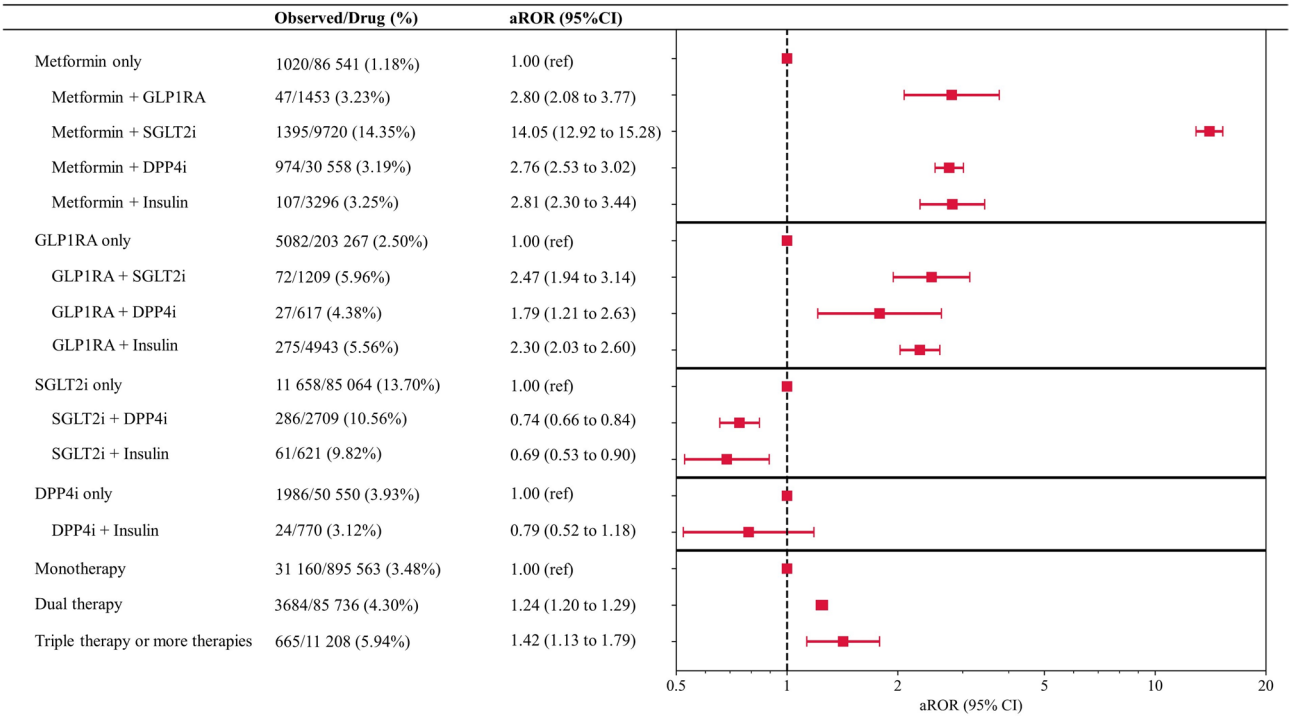


Fig. 2. Association between antidiabetic drug regimens and infection risk. Abbreviation: aROR, adjusted reporting odds ratio; DPP4i, dipeptidyl peptidase-4 inhibitors; GLP1RA, glucagon-like peptide-1 receptor agonists; ROR, reporting odds ratio; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

and genital infections, particularly Fournier's gangrene[20,21]. However, previous studies have reported conflicting results when comparing the risks of these infections with those associated with other antidiabetic drugs. Thus, further research is necessary to clarify these associations and better understand the potential risks linked to SGLT2 inhibitors[22].

DPP-4 inhibitors lower blood glucose levels by inhibiting the degradation of incretin hormones, thereby prolonging the activity of glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide. These hormones enhance insulin secretion in a glucose-dependent manner while suppressing glucagon release, thus improving glycemic control[23]. However, DPP-4 inhibitors may affect gallbladder motility and contractility through their mechanisms, potentially increasing the risk of gallbladder and biliary diseases, which are associated with bile stasis and secondary infections[24,25]. In contrast, similar effects have not been observed in individuals using GLP-1 RAs in our analysis, despite their overlapping mechanisms. This underscores the necessity for further research to clarify the unique impact of DPP-4 inhibitors on infection risk and to identify additional contributing factors.

The use of insulin alone in relation to nervous system infections requires a distinct perspective. Currently, no direct mechanism has been established linking insulin to the onset of nervous system infections. However, insulin is often administered in severe cases of type 2 diabetes mellitus, particularly when hemoglobin A1c levels exceed 10%, suggesting that these patients may be at increased risk for infections associated with diabetes[26]. Specifically, diabetic patients may have heightened exposure to pathogens such as Listeria and Klebsiella, which can lead to central nervous system infections[27].

Policy implication

Our study shows a distinct pattern in the association between diabetes medications and various types of infections, indicating that this association varies based on the specific regimen of combined medications and the total number of medications used. While diabetes is a recognized risk factor for infections[28], these unique patterns suggest a potential adverse drug reaction between diabetes medications and infections. Clinicians should be aware that certain diabetes medications may contribute to specific infections and recognize the increased susceptibility of diabetic patients to infections, necessitating heightened awareness and proactive management.

Traditionally, pharmacovigilance studies focus on identifying signals for specific adverse drug reaction[29]. However, our findings indicate that pharmacovigilance signals may show different patterns when medications are used in combination rather than as monotherapy. For instance, while signals for urinary tract infections, musculoskeletal infections, and genital infections were observed in patients receiving metformin, these signals were absent in the metformin-only group. This suggests that such adverse drug reactions are more likely attributable to the concurrent use of SGLT2 inhibitors rather than metformin itself. Given the frequent use of combination therapy in diabetes management[30], pharmacovigilance studies should consider these complexities, and well-designed observational studies are necessary to provide robust evidence supporting the pharmacovigilance signals identified in this context.

Limitations

This study is the first to comprehensively evaluate the association between antidiabetic drugs and infections, considering various antidiabetic drug prescription regimens. However, several limitations remain. First, VigiBase, as a spontaneous reporting database, has inherent limitations[31]. Well-known adverse drug reactions may be overreported, while lesser-known reactions may be underrepresented or obscured[32]. Additionally, differences in drug approval dates may introduce temporal biases that affect pharmacovigilance signal detection. Nonetheless, this database has amassed a substantial number of adverse drug reaction reports globally over an extended period. Given the application of well-established pharmacovigilance methodologies, the findings derived from this dataset remain reliable and valuable. Second, the dataset lacks additional clinical details, such as laboratory test results, physiological data, medication history, and previous medical history, that could provide valuable insights into the mechanisms underlying adverse drug reactions[33]. These factors may also act as potential confounders affecting the occurrence of adverse events, and their inclusion would enhance the accuracy of pharmacovigilance signal evaluation. However, the nature of the dataset limits the exploration of such aspects. In this study, we attempted to link records using unique identifiers to identify concomitantly used medications, but a more detailed characterization of individuals cases would require further research. Third, individuals using antidiabetic drugs typically have diabetes, a condition characterized by chronic hyperglycemia that increases baseline infection risk. In this context, medication adherence becomes a critical factor in evaluating drug-infection associations. Given this elevated background risk, the observed disproportionality signals are particularly noteworthy, as they may indicate meaningful patterns beyond expected susceptibility. These findings highlight the importance of ongoing surveillance and further targeted investigations to refine the safety profiles of antidiabetic therapies. Finally, as an association study, this research does not establish causal relationships between medications and adverse events[34]. In particular, longer intervals between drug administration and adverse event onset may increase the extent to which underlying patient conditions confound the observed association. While adverse events were reported in the context of drug use, establishing a temporal relationship, this study was not designed to confirm causality.

Conclusions

This study utilized a global pharmacovigilance database to evaluate pharmacovigilance signals associated with antidiabetic drugs and infections, focusing on combination regimens. Although the results from disproportionality analysis did not indicate causal relationship, we identified various infection types associated with each antidiabetic drug class and noted that these signals differed between monotherapy and combination therapy. Given the increased susceptibility of individuals with diabetes to infections and potential complications,

careful consideration of antidiabetic medication use is essential. Moreover, the common use of combination therapies highlights the need for caution in assessing pharmacovigilance signals without accounting for these regimens. This underscores the necessity for well-designed studies to further investigate these indirect risk signals.

Data availability

The data are available upon request. Study protocol and statistical code: Available from DKY (yonkkang@gmail.com). Dataset: Available from the Uppsala Monitoring Centre (WHO Collaborating Centre) or WHO through a data use agreement.

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Acknowledgements

The licensing agreement for our database was valid through February 7, 2025. The information presented does not represent official statements from the Uppsala Monitoring Centre or the World Health Organization. We acknowledge that certain terms in this manuscript may be interpreted as implying causality or clinical recommendations; however, this was not our intent. Terms such as "associated" or "related" are used descriptively to reflect patterns observed in VigiBase and do not imply confirmed causal relationships. We also recognize the inherent limitations of disproportionality analyses using pharmacovigilance data, including reporting biases and the inability to infer causality or individual-level risk. Therefore, these findings should be interpreted with caution and not used as the basis for clinical decision-making.

Author contributions

Dr. DKY had full access to all data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors have approved the final version of the manuscript before submission. Study concept and design: THK, KL, SP, JK, and DKY; Acquisition, analysis, or interpretation of data: THK, KL, SP, JK, and DKY; Drafting of the manuscript: THK, KL, SP, JK, and DKY; Critical revision of the manuscript for important intellectual content: JP, HJ, HL, HK, JC, SYR, AH, FB, and TS; Statistical analysis: THK, KL, SP, JK, and DKY; Study supervision: JK and DKY are corresponding authors and supervised the study. THK, KL, and SP contributed equally to this study as first authors. DKY is the senior author and served as the guarantor. The corresponding authors attest that all listed authors meet the authorship criteria, and others who do not meet the criteria have been omitted.

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Declarations

Competing interests

The authors declare no competing interests.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki. Approval for the use of anonymized and electronically processed individual case data was obtained from the Institutional Review Board of Kyung Hee University. Written informed consent was obtained from all participants and/or their legal guardians prior to data collection. No other ethical approval is required to conduct this study using secondary data, and the data were not altered or used for any other purposes.

Additional information

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