# Genital but Not Urinary Tract Infections Associated with SGLT2 Inhibitor Use: A Real-World Cohort Study from Portugal

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## Abstract

**Introduction:** Sodium–glucose cotransporter-2 inhibitors (SGLT2i) provide cardio–renal–metabolic benefits in type 2 diabetes mellitus (T2DM), although concern persists regarding genitourinary infections. This study assessed the incidence of genitourinary infections among patients with T2DM treated with SGLT2i in Portuguese primary care, by infection type, individual agent, and dosage, and evaluated treatment discontinuation and predictors of infection.

**Methods:** This multicentric retrospective cohort study used electronic health records from Portuguese primary care centers. Adults with T2DM receiving pharmacological treatment between 2019 and 2023 were classified according to SGLT2i use. Genitourinary infection incidence was compared between groups, with infections identified through clinical records, laboratory data, or targeted antimicrobial prescriptions.

**Results:** A total of 5865 patients were included: 2997 treated with SGLT2i and 2868 with other glucose-lowering agents. Overall genitourinary infections occurred in 9.8% of SGLT2i users and 11.1% of controls (OR 0.87, 95% CI 0.74-1.03; *p*=0.109). Urinary tract infections were not increased with SGLT2i: cystitis (6.5% *vs* 10.1%; OR 0.62, 95% CI 0.52-0.75), pyelonephritis (0.2% ***vs*** 0.5%; OR 0.48, 95% CI 0.19-1.18), and prostatitis in male patients (0.4% *vs* 0.8%; OR 0.53, 95% CI 0.21-1.37). Genital mycotic infections were more frequent with SGLT2i: balanitis in male patients (2.7% ***vs*** 0.7/%; OR 3.93, 95% CI 1.98-7.81) and vulvovaginal mycotic infection in female patients (3.5% *vs* 1.5%; OR 2.37, 95% CI 1.42-3.96). Treatment discontinuation due to infection occurred in 1.8%.

**Conclusion:** SGLT2i were associated with higher genital mycotic infection occurrence, but not with increased urinary tract infection risk, supporting their safety in routine care.

**Keywords:** Diabetes Mellitus, Type 2/drug therapy; Sodium-Glucose Transporter 2 Inhibitors/adverse effects; Urinary Tract Infections/chemically induced

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## INTRODUCTION

Sodium–glucose cotransporter-2 inhibitors (SGLT2i) have redefined the management of type 2 diabetes mellitus (T2DM), providing substantial cardio–reno–metabolic benefits beyond glycemic control.[1-3]

In Portugal, there has been a substantial increase in SGLT2 inhibitor prescriptions since 2019, consolidating their position as preferred first-line agents over older antidiabetic classes such as DPP-4 inhibitors, sulfonylureas, and thiazolidinediones.[4] Therefore, their prescription has expanded steadily among both diabetic and non-diabetic patients, as several studies have confirmed their cardiovascular and renal benefits,[5-11] establishing these drugs as major prognostic-modifying therapies. Notably, large landmark randomized controlled trials, such as EMPEROR-Reduced, EMPEROR-Preserved, DELIVER, CREDENCE, DAPA-CKD, EMPA-KIDNEY and EMPA-REG[5-11] — have consistently demonstrated significant reductions in heart failure hospitalization, slower chronic kidney disease (CKD) progression, and lower all-cause mortality among patients with T2DM and with or at high risk of heart failure, and/or CKD treated with these agents.[5-11]

In accordance with this evidence, the 2024 American Diabetes Association (ADA) guidelines recommended the preferential use of SGLT2i in patients with cardiovascular disease or high cardiovascular risk.[12]

Despite their revolutionary impact on the treatment paradigm, some adverse effects have been reported, particularly an increased risk of genitourinary infections (GUI), mostly of fungal etiology, an outcome theoretically expected due to their mechanism of action and consequent glycosuria.[13-15] However, randomized controlled trials may underestimate important adverse events and include selected populations that may not fully reflect routine clinical practice.[16] Conversely, several real-world studies have shown inconsistent and heterogeneous results regarding the incidence of GUI in T2DM patients treated with SGLT2i.[14,16-19]

Therefore, further evidence, especially from real-world clinical practice, is needed to clarify the incidence and risk factors of GUI associated with SGLT2i use in patients with T2DM. In clinical trials reporting higher GUI incidence, most infections were mild to moderate in severity and responded to standard therapy, allowing continuation of SGLT2i treatment.[13,15, 21] Notably, T2DM itself is an important independent risk factor for GUI[13, 21] and any potential increase in infection risk with SGLT2i could negatively affect quality of life and lead to discontinuation of a therapy that provides major prognostic benefits.[22]

In a study conducted in a Family Health Unit in Northern Portugal and published in March 2024, no statistically significant association was observed between SGLT2i use and the development of genitourinary infections. Although cystitis appeared less frequent among SGLT2i users in the unadjusted analysis, this association was not maintained after adjustment for potential confounders.[23]

Therefore, it is important to assess the incidence of these infections in a larger sample, using a representative sample from the Central region of Portugal, including patients followed in Family Health Units across various age groups and comorbidity profiles, to determine whether GUI are more frequent among SGLT2i users and to identify the main risk factors for their occurrence.

The primary objective was to compare the cumulative incidence of GUI among patients with T2DM treated with SGLT2i and those treated with other glucose-lowering agents.

The secondary objectives were: (1) to characterize patients diagnosed with GUI in terms of body mass index, glycated hemoglobin, serum creatinine, estimated glomerular filtration rate calculated by CKD-EPI 2021, and urinary albumin-to-creatinine ratio or microalbuminuria; (2) to assess whether the diagnosis of GUI led to discontinuation of SGLT2i therapy; and (3) to identify predictors of GUI.

## MATERIAL AND METHODS

We conducted a retrospective observational study using electronic medical records from the ***SClínico*** platform of Primary Care Centers (PCC) belonging to five Local Health Units (LHU) in the Central region of Portugal: LHU Coimbra, LHU Aveiro Region, LHU Viseu-Dão Lafões, LHU Cova da Beira, and LHU Leiria Region.

Each PCC included one investigator responsible for data collection according to a predefined protocol (*Supplementary material*).

The Ethical Committee approved this study, in agreement with institutional guidelines. Informed consent was waived, given the retrospective and noninterventional nature of the study.

### Participants

We selected as eligible all adult patients (≥18 years of age) with a diagnosis of T2DM receiving clinical follow-up at the respective PCC between January 1, 2019 and December 31, 2023, with at least one recorded scheduled in-person consultation.

Exclusion criteria consisted of the absence of laboratory data or appropriate follow-up during the study period, an estimated glomerular filtration rate <30 mL/min/1.73 m² and pregnancy.

The patients were classified into two cohorts according to treatment with SGLT2i: analysis cohort comprised individuals receiving SGLT2i (empagliflozin, dapagliflozin, canagliflozin or ertugliflozin), as monotherapy or in combination with other antidiabetic agents, whereas the control cohort included patients treated with antidiabetic agents other than SGLT2i.

In addition, for all patients, regardless of whether they developed a GUI, demographic and clinical data were collected, including age, sex, ethnicity, and the type of

antidiabetic drug class prescribed. Information on personal medical history potentially associated with increased GUI risk was also recorded, including benign prostatic hyperplasia (BPH), urinary incontinence, prior chemo-radiotherapy (CRT), obstructive urolithiasis, previous GUI episodes, and bladder neoplasia. These variables were included in the logistic regression analysis to identify independent risk factors for GUI.

Diagnosis of GUI was established according to at least one of the following criteria: (1) a documented diagnosis in the patient's clinical record, (2) clinical and laboratory evidence (urinalysis and/or urine culture with pathogen isolation), or (3) prescription of an antibiotic or antifungal agent specifically targeting a GUI.

For the main analysis, GUI was analysed at the patient level as a binary outcome, and each patient was counted only once according to the occurrence of at least one GUI during the study period. Recurrent genital or urinary infections in the same patient were not analysed as separate independent events. Previous/recurrent GUI was assessed through clinical record review and defined as documentation of at least two GUI episodes before the GUI diagnosis recorded during the 2019–2023 study period.

For all patients who developed a GUI, clinical and laboratory variables were collected at the time of GUI diagnosis, including BMI, glycated hemoglobin, serum creatinine, eGFR (calculated using the CKD-EPI Creatinine 2021 equation), and urinary albumin-to-creatinine ratio. These variables were used exclusively for descriptive characterization of patients with GUI.

Standard descriptive methods were employed to summarize the characteristics of study subjects. Categorical variables were presented as frequencies, while continuous variables were summarized using mean ± standard deviation.

Comparisons between the SGLT2i subgroup and other glucose-lowering agent subgroups were performed using the Chi-square test or Fisher's exact test for categorical variables and the independent samples t-test for continuous variables.

Among the variables collected, potential independent predictors of GUI were investigated using multivariable binary logistic regression analysis. GUI was analysed as a binary patient-level outcome, each patient was counted only once, and recurrent GUI episodes were not modelled as repeated events. Candidate predictors were selected a priori based on clinical plausibility and availability in electronic health records. In the overall population, the variables entered into the initial model were previous GUI, urinary incontinence, urinary lithiasis, and bladder cancer. Because benign prostatic hyperplasia is sex-specific, a separate male subgroup model was performed, including previous GUI, benign prostatic hyperplasia, urinary incontinence, urinary lithiasis, and bladder cancer. The final models were obtained using the backward conditional method.

Statistical analyses were performed using IBM Statistics version 28.0. A $p$-value < 0.05 was considered statistically significant.

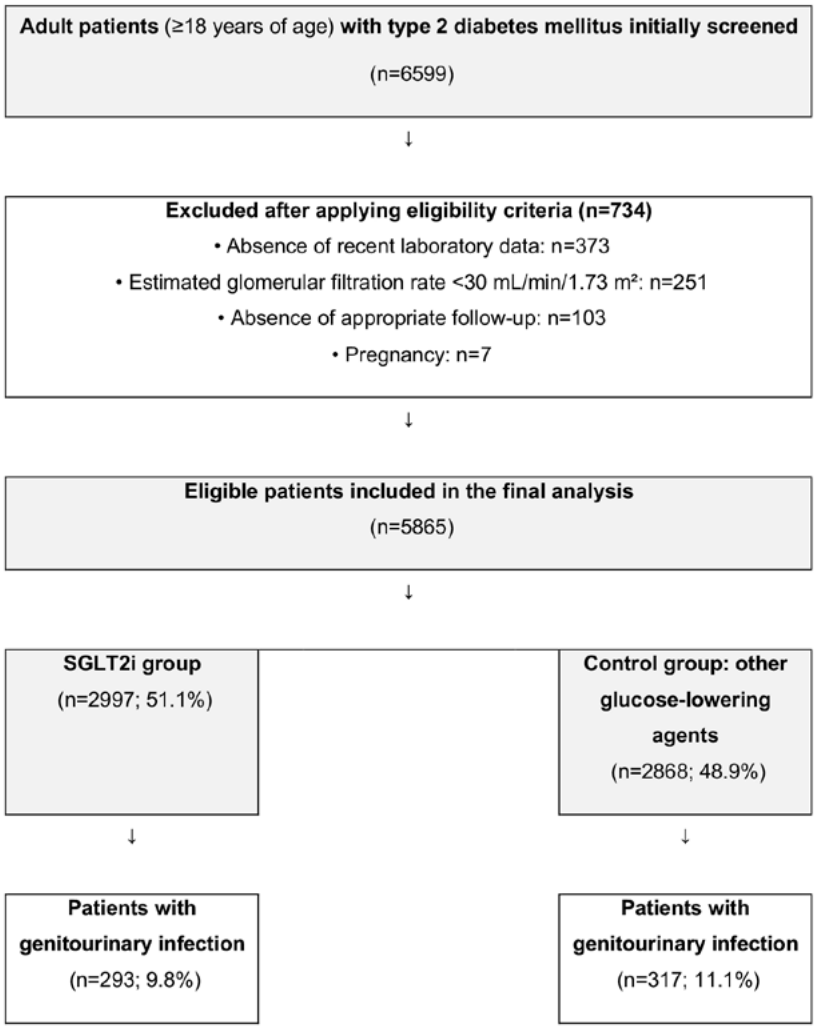


Figure 1. Flow diagram of patient selection

## RESULTS

A total of 6599 adult patients with a diagnosis of T2DM were initially screened. After applying exclusion criteria, 5865 patients were eligible and included in the final analysis.

The reasons for exclusion, presented in descending order of frequency and calculated based on the initially screened population, were: absence of recent laboratory data (n=373; 5.7%); estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m² (n=251; 3.8%); absence of appropriate follow-up within the study period (n=103, 1.6%) and pregnancy (n=7; 0.1%).

The final cohort comprised 5865 patients, of whom 2997 (51.1%) were treated with SGLT2i and 2868 (48.9%) were treated with antidiabetic agents other than SGLT2i.

### Baseline demographic and clinical characteristics

The baseline characteristics of the analysis cohort (n=2997) and control group (n=2868) are shown in Table 1.

Patients in the SGLT2i group were significantly younger than those in the control group (mean age 68.6 ± 10.7 *vs* 71.8 ± 10.9 years, $p<0.001$) and were more frequently male (55.9% *vs* 48.8%; $p<0.001$). Ethnic distribution also differed between groups ($p=0.028$), although the study population was predominantly White (> 95%).

In addition, SGLT2i group showed a higher proportion of concomitant use of other pharmacological classes for T2DM management, except for metformin ($p=0.051$) and alpha-glucosidase inhibitors ($p=0.405$). Dapagliflozin was the most frequently prescribed agent (58.1%; n=1742), followed by empagliflozin (36.0%; n=1080), canagliflozin (4.3%; n=128), and ertugliflozin (1.6%; n=47).

The most frequently prescribed doses were dapagliflozin 10 mg (58.1%; n=1742) and empagliflozin 10 mg (23.3%; n=697).

Regarding comorbidities potentially associated with increased GUI risk, there were no significant differences in terms of urinary lithiasis (7.6% in the SGLT2i group *vs* 6.9% in the control group; $p=0.255$), urinary incontinence

(5.4% in the SGLT2i group *vs* 4.9% in the control group; *p*=0.395) and bladder cancer (0.9% in the SGLT2i group *vs* 0.8% in the control group; *p*=0.670). Among male patients (n=3076), BPH was more prevalent in the control group compared to the SGLT2i group (31.0% *vs* 26.9%; *p*=0.013). A history of GUI before the study period was reported in 11.0% of the overall sample, with no statistically significant differences observed between groups (11.7% in the SGLT2i group *vs* 10.3% in the control group; *p*=0.075).

Table 1. Demographics, oral glucose-lowering agents and comorbidities associated with genitourinary infections

| | SGLT2i (n=2997) | Control (n=2868) | *p* value |
|---|---|---|---|
| Demographics | | | |
| Age, years (mean ± SD) | 68.6 ± 10.7 | 71.8 ± 10.9 | < 0.001 |
| Male, n (%) | 1675 (55.9) | 1401 (48.8) | < 0.001 |
| Ethnicity, n (%) | | | 0.028 |
| White, n (%) | 2854 (95.2) | 2772 (96.7) | - |
| Black, n (%) | 85 (2.8) | 62 (2.2) | - |
| Asian, n (%) | 7 (0.2) | 2 (0.1) | - |
| Other, n (%) | 51 (1.7) | 32 (1.1) | - |
| Oral glucose-lowering agents | | | |
| Metformin, n (%) | 2576 (86.0) | 2413 (84.1) | 0.051 |
| DPP-4 inhibitors, n (%) | 998 (33.3) | 753 (26.3) | < 0.001 |
| GLP-1 receptor agonists, n (%) | 325 (10.8) | 84 (2.9) | < 0.001 |
| Sulfonylureas, n (%) | 155 (5.2) | 97 (3.4) | < 0.001 |
| Thiazolidinediones, n (%) | 23 (0.8) | 9 (0.3) | 0.018 |
| Alpha-glucosidase inhibitor (acarbose), n (%) | 7 (0.2) | 4 (0.1) | 0.405 |
| Type of SGLT2i | | | |
| Empagliflozin, n (%) | 1080 (36.0) | NA | NA |
| Dapagliflozin, n (%) | 1742 (58.1) | NA | NA |
| Canagliflozin, n (%) | 128 (4.3) | NA | NA |
| Ertugliflozin, n (%) | 47 (1.6) | NA | NA |
| Dosage of iSGLT2 (mg) | | | |
| Empagliflozin 10 | 697 (23.3) | NA | NA |
| Empagliflozin 25 | 383 (12.8) | NA | NA |
| Dapagliflozin 10 | 1742 (58.1) | NA | NA |
| Canagliflozin 100 | 102 (3.4) | NA | NA |
| Canagliflozin 300 | 26 (0.9) | NA | NA |
| Ertugliflozin 5 | 22 (0.7) | NA | NA |
| Ertugliflozin 15 | 25 (0.8) | NA | NA |
| Comorbidities | | | |
| GUI, n (%) | 352 (11.7) | 295 (10.3) | 0.075 |
| BPH (male patients), n (%) | 451 (26.9) | 434 (31.0) | 0.013 |
| Urinary incontinence, n (%) | 161 (5.4) | 140 (4.9) | 0.395 |
| Urinary lithiasis (nephrolithiasis/urolithiasis), n (%) | 229 (7.6) | 197 (6.9) | 0.255 |
| Bladder cancer, n (%) | 26 (0.9) | 22 (0.8) | 0.670 |

Values are expressed as mean ± standard deviation (SD) or number (n) and percentage (%). DPP-4 – dipeptidyl peptidase 4; GLP-1 – glucagon-like peptide 1; SGLT2 – sodium–glucose cotransporter 2; GUI – genitourinary infection; BPH – benign prostatic hyperplasia; NA – not applicable.

## Descriptive clinical characteristics of patients with genitourinary infection

Among patients who developed a GUI (n=610), 293 (48.0%) were receiving SGLT2i therapy. Clinical and laboratory characteristics collected at the time of GUI diagnosis are detailed in Table 2. These variables were assessed only among patients with documented GUI and should not be interpreted as baseline characteristics of the overall cohort. Patients in the SGLT2i group had a higher mean BMI compared with the control group (29.4 ± 4.8 *vs* 28.6 ± 4.2 kg/m²; *p*=0.035), as well as significantly higher HbA1c levels (7.3 ± 1.3% *vs* 6.6 ± 1.1%; *p*<0.001). No significant differences were observed between groups in serum creatinine, estimated glomerular filtration rate, or albuminuria status.

Table 2. Clinical and laboratory characteristics of patients with genitourinary infection at the time of diagnosis

| | SGLT2i (n=293) | Control (n=317) | *p* value |
|---|---|---|---|
| Clinical parameters at the time of GUI diagnosis | | | |
| BMI (kg/m²), mean ± SD | 29.4 ± 4.8 | 28.6 ± 4.2 | 0.035 |
| HbA1c (%), mean ± SD | 7.3 ± 1.3 | 6.6 ± 1.1 | < 0.001 |
| Serum creatinine (mg/dL), mean ± SD | 0.88 ± 0.53 | 0.83 ± 0.20 | 0.179 |
| eGFR (mL/min/1.73 m²), mean ± SD | 82.9 ± 19.3 | 81.1 ± 17.4 | 0.229 |
| Albuminuria, n (%) | 66 (22.5) | 50 (15.8) | 0.103 |
| Microalbuminuria | 60 (20.5) | 46 (14.5) | - |
| Severely increased albuminuria | 6 (2.0) | 4 (1.3) | - |
| Without albuminuria | 227 (77.5) | 267 (84.2) | - |

Values are expressed as mean ± standard deviation (SD) or number (n) and percentage (%). SGLT2 – sodium–glucose cotransporter 2; BMI – body mass index; HbA1c – hemoglobin A1c; eGFR – estimated glomerular filtration rate.

## Association between SGLT2 inhibitor use and genitourinary infections

The incidence and association between SGLT2i therapy and genitourinary infections are shown in Table 3.

Table 3. Incidence and association between SGLT2 inhibitor use and genitourinary infections (2019–2023)

| | SGLT2i (n=2997) | Control (n=2868) | OR (95% CI) | *p* value |
|---|---|---|---|---|
| Type of infection | | | | |
| Any genitourinary infection, n (%) | 293 (9.8) | 317 (11.1) | 0.87 (0.74-1.03) | 0.109 |
| Cystitis, n (%) | 196 (6.5) | 289 (10.1) | 0.62 (0.52- 0.75) | < 0.001 |
| Vulvovaginal mycotic infection**, n (%) | 46 (3.5) | 22 (1.5) | 2.37 (1.42- 3.96) | < 0.001 |
| Balanitis*, n (%) | 46 (2.7) | 10 (0.7) | 3.93 (1.98- 7.81) | < 0.001 |
| Pyelonephritis, n (%) | 7 (0.2) | 14 (0.5) | 0.48 (0.19-1.18) | 0.103 |
| Prostatitis*, n (%) | 7 (0.4) | 11 (0.8) | 0.53 (0.21-1.37) | 0.184 |
| Trichomoniasis, n (%) | - | - | - | - |
| Discontinuation of anti-diabetic therapy due to infection, n (%) | 53 (1.8) | 0 (0.0) | 0.98 (0.98- 0.99) | < 0.001 |

Values are expressed as number (n) and percentage (%). Odds ratios (ORs) with 95% confidence intervals (CIs) were derived from 2×2 contingency tables comparing SGLT2 inhibitor users with controls. Statistically significant differences ($p < 0.05$) are indicated in bold. *P*-values were obtained from the chi-square test. No cases of trichomoniasis were documented. *Male participants (n=3076); **female participants (n=2789); a – chi-square test; SGLT2, sodium-glucose cotransporter-2.

During the study period, GUI were documented in 610 patients (10.4%) of the overall population. Sex-specific conditions were analyzed in the corresponding subgroups: BPH, prostatitis and balanitis were evaluated only in male patients, whereas vulvovaginal mycotic infection was assessed exclusively in female patients.

Cystitis was the most frequent diagnosis (8.3%), followed by vulvovaginal mycotic infection (2.4%) and balanitis (1.8%), while prostatitis (0.6%) and pyelonephritis (0.4%) were less common.

Overall, no significant association was observed between SGLT2i use and the occurrence of any GUI (OR 0.87, 95% CI 0.74–1.03; *p*=0.109). However, cystitis occurred significantly less frequently among patients receiving SGLT2i compared with the control group (6.5% *vs* 10.1%; OR 0.62, 95% CI 0.52–0.75; *p*<0.001). No statistically significant associations were observed for pyelonephritis (OR 0.48, 95% CI 0.19–1.18; *p*=0.103) or prostatitis (OR 0.53, 95% CI 0.21–1.37; *p*=0.184). In contrast, genital mycotic infections were more frequent among SGLT2i users, including balanitis (2.7% *vs* 0.7%; OR

3.93, 95% CI 1.98–7.81; *p*<0.001) and vulvovaginal mycotic infection (3.5% *vs* 1.5%; OR 2.37, 95% CI 1.42–3.96; *p*<0.001).

No cases of trichomoniasis were documented during the study period.

Discontinuation of SGLT2i therapy due to infection occurred in 53 patients, all from the SGLT2i group. This represented 1.8% of the 2997 patients treated with SGLT2i and 18.1% of the 293 SGLT2i users who developed a GUI.

## Genitourinary infections by SGLT2 inhibitor type and dosage

Analyses according to individual SGLT2i and infection type are presented in Tables 4 and 5.

The lower frequency of cystitis among SGLT2 inhibitor users was confirmed, particularly among patients treated with empagliflozin and dapagliflozin and this was supported by a significant association compared with the control group (empagliflozin: OR 0.70; *p*=0.008; dapagliflozin: OR 0.61; *p*<0.001).

In contrast, balanitis was more frequent among patients receiving empagliflozin and dapagliflozin, with a significant positive association compared with the control group (empagliflozin: OR 5.05; *p*<0.001; dapagliflozin: OR 3.53; *p*<0.001).

Similarly, vulvovaginal mycotic infections were more common among patients treated with empagliflozin (OR 2.13; *p*=0.023) and dapagliflozin (OR 2.61; *p*<0.001), also showing a significant association with SGLT2 inhibitor use.

No significant associations were identified between individual SGLT2i and pyelonephritis or prostatitis.

When evaluating potential dose–response relationships (Table 5), no statistically significant differences in the frequency of genitourinary infections were observed across different doses of empagliflozin or ertugliflozin.

For canagliflozin, a numerically higher frequency of infection was observed with the 300 mg dose compared with 100 mg; however, this difference did not reach statistical significance (*p*=0.076).

Table 4. Incidence and univariable association between individual SGLT2 inhibitors and types of genitourinary infection

| | Control | Empagliflozin | Dapagliflozin | Canagliflozin | Ertugliflozin |
|---|---|---|---|---|---|
| A. *Occurrence* of genitourinary infections | | | | | |
| Any genitourinary infection, n (%) | 317 (11.1) | 120 (11.1) | 162 (9.3) | 9 (7.0) | 2 (4.3) |
| Cystitis, n (%) | 289 (10.1) | 79 (7.3) | 111 (6.4) | 5 (3.9) | 1 (2.1) |
| Pyelonephritis, n (%) | 14 (0.5) | 3 (0.3) | 3 (0.2) | 1 (0.8) | 0 (0) |
| Prostatitis*, n (%) | 11 (0.8) | 1 (0.2) | 6 (0.6) | 0 (0) | 0 (0) |
| Balanitis*, n (%) | 10 (0.7) | 20 (3.5) | 25 (2.5) | 1 (1.4) | 0 (0) |
| Vulvovaginal mycotic infection**, n (%) | 22 (1.5) | 16 (3.1) | 28 (3.8) | 1 (1.8) | 1 (4.2) |
| Trichomoniasis, n (%) | NA | NA | NA | NA | NA |
| B. Odds ratios (95% CI) *versus* Control group (Wald test) | | | | | |
| | | Empagliflozin OR (95% CI) *p*-value | Dapagliflozin OR (95% CI) *p*-value | Canagliflozin OR (95% CI) *p*-value | Ertugliflozin OR (95% CI) *p*-value |
| Cystitis | - | 0.70 (0.54-0.91); 0.008 | 0.61 (0.48-0.76); <0.001 | 0.36 (0.15-0.89); 0.028 | 0.19 (0.03-1.41); 0.105 |
| Pyelonephritis | - | 0.57 (0.16-1.98); 0.374 | 0.35 (0.10-1.23); 0.101 | 1.61 (0.21-12.30); 0.649 | NA |
| Prostatitis* | - | 0.22 (0.03-1.72); 0.150 | 0.76 (0.28-2.05); 0.581 | NA | NA |
| Balanitis* | - | 5.05 (2.35-10.86); <0.001 | 3.53 (1.69-7.38); <0.001 | 1.99 (0.25-15.74); 0.515 | NA |
| Vulvovaginal mycotic infection** | - | 2.13 (1.11-4.09); 0.023 | 2.61 (1.48-4.60); <0.001 | 1.17 (0.16-8.86); 0.877 | 2.86 (0.37-22.09); 0.315 |
| Trichomoniasis | NA | NA | NA | NA | NA |

Values in panel A are expressed as number (n) and percentage (%). Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated using univariable binary logistic regression, with infection as the outcome and the control group (without SGLT2 inhibitors) as the reference category. *P*-values were obtained using the Wald test. No cases of trichomoniasis were documented. NA – not applicable. *Male participants (n=3076); **female participants (n=2789).

Table 5. Association between SGLT2 inhibitor dosage and cumulative incidence of genitourinary infections

| Type of SGLT2i | Dose (mg) | No genitourinary infection n (%) | Genitourinary infection n (%) | OR (95% CI) | *p* value |
|---|---|---|---|---|---|
| Empagliflozin (n=1080) | 10 | 621 (89.1) | 76 (10.9) | 0.94 (0.64–1.40) | 0.770 |
| | 25 | 339 (88.5) | 44 (11.5) | | |
| Canagliflozin (n=128) | 100 | 97 (95.1) | 5 (4.9) | 0.28 (0.07–1.14) | 0.076 |
| | 300 | 22 (84.6) | 4 (15.4) | | |
| Ertugliflozin (n=47) | 5 | 22 (100.0) | 0 (0.0) | NE | NA |
| | 15 | 23 (92.0) | 2 (8.0) | | |

Values are expressed as number (n), percentage (%) and odds ratios (ORs) with 95% confidence intervals (CIs). Statistically significant differences ($p < 0.05$) are indicated in bold. Analyses were performed separately for each drug. Odds ratios were estimated using univariable binary logistic regression, with the lowest available dose as the reference category. Dapagliflozin was excluded from this analysis because only one dosage was available. For ertugliflozin, the OR could not be estimated due to the absence of events in one dose category. NA – not applicable; NE – not estimable.

## Predictors of genitourinary infection

Multivariable binary logistic regression analysis for predictors of genitourinary infection in the overall population is presented in Table 6.

A personal history of GUI was identified as an independent predictor of infection (OR 133.15; 95% CI 102.91–172.28; $p<0.001$). A personal history of urinary incontinence showed a borderline association ($p=0.052$).

In the male subgroup (Table 7), personal history of GUI remained a strong independent predictor (OR 209.30; 95% CI: 130.60–335.42; $p<0.001$), whereas BPH exhibited a borderline association ($p=0.087$).

Both models demonstrated good explanatory power, with Nagelkerke $R^2$ values of 0.613 and 0.603, respectively.

Table 6. Logistic regression model for predictors of genitourinary infection in the overall population

| | Estimate (B) | Standard Error | OR (95% CI) | *p* value |
|---|---|---|---|---|
| Personal history of genitourinary infection | 4.891 | 0.131 | 133.15 (102.91–172.28) | <0.001 |
| Personal history of urinary incontinence | 0.464 | 0.238 | 1.59 (1.00–2.54) | 0.0521 |

GUI – genitourinary infection; UI – urinary incontinence; OR – odds ratio; CI – confidence interval. Nagelkerke $R^2 = 0.613$.

Multivariable binary logistic regression was performed using the backward conditional method. Step 4 represents the final model after exclusion of non-significant variables. Variables entered into the initial model were previous genitourinary infection, urinary incontinence, urinary lithiasis, and bladder cancer. The Table 6 presents the final model after backward conditional selection. Odds ratios (ORs) are adjusted for all variables retained in the final model.

Table 7. Logistic regression model for predictors of genitourinary infection in male patients

| | Estimate (B) | Standard Error | OR (95% CI) | p value |
|---|---|---|---|---|
| Personal history of genitourinary infection | 5.344 | 0.241 | 209.30 (130.60 – 335.42) | <0.001 |
| Personal history of benign prostatic hyperplasia | 0.419 | 0.245 | 1.52 (0.94 – 2.46) | 0.0871 |

A *p*-value <0.05 was considered statistically significant. GUI – genitourinary infection; BPH – benign prostatic hyperplasia; OR – odds ratio; CI – confidence interval. Nagelkerke $R^2 = 0.603$.[1] Borderline association ($p = 0.087$).

Multivariable binary logistic regression was performed using the backward conditional method in male participants only. The final model is presented after exclusion of non-significant variables. Variables entered into the initial male subgroup model were previous genitourinary infection, benign prostatic hyperplasia, urinary incontinence, urinary lithiasis, and bladder cancer. The Table 7 presents the final model after backward conditional selection. Odds ratios (ORs) are adjusted for all variables retained in the final model.

## DISCUSSION

In this multicentric, retrospective, real-world study including 5865 patients with T2DM, genitourinary infections (GUI) occurred in 10.4% of the overall cohort, without significant differences between those treated with SGLT2i

and those receiving other antidiabetic agents. However, consistent with previous evidence,[13-15] a higher frequency of genital mycotic infections, including balanitis and vulvovaginal infections, was observed among SGLT2i users, while cystitis was less frequent in this group. No significant differences were found for pyelonephritis or prostatitis.

The findings of this study are consistent with both randomized clinical trials and real-world evidence regarding the genitourinary safety of SGLT2i. In major outcome trials such as EMPA-KIDNEY,[8] DAPA-CKD,[9] and CREDENCE,[10] SGLT2i therapy significantly reduced cardiovascular and renal events without clinically meaningful increases in overall GUI. Although mild to moderate genital infections were more frequent among SGLT2i users, urinary tract infection rates remained comparable to placebo. Similarly, the VERTIS-SU trial reported comparable rates of urinary tract infections between ertugliflozin and glimepiride, with only mild genital infections occurring more frequently in the SGLT2i group.[20] Meta-analyses and large real-world cohorts have confirmed this pattern, showing a modest increase in genital mycotic infections but no significant increase in urinary tract infections, urosepsis, or hospitalization for severe urinary tract infection among SGLT2i users compared with other glucose-lowering agents.[14-16,18]

The higher frequency of genital infections, specifically balanitis and vulvovaginitis, among SGLT2i users is consistent with the pharmacological mechanism of glycosuria induced by SGLT2 inhibition, which promotes fungal proliferation in the genital area.[13] Evidence from previous studies suggests that most GUI associated with SGLT2 inhibitor use are mild to moderate in severity and respond well to standard therapy, allowing treatment continuation.[13,15,21]

The absence of a significant increase in urinary tract infections, particularly cystitis, suggests that increased glycosuria does not substantially increase urinary tract infection risk.[13] Interestingly, cystitis was less frequent among SGLT2i users in our cohort. This finding is consistent with a previous Portuguese primary care case-control study, in which cystitis was also less frequent among SGLT2i users, although the association lost statistical significance after adjustment for sex, age, and urinary incontinence.[23] Therefore, the lower frequency of cystitis observed in our study should be interpreted cautiously and may reflect baseline differences between groups, prescribing patterns, residual confounding, or differences in clinical coding rather than a true protective effect. Overall, these findings are consistent with large real-world cohorts showing no increased risk of severe urinary tract infections among SGLT2i users compared with other glucose-lowering agents.[16,18]

Conversely, some earlier observational studies suggested a possible increase in genital infections, particularly among women and individuals with poor glycemic control.[14] However, more recent analyses conducted in older adults and in adults with T2DM did not demonstrate an increased risk of urinary tract infections, reinforcing the safety of SGLT2i across different clinical subgroups.[17,19]

Infection-related discontinuation of SGLT2i therapy occurred in 53 patients, representing 1.8% of the 2997 patients treated with SGLT2i and 18.1% of the 293 SGLT2i users who developed a GUI. This proportion is clinically relevant, although lower than that reported in recent real-world evidence. In a large territory-wide cohort of patients with T2DM prescribed SGLT2 inhibitors, Wu *et al.* reported that 32.31% of patients discontinued SGLT2 inhibitors after an incident urinary tract infection.[22] Importantly, discontinuation was associated with higher cardiovascular and renal risk and was not associated with a lower risk of recurrent urinary tract infection. These findings support a cautious approach to treatment interruption after GUI and reinforce the importance of early recognition, prompt treatment, and patient counselling to avoid unnecessary discontinuation of therapies with established cardio–renal–metabolic benefits.

In the present study, no dose–response relationship was observed between empagliflozin and canagliflozin dosage and the incidence of GUI. Although previous evidence suggests that higher doses of dapagliflozin may be associated with an increased risk of urinary tract infection, this could not be assessed in the present study, as all patients treated with dapagliflozin were receiving the 10 mg formulation.[15] These findings suggest a reassuring safety profile of SGLT2 inhibitors across different doses in the present cohort. However, conclusions regarding dose escalation should be interpreted cautiously, as previous evidence on dose-related infection risk remains limited and mixed.[15]

Logistic regression analysis identified a personal history of GUI as the only independent predictor of infection during the study period, both in the overall population and in male patients. This finding is consistent with previous reports suggesting that prior infection predisposes to recurrence, irrespective of glycemic control or pharmacological treatment.[17] Laboratory parameters such as HbA1c, eGFR, and urinary albumin excretion, collected only among patients with documented GUI, did not differ significantly between groups at the time of infection, and therefore cannot be interpreted as predictors of infection risk in the overall cohort.

The main strengths of this study include its large, multicentric sample, the use of real-world data extracted from primary care electronic medical records, and the inclusion of a control group treated with other glucose-lowering agents. PCCs were randomly selected to ensure balanced geographic representation across the Central region of Portugal, and all participating centers met the criterion of having data collected of at least 50% of their patients diagnosed with T2DM, supporting data completeness and reliability.

To the best of the authors' knowledge, this is the first multicentric real-world study conducted in Portugal assessing

GUI occurrence among patients treated with SGLT2i. Previous national evidence was limited to a single-center case–control study conducted in a Family Health Unit in the Northern region, which included a smaller sample size.[23] The broader geographic scope and larger population of the present study enhance the external validity of its findings and provide valuable epidemiological insight into clinical practice across the Central region.

However, several limitations should be acknowledged. First, as a retrospective study based on electronic medical records, mild or self-treated infections may have been underreported, potentially leading to underestimation of infection occurrence. Second, infection severity and recurrence were not assessed, limiting conclusions regarding the clinical burden and repeated episodes of GUI. Third, variability in follow-up duration and data recording across centers may have influenced event detection, although predefined inclusion criteria aimed to minimize this effect. Fourth, associations between SGLT2i use and specific genital infection subtypes were based on univariable analyses; therefore, residual confounding by factors such as age, glycemic control, and comorbidities cannot be excluded. Finally, time-to-event analysis was not performed because reliable and comparable data on treatment initiation, exposure duration, censoring dates, and time to first GUI were not consistently available. Consequently, the findings should be interpreted as cumulative infection proportions during the study period rather than incidence rates accounting for person-time or time-to-event estimates.

## CONCLUSION

In this large real-world primary care cohort, overall GUI was not more frequent among SGLT2i users than among patients receiving other glucose-lowering agents. Genital mycotic infections, specifically vulvovaginal candidiasis and balanitis, were more frequent among SGLT2i users, whereas urinary tract infections were not increased. Treatment discontinuation due to infection was infrequent, supporting the overall tolerability and continued use of SGLT2i in eligible patients.

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**Confidentiality of Data:** The authors declare that they have followed the protocols of their work center on the publication of patient data.

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### Contributorship Statement

**HM:** Drafted the manuscript and was responsible for data analysis.

**JG and LR:** Contributed to the critical review of the manuscript from a nephrology point of view.

**SS, SO, RS, CP, AM, IP, CS, RR, AC, AF, LA and LN:** Were responsible for data acquisition.

**IR:** Provided support in data analysis and senior advisory counselling.

All authors approved the final version of the manuscript for publication and assume responsibility for all aspects of the work, ensuring the accuracy and integrity of the data presented.

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