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Sodium-glucose cotransporter-2 inhibitors and risk for genitourinary infections in older adults with type 2 diabetes

Navya Varshney*, **Sarah J. Billups, Joseph J. Saseen and Cy W. Fixen**

Abstract

Background and aims: Although landmark clinical trials have demonstrated an increased risk for genitourinary infection (GUI) after initiation of sodium-glucose cotransporter-2 inhibitor (SGLT2i) therapy that led to an FDA label warning, real world findings have been inconsistent and evidence specifically in older adults is lacking. The objective of the study was to examine the incidence of GUI in patients aged 65 years or older initiated on SGLT2i compared with glucagon-like peptide-1 receptor agonist (GLP1-RA) therapy at a large academic health system.

Methods: A retrospective population-based cohort study was conducted using electronic health records of patients aged 65 years and older with a diagnosis of type 2 diabetes mellitus. Patients newly initiated on SGLT2i or GLP1-RA therapy with estimated glomerular filtration rate (eGFR) ⩾30 mL/min per 1.73 m² and active within the health system for at least 1 year prior to initiation were included. We compared the incidence of inpatient, emergency room, or outpatient diagnosis of GUI (bacterial and mycotic) within 6 months of SGLT2i or GLP1-RA initiation. A chi-square or Fisher's exact test were used to analyze between-group differences for categorical variables, while a *t*-test was used for continuous variables. A Cox proportional hazards model was used to estimate the impact of confounding variables on the primary outcome.

Results: One hundred and thirty-three patients were initiated on SGLT2i therapy and 341 patients newly initiated on GLP1-RA therapy. After adjusting for differences in age, A1c, body mass index, eGFR, race and sex, there was no statistically significant difference in GUI incidence within 6 months of SGLT2i *versus* GLP1-RA initiation (3.8% *versus* 6.5%, adjusted hazard ratio: 0.784, 95% confidence interval 0.260–2.367).

Conclusion: We found no increased risk of composite GUI within 6 months of initiating SGLT2i compared with GLP1-RA therapy. These real-world data in older adults add to previous findings, which suggest no increased risk of urinary tract infection with SGLT2i initiation.

Plain language summary

A class of antidiabetic medications and risk for genitourinary infections in older adults with type 2 diabetes

Older adults with type 2 diabetes often benefit from a class of antidiabetic medications known as sodium-glucose cotransporter-2 inhibitors (SGLT2is) which help to lower blood glucose, decrease risk for cardiovascular disease and prevent kidney disease progression. However, there is concern that these medications may increase risk for urinary tract infections and/or genital fungal infections in older adults based on clinical trial evidence. Our study evaluated the real-world occurrence of these safety events in patients aged 65 years or older who were newly started on these medications. We compared these patients with a group of patients newly started on an alternative class of antidiabetic agents

Correspondence to:
Cy W. Fixen
University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, 12850 E. Montview Blvd., Campus Box C238, Room V20-1127A, Aurora, CO 80045, USA
cy.fixen@cuanschutz.edu

Navya Varshney
Department of Pharmacy, Johns Hopkins Health System, Baltimore, MD, USA

Sarah J. Billups
Joseph J. Saseen
University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences; University of Colorado School of Medicine, Aurora, CO, USA

*At the time this project was completed, Navya Varshney was a PGY2 resident at the University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences

which are not expected to increase risk for infections, known as glucagon-like peptide-1 receptor agonists (GLP1-RA). In our study, we included 133 patients who started an SGLT2i and 341 patients who started a GLP1-RA at a large teaching hospital. We evaluated the occurrence of infection up to 6 months after initiation of these mediations. We found no significant difference in infection rate between these two groups. We conclude in the study that the use of SGLT2i in older adults was not associated with increased risk for urinary tract infections or genital fungal infections when compared with GLP1-RA use.

Keywords: cohort study, genital mycotic infection, GLP1-RA, risk of infection, urinary tract infection, yeast infection

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Introduction

Sodium-glucose cotransporter-2 inhibitor (SGLT2i) medications act on the kidney to promote urinary glucose excretion and continue to show beneficial effects independent of improving glycemic control in patients with type 2 diabetes mellitus (T2DM) and concurrent chronic kidney disease (CKD), heart failure, or atherosclerotic cardiovascular disease (ASCVD).[1–7] Little evidence exists describing or evaluating current real-world use or long-term safety, such as risk for genitourinary infection (GUI), and efficacy amongst patients of advanced age. Less than half of the patients in the landmark SGLT2i cardiovascular outcome trials were older than 65 years of age.[1–3] Additionally, adults ⩾65 years old encompass approximately 45% of patients with diabetes, and advanced age is an independent risk factor for GUI occurrence, which may confound the role of SGLT2i medications causing GUI.[8,9]

Several cases of urosepsis and pyelonephritis in patients taking SGTL2i medication were reported to the FDA between 2013 and 2014, which led to the class-wide warning being added to the label for each drug in 2015.[10] Since then, meta analyses and cohort data do not support an increased risk of urinary tract infection (UTI) or urosepsis with SGLT2i therapy but do suggest an increased risk of genital mycotic infection.[11–14] However, older adults and those with concomitant CKD or ASCVD are not well-represented in these data. A population-based cohort study of patients with diabetes older than 65 years demonstrated a 2.47-fold increased risk of genital mycotic infection within 30 days of SGLT2i initiation compared with dipeptidyl peptidase 4 inhibitor (DPP-4i) initiation, with no significant increase in UTI risk.[15] However, this study did not assess laboratory values or glycemic control, which limits the generalizability and interpretation of results. As such, incidence of GUI in patients who are 65 years of age or older on SGLT2i remains uncertain. Because advanced age and diabetes are both independent risk factors for GUI, it is unclear whether older adults would be at higher risk for GUI after initiation of SGLT2i therapy in comparison with populations previously studied.

This study evaluated the incidence of GUI related to SGLT2i use in an older adult patient population.

Materials and methods

This retrospective cohort study was conducted using electronic health record (EHR) data from patients within the University of Colorado Health (UCHealth) system who were newly initiated on SGLT2i or glucagon-like peptide-1 receptor agonist (GLP1-RA) therapy. The use of EHR data was approved as exempt from review under the institution's investigational review board. The study included patients aged 65 years or older within the UCHealth system with a diagnosis of T2DM who were initiated on either SGLT2i or GLP1-RA therapy (Appendix 1). Initiation was defined as a new prescription order for SGLT2i or GLP1-RA therapy between 1 January 2014 and 31 December 2019 with no prescription for either class of medication in the prior 1 year. The prescription order date was the index date. Patients were required to have been followed in the health system for at least 1 year prior to the index date to reduce the possibility that patients could have been prescribed study medications at

an outside health system. The only exclusion criterion was estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73 m². The GLP1-RA comparator group was selected as a comparison group as these medications have a similar place in therapy for the treatment of diabetes and are not expected to increase risk for GUI.[16]

The primary outcome was a composite of inpatient, emergency room, or outpatient diagnosis of GUI (bacterial or mycotic) within 6 months of SGLT2i or GLP1-RA initiation identified using ICD-9/10 and CPT codes (Appendix 2). Secondary outcomes included the incidence of each component of the primary outcome.

Baseline demographics were collected at the time of the index date. These included age, sex, body mass index (BMI), A1c, eGFR, presence or absence of heart failure (HF) status, and ASCVD status. History of conditions that increase risk for GUI were also collected, including urinary catheterization, benign prostatic hyperplasia (BPH), history of UTI, history of vaginitis, urinary incontinence, prostatitis, nephrolithiasis, urinary obstruction, history of organ transplant, bladder cancer, neurogenic bladder, and human immunodeficiency virus (HIV) (Appendix 3).

Comparisons between groups were analyzed using the chi-square statistic or Fisher's exact test for categorical variables, and *t*-test for continuous variables. The primary outcome was analyzed at the time of the first end point occurring during the follow-up of up to 6 months. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using the Cox proportional hazards model after adjustment for factors shown to increase risk for GUI, including age, A1c, sex, non-White race, eGFR (⩾ *versus* <60 mL/min), and BMI.[9,17] Separate models were used for the composite endpoint and for bacterial and mycotic infections individually, both using the GLP1-RA cohort as the reference group. Descriptive data were collected and reported among patients prescribed an SGLT2i medication who experienced an event, including concomitant medications and GUI treatment.

Results

The SGLT2i cohort included 133 patients, with a mean age of 73.9 ± 5.2 (SD) years, and the GLP1-RA cohort included 341 patients, with a mean age of 72.8 ± 5.2 (SD) years. Empagliflozin was the most common SGLT2i prescribed (59.4%) and liraglutide was the most common GLP1-RA prescribed (45.5%). In both cohorts, most patients were obese (BMI ⩾30 kg/m²) and White or Caucasian. Baseline A1c was similar among SGLT2i and GLP1-RA groups (Table 1). Although most baseline demographics were similar across both groups, there were more males and fewer patients with decreased renal function (eGFR 30–44 mL/min per 1.73 m²) in the SGLT2i group. In regard to risk factors for GUI, both cohorts had a similar and relatively low overall prevalence of GUI risk factors (Table 1).

The incidence of composite bacterial and mycotic infection within 6 months of SGLT2i *versus* GLP1-RA initiation was 3.8% in the SGLT2i cohort *versus* 6.5% in the GLP1-RA cohort, unadjusted $p = 0.38$. In the SGLT2i group, five patients experienced a GUI event (three women, two men) and most (80%) were genital mycotic infections. In the GLP1-RA group, 22 patients experienced a GUI event (all women) and most (77%) were bacterial infections (Table 2). After adjusting for differences in age, BMI, renal function, race, A1c, and sex, the outcome remained unchanged between SGLT2i *versus* GLP1-RA (adjusted HR = 0.78, 95% CI 0.26–2.37).

Review of patients who experienced a GUI event in the SGLT2i cohort did not reveal any concomitant medications expected to increase GUI risk (e.g. chemotherapeutic agents, immunosuppressants, antihistamines, anticholinergics, or recent broad-spectrum antibiotics). All patients in the SGLT2i cohort who experienced a yeast infection were treated with topical or systemic antifungal medication and the patient that experienced a UTI did not require treatment. GUI occurrence did not lead to treatment discontinuation in any of these patients.

Discussion

Our study is the first population-based study to assess GUI risk associated with SGLT2i use in the older adult population when compared with GLP1-RA use, a medication class not expected to increase risk for GUI. Our findings revealed no association between incidence of GUI after SGLT2i initiation compared with GLP1-RA initiation, though it is possible our study lacked sufficient power to detect a difference. Of the few

Table 1. Summary of baseline characteristics comparing SGLT2i *versus* GLP1-RA cohorts.

	SGLT2i ***n*** **= 133**	**GLP1-RA** ***n*** **= 341**	***p*-value**
Demographics			
Mean age (SD), years	73.9 (±5.2)	72.8 (±5.2)	0.04
Male sex, *n* (%)	84 (63.2)	164 (48.1)	<0.01
Race, *n* (%)			0.19
White/Caucasian	100 (75.2)	247 (72.4)	
Other	22 (16.5)	46 (13.5)	
Black	11 (8.3)	48 (14.1)	
Medication, *n* (%)	Empagliflozin: 79 (59.4)	Liraglutide: 155 (45.5)	–
	Canagliflozin: 40 (30.1)	Exenatide: 103 (30.2)	
	Dapagliflozin: 14 (10.5)	Dulaglutide: 65 (19.1)	
		Semaglutide: 10 (2.9)	
		Albiglutide: 8 (2.3)	
Mean A1c (SD), %	8.4 (±1.6)	8.2 (±1.7)	0.37
BMI, *n* (%)			
<25	20 (15.0)	26 (7.6)	0.01
25–29.9	46 (34.6)	108 (31.7)	0.54
⩾30	67 (50.4)	207 (60.7)	0.04
eGFR, *n* (%)			
⩾60	96 (72.2)	190 (56.1)	<0.01
45–59	25 (18.9)	91 (26.7)	0.07
30–44	12 (9.1)	60 (17.7)	0.02
ASCVD, *n* (%)	52 (39.1)	115 (33.7)	0.27
HF, *n* (%)	11 (8.3)	37 (10.9)	0.40
Risk factors#, *n* (%)			0.84
Any	52 (38.5)	134 (37.5)	
BPH	23 (17.3)	62 (18.2)	
UI	21 (15.8)	59 (17.3)	
Prostatitis	3 (2.3)	4 (1.2)	
Nephrolithiasis	11 (8.3)	22 (6.5)	
Urinary obstruction	1 (0.8)	3 (0.9)	
UTI	2 (1.5)	6 (1.8)	
Vaginitis	0 (0)	2 (0.6)	
Other*	3 (2.3)	16 (4.7)	

#No patients in either cohort had a urinary catheter in place.
*Kidney transplant, liver transplant, bladder cancer, neurogenic bladder, HIV.
ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BPH, benign prostatic hyperplasia; eGFR, estimated glomerular filtration rate; GLP1-RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; SD, standard deviation; SGLT2i, sodium-glucose cotransporter-2 inhibitor; UI, urinary incontinence; UTI, urinary tract infection.

Table 2. Incidence of GUI within 6 months of SGLT2i *versus* GLP1-RA initiation.

	SGLT2i *n* = 133)	GLP1-RA *n* = 341	Adjusted HR* (95% CI)
Composite GUI, *n* (%)	5 (3.8)	22 (6.5)	0.78 (0.26–2.37)
Bacterial GUI, *n* (%)	1 (0.8)	17 (5.0)	0.34 (0.04–2.65)
Mycotic GUI, *n* (%)	4 (3.0)	5 (1.5)	1.63 (0.37–7.15)

*Adjusted for age, A1c, body mass index, estimated glomerular filtration rate, race, and sex.
CI, confidence interval; GLP1-RA, glucagon-like peptide-1 receptor agonist; GUI, genitourinary infection; HR, hazard ratio; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

GUI events observed after SGLT2i initiation, most were genital mycotic infections which resolved with standard treatment and did not lead to treatment discontinuation. Although a general consensus is lacking regarding how long patients are at increased risk for GUI after SGLT2i initiation, we chose a follow-up duration of 6 months based on data that support an increased risk shortly after initiation.[18]

Older age, uncontrolled diabetes, female sex, increased BMI, CKD, and non-White race are all considered independent risk factors for GUI.[9,17] This could lead to use of caution with SGLT2i initiation in these populations. Additional factors, such as history of GUI or risk for volume-depletion side effects (e.g. hypotension, dizziness), are often considered to further inform decision making on which antidiabetic class to preferentially add to a patient's regimen. Also, while evidence from landmark SGLT2i trials have shown several benefits independent of glucose reduction, the glycemic benefit associated with SGLT2i use is diminished with impaired renal function given the mechanism of action. This potentially limits their utility in practice for patients with comorbid uncontrolled T2DM and CKD. In our study, the differences in baseline demographics between groups (i.e. more men and fewer patients having eGFR <45 mL/min per 1.73 m^2 in the SGLT2i cohort) suggests that clinicians are likely selecting patients to start SGLT2i medication that factor in the above considerations that would both optimize benefits and limit risks.

Despite the proven clinical benefits, SGLT2i medications are often underutilized by prescribers in older adults partly due to concern for GUI risk.[19,20] The use of an SGLT2i proven to be associated with GUI has varied across trials. However, a meta-analysis and two cohort studies all reported no increase in risk for UTI.[12–14] Rather, SGLT2i use has been associated with increased glucosuria and risk for genital mycotic infections.[11,12,20–22] When compared with DPP-4i initiation, SGLT2i use was associated with increased risk for genital mycotic infection without an increased risk for UTI in older adults, though events were still rare.[15] An analysis of safety outcomes in the elderly and very elderly from the Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58 study revealed no significant increase in UTI but more frequent genital infections that led to treatment discontinuation with dapagliflozin compared with placebo.[23] While the results of this dapagliflozin study were similar to the findings of our study, it should be noted that most patients in our study were prescribed empagliflozin, so differences in molecular structure between medications could result in different outcomes. Our findings are unique in that we included patients with comorbid CKD down to an eGFR of 30 mL/min, ASCVD, and HF, as well as an assessment of baseline A1c. This increases the generalizability of our results to real-world patients who are older. The average age of 73.1 years in our study is higher than that observed in other studies and provides additional insight into the tolerability of SGLT2i medications in older patients. The 2021 American Diabetes Association Standards of Medical Care in Diabetes notes that side effects may be more common among older adults using SGLT2i medications but does not caution against use or specifically comment on GUI events. The guideline offers support for its convenient oral administration and cardiovascular, renal, and HF benefits in older patients.[24] Our data suggest that risk for GUI may not limit use of SGLT2i medications in appropriately selected older adults.

There are limitations to our findings. The sample size was relatively small. A post-hoc power calculation showed that our study was powered to detect an absolute difference in the incidence of GUI of 10%. The retrospective nature of our study and reliance on diagnosis within the UCHealth system and use of appropriate ICD and CPT coding may not account for all

confounders and GUI events. Some mycotic infections may have been treated with over the counter medications, potentially underestimating our outcome. Adherence was not assessed, and medication initiation was determined *via* prescription orders within the health system. Additional concerns with SGTL2i use in older adults, such as occurrence of volume-depletion side effects, were not assessed.

Conclusions

SGLT2i medication use was not associated with increased incidence of GUI among older adults within 6 months of initiation when compared with GLP1-RA medication use. Among the SGTL2i cohort, most events were genital mycotic infections. These results are consistent with other published findings but broaden available evidence by including real-world data that include an older patient population with multiple pertinent comorbidities. Our findings indicate that initiating SGLT2i in older patients was safe from the perspective that it did not result in an increase in GUI.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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ORCID iD

Navya Varshney https://orcid.org/0000-0002-1161-7319

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Appendix 1. Medications included in analysis

SGLT2i medications: canagliflozin, canagliflozin-metformin, dapagliflozin, dapagliflozin-metformin, dapagliflozin-sitagliptin, dapagliflozin-sitagliptin-metformin, empagliflozin, empagliflozin-metformin, empagliflozin-linagliptin, ertugliflozin, ertugliflozin-sitagliptin, ertugliflozin-metformin

GLP1-RA medications: albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, insulin glargine/lixisenatide, insulin degludec/liraglutide

Appendix 2. Hospitalization, emergency department discharge, or outpatient diagnosis (listed as primary or secondary reason for visit) ICD-10 codes

Bacterial infections:

- Cystitis: 'N30.0', 'N30.3', 'N30.4', 'N30.8', 'N30.9', 'N39.0';
- Pyelonephritis: 'N10';
- Prostatitis: 'N41.0';
- Ureteritis/urethritis: 'N34.1', 'N34.2', 'N34.3'.

Genital mycotic infections:

- Vulvovaginal/vaginal infection: 'A56.02', 'A59.01', 'A60.04';
- Balanitis: 'N48.1', 'B37.42';
- Vulvovaginal Candsidiasis: 'B37.3', 'B37.41', 'B37.49', 'B37.7';
- Vaginitis/vulvitis/vulvovaginitis: 'N77.1', 'N76.0', 'N76.2', 'N76.4'.

Appendix 3. Risk factors associated with GUI ICD-10 and CPT codes

- HIV: 'B20';
- Spinal cord injury: 'S14.0', 'S14.1', 'S14.2', 'S14.3', 'S14.4', 'S14.5', 'S14.8', 'S14.9';
- Hydronephrosis: 'N13.0', 'N13.1', 'N13.2', 'N13.3', 'N13.4', 'N13.5', 'N13.6', 'N13.7', 'N13.8', 'N13.9', 'Q62.0';
- Occlusions/obstructive defects of renal pelvis and ureter: 'Q62.10', 'Q62.11', 'Q62.12', 'Q62.31', 'Q62.32', 'Q62.39', 'Q62.60', 'Q62.61', 'Q62.62', 'Q62.63', 'Q62.69', 'Q62.8', '753.20', '753.21', '753.22', '753.23', '753.29';
- Organ transplant: 'Z94.0', 'Z94.1', 'Z94.2', 'Z94.3', 'Z94.4', 'Z94.5', 'Z94.6', 'Z94.7', 'Z94.8', 'Z94.9', 'Z94.81', 'Z94.82', 'Z94.83', 'Z94.84', 'Z94.89';
- BPH: 'N40.0', 'N40.1', 'N40.2', 'N40.3', 'Z87.430';
- Urethral strictures: 'N35.01', 'N35.02', 'N35.11', 'N35.12', 'N35.8', 'N35.9', 'N99.11', 'N99.12', 'Q64.32';

- Urinary/bladder calculi: 'Z87.442', 'N20.0', 'N20.1', 'N20.2', 'N20.9', 'N21.0', 'N21.1', 'N21.8', 'N21.9';
- Kidney/bladder/urethral tumors: 'C7A.093', 'D3A.093', 'D30.00', 'D30.01', 'D30.02', 'D30.10', 'D30.11', 'D30.12', 'D30.20', 'D30.21', 'D30.22', 'D30.3', 'D30.4', 'D30.8', 'D30.9', 'Z85.520', 'Z85.528', 'Z85.50', 'Z85.51', 'Z85.53', 'Z85.54', 'Z85.59', 'C67.0', 'C67.1', 'C67.2', 'C67.3', 'C67.4', 'C67.5', 'C67.6', 'C67.7', 'C67.8', 'C67.9';
- Bladder diverticula: 'N36.1', 'Q64.6';
- Neurogenic bladder: 'N31.0', 'N31.1', 'N31.2', 'N31.8', 'N31.9';
- Chronic and/or recurrent UTI: 'N11.0', 'N11.1', 'N11.8', 'N11.9', 'N30.1', 'N30.2', 'Z87.440', 'N41.1';
- Chronic vaginitis/vulvitis: 'N76.1', 'N76.3';
- Urinary incontinence: 'N39.3', 'N39.490', 'N39.498', 'N39.492', 'N39.41', 'N39.42', 'N39.43', 'N39.44', 'N39.45', 'N39.46', 'R32', 'R39.81';
- Urinary catheterization infections ICD-10 codes: 'T83.510A', 'T83.510D', 'T83.510S', 'T83.511A'; 'T83.511D', 'T83.511S', 'T83.512A', 'T83.512D', 'T83.512S', 'T83.518A', 'T83.518D', 'T83.518S';
- Urinary catheterization CPT codes: 51702, 51703.