ORIGINAL RESEARCH PAPER

Internal Medicine

COMPARATIVE INCIDENCE AND RISK FACTORS OF GENITOURINARY INFECTIONS IN PATIENTS WITH AND WITHOUT DIABETES ON SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS: AN OBSERVATIONAL STUDY

KEY WORDS: Sodium-glucose Cotransporter-2 Inhibitors, Genitourinary Infections, Type 2 Diabetes, Glucosuria, Hygiene, South Asia

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ABSTRACT

Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are widely used for type 2 diabetes mellitus (T2DM), heart failure, and chronic kidney disease, but glucosuria may increase genitourinary infection (GUI) risk. **Objective:** To compare GUI incidence, types, and risk factors in diabetic versus non-diabetic patients on SGLT2i. **Methods:** This hospital-based observational study enrolled 100 patients (50 diabetic, 50 non-diabetic) prescribed SGLT2i for ≥4 weeks at Ascoms Sidhra Jammu, India, from March to November 2024. Data on demographics, clinical characteristics, GUI incidence, and laboratory findings were collected. Chi-square tests and t-tests/Mann-Whitney U tests were used for comparisons ($p<0.05$ significant). **Results:** GUIs occurred in 15% of patients, with a higher incidence in diabetics (22%) than non-diabetics (8%; $p=0.047$). Diabetics had more urinary tract infections (UTIs; 12% vs. 4%) and genital fungal infections (10% vs. 4%). Poor genital hygiene was a significant risk factor ($p=0.01$). Most infections were mild, resolved with treatment, and did not require SGLT2i discontinuation. **Conclusion:** Diabetic patients on SGLT2i have a higher GUI risk than non-diabetics, with poor hygiene as a modifiable risk factor. Enhanced patient counseling is essential for safe SGLT2i use.

INTRODUCTION

Sodium-glucose cotransporter-2 inhibitors (SGLT2i), such as empagliflozin, dapagliflozin, and canagliflozin, have revolutionized the management of type 2 diabetes mellitus (T2DM) by inhibiting glucose reabsorption in the renal proximal tubule, promoting glucosuria, and lowering blood glucose levels independent of insulin [1,2]. This mechanism also facilitates weight loss and blood pressure reduction, enhancing their appeal for T2DM management [3,4]. Beyond glycemic control, landmark trials, including the CANVAS Program, EMPA-REG OUTCOME, and DAPA-HF, have demonstrated significant reductions in major adverse cardiovascular events, heart failure hospitalizations, and chronic kidney disease progression, expanding SGLT2i indications to non-diabetic patients with heart failure and chronic kidney disease [5-7]. These cardiorenal benefits are attributed to mechanisms such as improved hemodynamic stability, reduced glomerular hyperfiltration, and anti-inflammatory effects [8,9].

The global burden of T2DM, heart failure, and chronic kidney disease has driven widespread SGLT2i adoption, particularly in regions like South Asia, where India accounts for over 77 million adults with diabetes, one of the highest prevalences worldwide [10,11]. South Asian populations face unique challenges, including earlier T2DM onset, higher complication rates, and socioeconomic barriers to healthcare access, underscoring the need for effective and safe therapies [12,13]. SGLT2i have shown particular promise in this region, with studies confirming their efficacy in Asian patients with T2DM [14]. However, the induction of glucosuria, a core therapeutic mechanism, raises concerns about increased genitourinary infection (GUI) risk, as glucose-rich urine fosters the growth of pathogens like Escherichia coli and Candida species [15,16].

Diabetic patients are particularly susceptible to GUIs due to chronic hyperglycemia, which impairs immune responses, including neutrophil dysfunction, and predisposes to urologic complications such as diabetic cystopathy, leading to urinary stasis [17,18]. Clinical studies report GUI rates of 5-10% for urinary tract infections (UTIs) and 3-6% for genital fungal infections in diabetic SGLT2i users, with women and uncircumcised men at higher risk due to anatomical factors [19,20]. Common genital infections include vulvovaginitis in females and balanitis in males, often caused by Candida species thriving in glucose-rich environments [21]. While most infections are mild, severe cases, such as pyelonephritis or rare instances of Fournier's gangrene, have been reported, necessitating vigilant monitoring [22,23].

In non-diabetic patients, GUI risk is less well-characterized but potentially lower due to the absence of chronic hyperglycemia [24]. However, SGLT2i-induced glucosuria may still predispose these patients to infections, particularly in the presence of risk factors like poor hygiene or compromised renal function [25]. With SGLT2i increasingly prescribed for heart failure and chronic kidney disease in non-diabetic populations, understanding comparative GUI risks is critical for optimizing patient safety [26]. Additional factors, such as age, sex, and comorbidities, may modulate infection risk, requiring tailored clinical approaches [27].

In South Asia, unique microbial flora, varying hygiene practices, and limited access to timely healthcare may further influence GUI profiles [11,28]. For instance, studies suggest higher rates of antimicrobial resistance in this region, complicating infection management [29]. Despite the growing evidence, few studies have directly compared GUI incidence between diabetic and non-diabetic SGLT2i users in a single cohort, particularly in high-risk populations like South Asians [30]. Moreover, real-world data on infection patterns in diverse settings remain limited, highlighting the need for region-specific studies to inform clinical practice [31].

This study aims to address these gaps by comparing the incidence, types, and risk factors of GUIs in diabetic versus non-diabetic patients on SGLT2i at a tertiary care center in Jammu, India. By focusing on a South Asian cohort, the findings seek to provide insights into regional infection patterns, enhance patient counseling, and guide strategies for infection prevention in both diabetic and non-diabetic populations.

Aims and Objectives

Aim:

To compare the incidence and characteristics of GUIs in diabetic versus non-diabetic patients receiving SGLT2i.

Objectives:

1. Determine the prevalence of GUIs in patients on SGLT2i.
2. Compare the frequency and types of GUIs between diabetic and non-diabetic patients.
3. Assess the severity and clinical outcomes of GUIs in both groups.
4. Identify risk factors (e.g., age, sex, glycemic control, hygiene practices) associated with GUIs.

MATERIALS AND METHODS

Study Design: Hospital-based, observational, comparative study.

Setting: Department of General Medicine, Ascoms Sidhra Jammu, India.

Duration: March to November 2024.

Population: Adults (≥18 years) prescribed SGLT2i for ≥4 weeks, attending inpatient or outpatient services.

Inclusion Criteria

- Age ≥18 years.
- Prescribed SGLT2i (e.g., empagliflozin, dapagliflozin, canagliflozin) for ≥4 weeks.
- Provided informed consent.

Exclusion Criteria

- Pre-existing urinary tract abnormalities (e.g., urolithiasis, neurogenic bladder, indwelling catheters).
- Immunocompromised states (e.g., HIV, chronic steroid use, active malignancy).
- Pregnant or lactating women.
- Concurrent antibiotic/antifungal use at enrollment.
- Incomplete medical records or lost to follow-up.

Sample Size: 100 patients (50 diabetic, 50 non-diabetic), based on an expected GUI incidence of 15% in diabetics and 5% in non-diabetics (80% power, =0.05).

Sampling: Consecutive sampling of eligible patients.

Data Collection

- Demographics (age, sex, BMI).
- SGLT2i type and duration.
- Diabetes status and glycemic control (HbA1c).
- Clinical data: symptoms (e.g., dysuria, genital itching), urine routine/microscopy, urine culture, complete blood count (CBC), renal function tests.
- Outcomes: infection type, severity, treatment, hospitalization, and resolution.

Statistical Analysis:

- Descriptive statistics: mean ±SD, percentages.
- Comparative analysis: Chi-square test for categorical variables; t-test or Mann-Whitney U test for continuous variables.
- Risk factor analysis: logistic regression for GUI associations.
- $p<0.05$ considered significant.
- Software: SPSS version 26.

Ethical Considerations: Approved by the institutional ethics committee (Approval No. ASCOMS/IEC/2024/03). Informed consent was obtained, and data were anonymized per the Declaration

RESULTS

1. Study Population

A total of 100 patients were enrolled in the study, comprising 50 diabetic and 50 non-diabetic patients who were on SGLT2 inhibitor therapy for various indications including diabetes mellitus, heart failure, and chronic kidney disease. All patients were followed for genitourinary symptoms during the treatment period.

2. Baseline Characteristic

Parameter	Diabetic (n = 50)	Non-Diabetic (n = 50)	p-value
Age (mean ±SD, years)	58.2 ± 9.1	56.3 ±8.4	0.26
Sex (Male:Female)	28 : 22	26 : 24	0.68
BMI (kg/m²)	27.4 ±2.6	26.9 ±2.3	0.38
Most common SGLT2i used	Empagliflozin (62%)	Dapagliflozin (58%)	—
Duration of SGLT2i therapy	6.2 ±2.1 months	5.9 ±1.9 months	0.41
Mean HbA1c (Diabetics only)	8.2 ±1.1 %	—	—

There was no statistically significant difference in demographic or baseline clinical variables between the two groups

3. Incidence and Type of Genitourinary Infections (GUIs)

Statistically significant difference in overall GUI prevalence between groups.

Among diabetics, 6 patients developed UTIs confirmed by symptoms and urine culture, while 5 developed genital fungal infections (4 females and 1 uncircumcised male). In the non-diabetic group, 2 patients had UTIs and 2 had genital fungal infections.

4. Laboratory Findings in Patients with GUI (n = 15)

- Urine Routine and Microscopy: Pyuria present in 11/15 (73.3%)
- Urine Culture:
  - E. coli isolated in 6 patients (all diabetics)
  - Candida albicans detected in 3 patients (2 diabetics, 1 non-diabetic)
- CBC Findings: Mild leukocytosis (WBC >11,000/mm³) in 5 patients
- Renal Function Tests: No significant change in eGFR in GUI patients

5. Management and Clinical Outcome

Parameter	Diabetic (n = 11 GUIs)	Non-Diabetic (n = 4 GUIs)
Antibiotics prescribed	9 (81.8%)	3 (75%)
Antifungals prescribed	5 (45.5%)	2 (50%)
Required hospital admission	2 (18.2%)	0
Clinical resolution of infection	11 (100%)	4 (100%)

No patients required discontinuation of SGLT2 inhibitors due to infection.

6. Risk Factor Analysis for GUI

Risk Factor	GUI Present (n = 15)	GUI Absent (n = 85)	p-value
Female gender	9 (60%)	37 (43.5%)	0.26
Poor genital hygiene	6 (40%)	11 (12.9%)	0.01 *
HbA1c > 8% (in diabetics)	7 of 11 (63.6%)	15 of 39 (38.5%)	0.09
eGFR < 60 mL/min	2 (13.3%)	6 (7.1%)	0.31

Poor genital hygiene was found to be a statistically significant risk factor for GUIs ($p = 0.01$), irrespective of diabetes status.

Summary of Key Findings:

- Overall incidence of GUI: 15%
- Diabetic patients had nearly 3x higher risk of GUI compared to non-diabetics (22% vs. 8%)
- Most infections were mild and resolved with treatment
- Poor genital hygiene was significantly associated with higher GUI risk

- No patients discontinued SGLT2 inhibitors due to infections

DISCUSSION

This study confirms a higher GUI incidence in diabetic patients on SGLT2i (22%) compared to non-diabetics (8%; p=0.047), consistent with prior reports [21,22,28]. The predominance of UTIs (53.3%) and genital fungal infections (46.7%), as shown in Figure 1, aligns with the glucosuria-driven mechanism of SGLT2i [15,16]. Diabetic patients' increased risk likely reflects hyperglycemia and immune dysfunction [17,18].

Non-diabetic patients also experienced GUIs, suggesting glucosuria as an independent risk factor [26,29]. Poor genital hygiene was a significant predictor across both groups (p=0.01), emphasizing the need for patient education [30]. The association between poor glycemic control (HbA1c >8%) and GUIs in diabetics (p=0.06) highlights the importance of optimizing diabetes management [31].

Compared to trials like EMPA-REG OUTCOME, this study offers a direct comparison of diabetic and non-diabetic patients in a South Asian context, where T2DM prevalence is high [12,17].The 15% overall GUI incidence aligns with meta-analyses [18,19]. Most infections were mild, supporting the safety of SGLT2i with proper monitoring [20].

Limitations:

- Small sample size (n=100) may limit subgroup analysis power.
- Single-center design may reduce generalizability.
- Microbiological confirmation was not universal.
- Short follow-up (8 months) may miss recurrent infections.

Future Directions: Larger, multicenter studies with longer follow-up are needed to assess recurrent infections and evaluate hygiene-focused interventions.

CONCLUSION

Diabetic patients on SGLT2i have a significantly higher GUI risk than non-diabetics, driven by glucosuria, poor glycemic control, and inadequate hygiene. While infections were manageable, targeted counseling on hygiene and glycemic management is essential for safe SGLT2i use.

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