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# Prevalence of Bacterial Urinary Tract Infection Among Patients With Type 2 Diabetes Mellitus on Sodium-Glucose Cotransporter-2 Inhibitors: A Prospective Real-World Setting Study

Pankaj Ferwani, Aasim Maldar, Nishitkumar Shah, Phulrenu Chauhan, Manoj Chadha

*Department of Endocrinology, P. D. Hinduja National Hospital and Medical Research Centre, Mumbai, Maharashtra State, India*

**Abstract**

Background. Genitourinary tract infections, mycotic as well as bacterial, as defined by clinical symptoms, are one of the common adverse effects associated with the use of sodium-glucose cotransporter-2 inhibitors (SGLT2i) in type 2 diabetes mellitus (T2DM) patients in clinical trials. However, Indian data in terms of the prevalence of culture-proven bacterial type of urinary tract infection (UTI), and the causative organism is limited.

Objective. This study aimed to determine the prevalence and causative agents of bacterial UTI among patients with T2DM on SGLT2i.

Methodology. This was a prospective longitudinal study involving all patients with T2DM who were prescribed with SGLT2i, uncontrolled on other oral anti-diabetic medications, from June 2019 to February 2020. Prevalence of bacterial UTI was evaluated at baseline and 12 weeks after initiation of SGLT2i.

Results. A total of 80 patients were started on SGLT2i. One female patient on canagliflozin had significant asymptomatic bacteriuria and the causative agent was *Acinetobacter baumannii*. One male patient on dapagliflozin had symptomatic UTI with negative urine culture study. Four patients developed genital mycotic infection.

Conclusion. In this real-world study, SGLT2i as a class, was well tolerated with favorable safety profile, and risk of developing significant bacteriuria and/or symptomatic UTI was minimal.

*Key words: SGLT2i, type 2 diabetes mellitus, UTI, significant bacteriuria*

## INTRODUCTION

Diabetes mellitus is the most common endocrine disease of the century. It is discouraging to contemplate the burden Type 2 diabetes may impose on India in the future.

The significant morbidity and mortality, high rates of complications and the cost of therapy can have a huge socio-economic impact on individuals and families.[1,2] The treatment of T2DM in India has been traditionally based on metformin, sulfonylureas, voglibose and insulin. However, newer agents such as dipeptidyl peptidase 4 inhibitors (DPP4i), sodium-glucose cotransporter-2 inhibitors (SGLT2i), and glucagon-like peptide-1 (GLP1) receptor agonists promise a substantial benefit in the treatment of naive, as well as uncontrolled diabetes patients.[3,4] Inhibition of SGLT-2 offers potential add-on benefits of weight loss, blood pressure (BP) reduction, and cardiovascular-renal benefits, with a low risk of hypoglycemia.[5,6]

Dapagliflozin, canagliflozin, empagliflozin and remogliflozin are currently available in India. They have been approved for the treatment of T2DM as monotherapy and as second- or third-line agents in combination with other therapeutic options for diabetes. This drug class may be used at any stage of T2DM owing to its novel insulin-independent mechanism of action, provided the renal function is above a certain threshold.[7,8] Genitourinary tract (GUT) infections are the most common adverse effect of SGLT2i use in clinical trials.[9-11] People with diabetes are at increased risk for GUT infections due to glucosuria, bacterial adherence to uroepithelium and immune dysfunction.[12]

The prevalence of bacterial urinary tract infections (UTI), defined by clinical symptoms, among patients with T2DM on SGLT2i is 9%.[10] There is limited Indian data on the prevalence of culture-proven bacterial UTI, type of UTI, and the causative organism in T2DM patients on SGLT2i.[13] Real-world data will help ascertain if the safety results

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*Corresponding author: Aasim N. Maldar, MD, DNB*
*Junior Consultant, P. D. Hinduja National Hospital and Medical Research Centre, Veer Savarkar Road, Mahim, Mumbai, 400016, Maharashtra state, India*
*Tel. No.: +91 22 24452222*
*Fax No.: +91 22 24449151*
*Email: aasim.maldar@gmail.com*
*ORCiD: https://orcid.org/0000-0002-4878-6845*

of SGLT2i seen in clinical trials can be extrapolated to clinical practice. No prospective studies have specifically addressed this issue in India.

Hence, we performed this study to assess the prevalence of bacterial UTI in patients with T2DM on SGLT2i in Indian patients in the ambulatory setting.

## METHODOLOGY

This was a prospective longitudinal study conducted in a tertiary care center among patients with T2DM who were started on SGLT2i uncontrolled on other oral antidiabetic medications [glycosylated hemoglobin (HbA1c) >7% and/or fasting venous plasma glucose (FPG) >120 mg/dL]. Patients less than 18 years of age, with estimated glomerular filtration rate (eGFR) <45 ml/min/1.73m$^2$, pregnant/ lactating women, and evidence of UTI within the past 3 months were excluded. Patients were included after giving them complete relevant information and obtaining a written consent.

The baseline FPG, post-lunch venous plasma glucose (PPG) and HbA1c were recorded. Urine sample for bacterial culture was collected at baseline prior to initiation of SGLT2i. Patients were prescribed any one of the 4 available SGLT2i – dapagliflozin, empagliflozin, canagliflozin or remogliflozin.

Patients were educated about maintaining genital and perineal hygiene. Instructions were given about washing of genital organs with clean water after urination and defecation and routine use of hygienic wipes. Women were advised to wash from front to back, while uncircumcised males were counseled to retract the prepuce before cleaning. Patients were advised to use mild soap if required and avoid alcohol-based disinfectants for washing.

Patients who developed symptoms of UTI at any time during the 12-week period were advised to report to the clinic immediately and a midstream urine sample for bacterial culture was collected as necessary. After 12 weeks on SGLT2i, information regarding symptoms of UTI such as dysuria, fever, frequency, urgency and a midstream urine sample for bacterial culture were collected. A detailed physical examination with special emphasis on temperature, pulse rate, blood pressure, suprapubic tenderness, costovertebral angle tenderness and mass on deep abdominal palpation were carried out. A genital examination was also done. Patients with symptoms and/or signs suggestive of genital mycotic infections and had a positive response to antifungal treatment were considered to have genital mycotic infections.

For collection of midstream urine: Patients were asked to clean the genital region before micturition. Men were asked to clean the glans penis with swabs soaked in clean tap water, pass about 50 ml of urine into a toilet or bowl, and collect the next portion (10 to 20 ml) into a clean sterile bottle. In women, labia were separated by the patient or nurse and the vulva was wiped twice in an antero-posterior direction with swabs soaked in clean tap water and then cleaned with a dry swab before collection of urine. Urine was then collected with the labia held apart. Urine samples were immediately sent to the laboratory for bacterial culture.

For urine culture, samples were incubated at 37 degrees Celsius for 24 to 48 hours in a Blood/ Chocolate agar and MacConkey agar plate. Organisms identified were based on colony characteristics, lactose fermentation and biochemical tests.

The diagnosis was based on symptoms of UTI regardless of urine culture results, or a positive urine culture regardless of symptoms. Urinalysis was not done at baseline or at 12 weeks. The outcome measured was the proportion of patients having symptoms of UTI, or positive urine culture, i.e., significant bacteriuria (>$10^5$ cfu/mL) at 12 weeks of SGLT2i therapy. Analysis of adverse effect profile (bacterial UTI) was done as a class effect, rather than an individual drug effect.

Statistical analysis was done using "R software 3.5.1." Continuous variables were expressed as mean ± standard deviation (SD). Results of qualitative variables such as fever, frequency, urgency, dysuria, significant bacteriuria and genital mycotic infection symptoms were expressed as frequency and percentages.

The study was approved by the Institutional Ethics Committee. All the patients' details were kept confidential and participants' identity was coded for further analysis.

## RESULTS

A total of 80 T2DM patients (47 males and 33 females) were initiated on SGLT2i over a period of 3 months. Four patients discontinued the drug (1 patient underwent prostate surgery, 1 patient had inguinal hernia surgery and 2 patients had subjective non-specific weakness) and 1 patient could not be contacted. At 12 weeks, 75 patients were evaluated.

The baseline characteristics of patients is shown in Table 1. Majority (50 out of 80, 62.5%) of participants were 46-65 years (mean 52.44 ± 10.24 years). The duration of diabetes was more than 5 years in 52 (69.3 %) participants (mean 8.71 ± 0.99 %). The body mass index (BMI) was >25 kg/m$^2$ in 62 (82.7%) participants, none had BMI > 35 kg/m$^2$ (mean 26.99 ± 2.24 kg/m$^2$).

**Table 1**. Baseline characteristics

| Characteristic | Value |
|---|---|
| Mean age (years) ± SD | 52.44 ± 10.24 |
| Gender (Male: Female) | 47:33 |
| Mean duration of T2DM (years) ± SD | 8.95 ± 4.84 |
| Mean HbA1c (%) ± SD | 8.71 ± 0.99 |
| Mean BMI (kg/m$^2$) ± SD | 26.99 ± 2.24 |

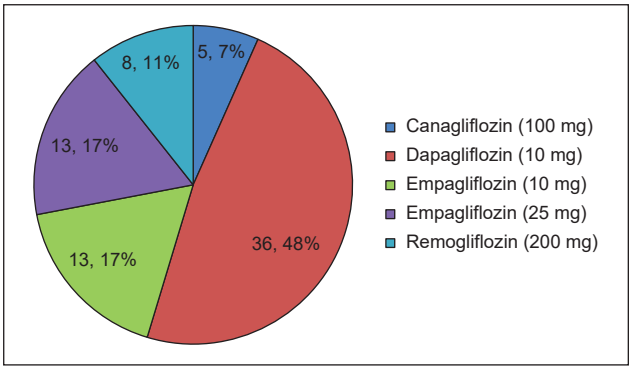


**Figure 1.** Distribution as per specific SGLT2i taken.

**Table 2.** Distribution as per significant bacteriuria and symptoms of UTI at 12 weeks

| | | Total (%) |
|---|---|---|
| Significant bacteriuria | Absent | 74 (98.7) |
| | Present | 1 (1.3) |
| Symptoms of UTI | Absent | 74 (98.7) |
| | Present | 1 (1.3) |

**Table 3.** Distribution as per genital mycotic infection at 12 weeks

| Genital mycotic infection at 12 weeks | Gender | | |
|---|---|---|---|
| | Total | Female (n=30) Number (%) | Male (n=45) Number (%) |
| Absent | 71 | 29 (96.7) | 42 (93.3) |
| Present | 4 | 1 (3.3) | 3 (6.7) |

Of the 75 participants who completed the study, 36 (48%) were on dapagliflozin 10 mg daily; 13 (17.3%) on empagliflozin 10 mg daily; 13 (17.3%) on empagliflozin 25 mg daily; 8 (10.6%) on remogliflozin 100 mg twice a day; and 5 (6.6%) were on canagliflozin 100 mg daily (Figure 1).

One (1.3%) female patient who received canagliflozin had significant asymptomatic bacteriuria at 12 weeks. The causative organism identified was *Acinetobacter baumannii* (Table 2). One (1.3%) male patient had symptomatic UTI with dysuria 4 weeks after starting dapagliflozin. Urine culture of the patient was negative. (Table 2). One (3.3%) female who received empagliflozin 25 mg and 3 (6.7%) male patients on dapagliflozin had genital mycotic infection as shown in Table 3.

## DISCUSSION

The post-hoc power of our study to calculate the prevalence of bacterial UTI and symptomatic UTI was ~80%. The reported prevalence of significant bacteriuria in T2DM patients at baseline, and in control groups ranged from 7.7% to 26%.[10,14,15] In our study, the overall prevalence of significant asymptomatic bacteriuria at 12 weeks of SGLT2i treatment was 1.3%. The patient was on canagliflozin. The prevalence of significant bacteriuria reported in the study conducted by Nicolle et al. was 7.7% at baseline and 6.4% at 12 weeks after taking canagliflozin with no dose dependency.[14] The lack of association of bacteriuria or symptomatic UTI with SGLT2i therapy may be because glucosuria is not the only risk factor for symptomatic UTIs or bacteriuria, and other factors such as hyperglycemia, presence of bladder autonomic neuropathy and urinary tract abnormalities can influence development of symptomatic UTIs or bacteriuria.[9,12]

The prevalence of symptomatic UTI was 1.3% in our study. The patient was taking dapagliflozin 10 mg daily. The prevalence of symptomatic UTI we report was lower than studies conducted by List,[16] Bode[17] and Rosenstock[18] where it was found in 5 to 12%, 5.8 to 8.1%, and 4% patients respectively. The prevalence was similar to the study conducted by Mathieu,[19] (1%), and was higher than in the studies from India by Sosale[20] and Ghosh,[21] where it was 0% and 0.01% respectively.

In our study, the prevalence of genital mycotic infection was 5.3%. The same prevalence was observed in the study of Wan Seman et al.[22] The prevalence was less than the studies conducted by Bode[17] and Aggarwal,[23] where it was 18.6% and 26% respectively; and was more than the study conducted by Kohler,[24] where it was 1% amongst the canagliflozin treated patients.

The likely explanation for the low rate of genital mycotic infections among our patient population may be good genital hygiene, knowledge of side effects and precautions taken while on SGLT2i.

The strengths of our study are that it is a real-world prospective study done in a heterogeneous urban population and the diagnosis of bacterial UTI was based on urine culture done on all patients, regardless of symptoms. We acknowledge that the study period of 12 weeks was relatively short, and UTI as an outcome with more prolonged therapy require further assessment. Lack of a control group and lack of routine urinalysis and microscopy were the limitations of our study. Also, due to small number of outcomes in our study, it is not possible to comment on the choice of specific drug from the SGLT2i drug class.

## CONCLUSIONS

In this real-world study, the risk of developing significant bacteriuria and/or symptomatic UTI was minimal in patients with T2DM on SGLT2i. Furthermore, the risk of clinically diagnosed genital mycotic infection was also low. SGLT2i was well tolerated with a favorable safety profile. Additional adequately powered longitudinal randomized real-world studies using urine culture and urine routine analysis may be undertaken to confirm the safety of SGLT2i with regards to the development of significant bacteriuria and/or UTI.

The genital mycotic infections and bacterial UTI may be preventable if patients are diligently educated about maintaining good genital hygiene.

As there was only one patient with asymptomatic bacteriuria, and another patient with dysuria with a negative urine-culture, it is not possible to comment on the choice of specific drug from the SGLT2i drug class.

**Statement of Authorship**

All authors certified fulfillment of ICMJE authorship criteria.

**Author Contributions Statement**

PF conceived the study, developed the methodology, applied statistical techniques to synthesize the study data, conducted investigation, curated the data, prepared the original draft of the manuscript, prepared data presentation; AM validated research outputs, helped in the formal analysis of the study data, curated the data, wrote the original draft, helped in creating data presentation; NFS conceived the study, developed the methodology, validated research outputs, analyzed study data, provided study materials, wrote, reviewed and edited the manuscript, supervised, managed and coordinated the research activity; PC and MC provided study materials, wrote, reviewed and edited the manuscript, supervised the research activity.

**Author Disclosure**

The authors declared no conflict of interest.

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