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INCIDENCE OF URINARY TRACT INFECTION IN PATIENTS TAKING SODIUM-DEPENDENT GLUCOSE COTRANSPORTERS-2 INHIBITORS: A COMPARATIVE STUDY

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Abstract

Background: New drug classes for treating type 2 Diabetes Mellitus (D.M.) have emerged, such as inhibitors of renal sodium-glucose co-transporter-2 (SGLT2). Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are commonly prescribed anti-hyperglycemic agents worldwide due to extensive evidence supporting their efficacy in controlling hyperglycemia. Despite these benefits, SGLT-2 inhibitors are hypothesized and linked to a higher incidence of urinary tract infections (UTIs). Thus, the United States Food and Drug Administration issued a safety warning for prescribers and patients using SGLT-2 inhibitors in 2015. With this background, a study was planned to determine the incidence of UTIs in patients with Type 2 Diabetes Mellitus.

Material & Methods: This study was conducted in the Medicine Department, NIMS Hospital, Jaipur, between July 1, 2022, and May 31, 2023, and included patients of age 30-80 years presented with Diabetes Mellitus using SGLT-2 inhibitors (cases) and not using SGLT-2 inhibitors (controls).

Results: Urinary tract infections generally were reported to be 42% using SGLT-2 inhibitors (cases) and 16% patients not using SGLT-2 inhibitors (controls). Study subjects using SGLT-2 inhibitors have twice fold of risk of UTI than those treated with non-SGLT-2 inhibitors with an odds ratio +/- 95% CI of 2.75 (1.73–4.37);

Conclusion: This study investigated the high incidence of UTI in patients treated with SGLT-2 inhibitors. Females gender and older age had a higher risk of UTI, as prevalent in previous studies.

Keywords: Diabetes Mellitus (D.M.), Urinary Tract Infections (UTIs), Sodium-Glucose Co-Transporter-2 (SGLT2)

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1. BACKGROUND

New drug classes for treating type 2 Diabetes Mellitus (D.M.), including renal sodium-glucose co-transporter-2 (SGLT2) inhibitors, have emerged. Inhibitors of sodium-glucose cotransporter-2 (SGLT-2) are a new family of oral anti-hyperglycemic agents used worldwide due to extensive evidence supporting their efficacy in controlling hyperglycemia. The mechanism of SGLT2 inhibitors involves the inhibition of glucose renal reabsorption, boosting glucose excretion and lowering blood glucose levels in diabetic individuals [1].

Although some studies stated that there were many documented adverse incidents linked to the use of SGLT2 inhibitors, such as urinary tract infection (UTI) and polyuria, in 2015, the Food and Drug Administration of the United States (US FDA) launched a warning about the risks of severe UTIs due to SGLT2 inhibitors [2].

According to several research, people with type 2 diabetes mellitus who used SGLT2 inhibitors had a significantly higher risk of UTI than those who used a placebo or other oral anti-diabetic agents [3,4]. Conversely, some meta-analysis studies concluded no significant difference in the risk of UTI between patients with SGLT2 inhibitors and placebo [5,6]. As a result, the risk of UTI caused by SGLT2 inhibitors is still controversial. With this background, a study was planned in our population to determine the incidence of UTIs in patients with Type 2 Diabetes Mellitus.

2. MATERIAL & METHODS

Study area and type:

This case-control comparative study was conducted in the Medicine Department, National Institute of Medical Sciences & Research, Jaipur, Rajasthan, Jaipur between July 1, 2022, and May 31, 2023.

Study population:

All patients aged 30-80 years presented with Diabetes Mellitus type 2 patients using SGLT-2 inhibitors were selected randomly as cases, and those not using SGLT-2 inhibitors were selected as controls.

Inclusion criteria:

- Age 30-80 years & both genders
- All Type-2 D.M. patients have been on SGLT-2 inhibitors (dapagliflozin /canagliflozin/remogliflozin/empagliflozin) for over a month.
- Those giving consent

Exclusion criteria:

- Previous and recurrent UTI.
- Regular use of antibiotics.
- Everyday use of corticosteroids.
- The patient is on renal replacement therapy.
- A patient who received a renal transplant.
- Urinary calculous disease.

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Methodology:

A hundred cases (Diabetes Mellitus type 2 using SGLT-2 inhibitors) and 100 controls (Diabetes Mellitus type 2 patients not using SGLT-2 inhibitors were selected randomly. After taking informed consent, the following baseline data were collected: age, sex, height, weight, diabetes duration, menopausal status if female, HbA1c, creatinine value, and use of concomitant diabetes medications at the time of SGLT2 inhibitor initiation in predesigned performa. Complete blood count and urinalysis results were also recorded at the time of genitourinary tract infection diagnosis. Clinical profile as signs and symptoms of genitourinary tract infections (dysuria, frequency, urgency, hesitancy, nocturia, hematuria, back pain, fever, pruritus, erythema, and swelling of the glans penis or labia majora and vaginal curd-like discharge were also recorded. Patients were then assessed if they developed UTI (positive urinalysis result and w/ symptoms) and genital infection in at least three and at six months follow-up: urinary tract infection (UTI) as evidenced by a urinalysis result with positive bacteria and pus cells and with any symptoms mentioned and genital infection as verified by symptoms stated above.

Statistical analysis:

All the above variables were recorded simultaneously in a predesigned, structured schedule and M.S. Excel and Epi data software. With SPSS (Statistical Package for the Social Sciences), data analysis was carried out.

The frequency (%) of categorical variables was described, and continuous parameters were employed, sing mean ± standard deviation. The two groups' differences were compared using the Student T-test. The statistical comparison tool employed was the nonparametric Mann-Whitney test. The Chi-square test compared categorical variables between two or more groups. A two-tailed p-value of less than 0.05 was deemed statistically significant for all analyses.

3. OBSERVATION & RESULTS

100 cases (Diabetes Mellitus type 2 using SGLT-2 inhibitors) and 100 controls (Diabetes Mellitus type 2 patients not using SGLT-2 inhibitors were included in this study. The age-wise distribution of study participants showed that most were above or up to 40 years of age. The mean age of the study cases was 50.54 ± 10.02& study controls were 48.46 ± 12.83. (Table 1). In cases and controls, male predominance was observed (69/100) & (62/100) respectively. [figure 1]

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Table: Age-wise distribution of study participants

Age group (years)	Cases		Controls	
	Frequency	Percent (%)	Frequency	Percent (%)
30-40	20	20%	17	17%
40-50	32	32%	35	35%
50-60	30	30%	33	33%
60 and above	18	18%	15	15%

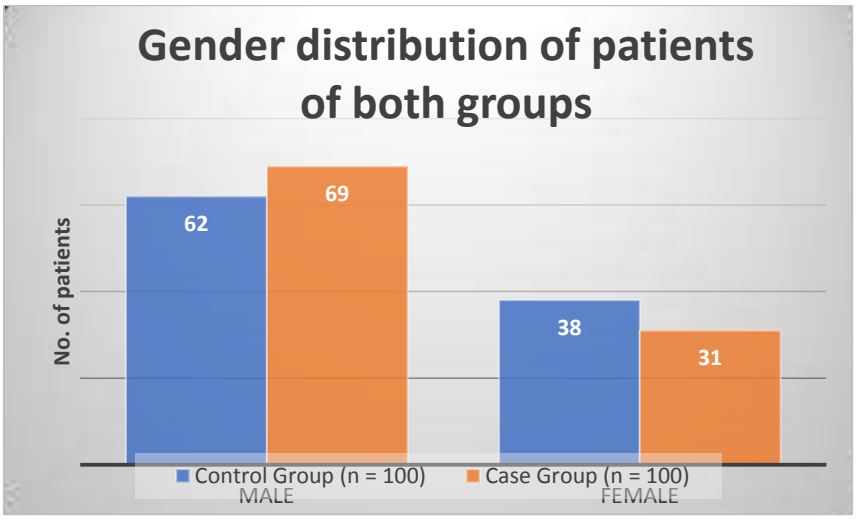

Figure 1: Distribution by Gender of patients of both groups

Laboratory results of both groups are also shown in Table 2. The mean baseline cases of HbA1c were not different from the non-SGLT2 inhibitors group (8.6 and 8.73%, respectively). The mean baseline FBS was also similar between both groups (164.32 and 174.18 mg/dL, respectively). Moreover, the mean baseline serum creatinine in patients treated with SGLT2 inhibitors was 0.97 mg/dL, similar to 0.86 mg/dL in patients with non-SGLT2 inhibitors. [Table 2]

Table 2: Laboratory parameters of both study groups

Characteristics	Case Group	Control Group
HbA1c, %	8.60 (8.39–8.79)	8.73 (8.43–9.00)
FBS, mg/dL	164.32 (158.97–169.68)	174.18 (167.69–180.67)
S. creatinine, mg/dL	0.97 (0.92–0.99)	0.86 (0.82–0.88)
BMI	26.51 (25.78–26.73)	25.78 (25.02–26.43)

Sixty per cent of patients developed a genitourinary infection within six months from SGLT2 inhibitor initiation, while only 22% of patients developed a genitourinary infection in the control group. The median time to first genitourinary infection is six months (IQR: 3.09−6.15). The 3-month incidence of genitourinary infections among patients treated with SGLT2 inhibitors was 2.37% (95% CI:1.07−5.20%), while the 6-month incidence was 21.78% (95% CI: 17.18−27.40%).

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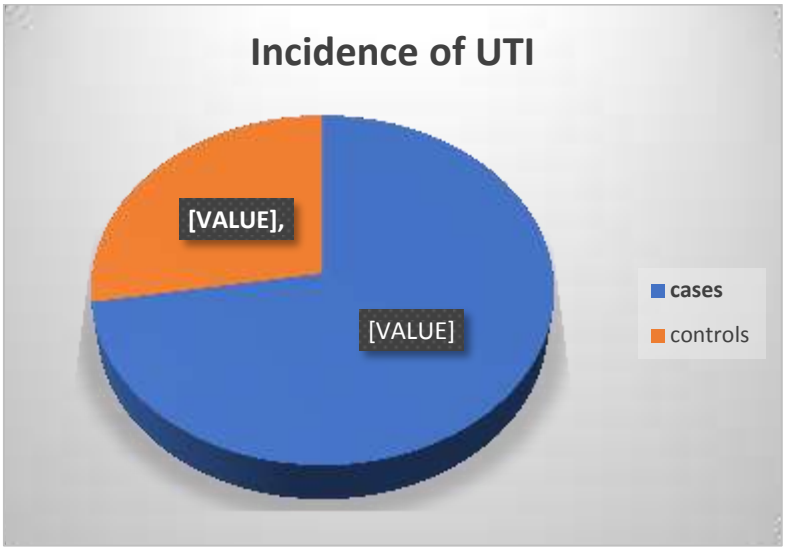

Figure 2: incidence of UTIs in both study groups

The results indicated that gender and the older age group were the risk factors associated with UTI. In particular, the female gender had a 1.75 times higher risk than the male gender (p-value 0.031). Patients under 40 years had a 0.55 times (95% CI 0.30–0.99) decrease in UTI risk compared with people older than 40 years. Other factors not associated with UTI events included BMI, religion, blood sugar levels, and serum creatinine.

Urinary tract infections generally were reported to be 42% using SGLT-2 inhibitors (cases) and 16% patients not using SGLT-2 inhibitors (controls). The incidence rate of patients who used SGLT2 inhibitors was significantly higher than those who used non-SGLT2 inhibitors (p-value < 0.001).

Study subjects using SGLT-2 inhibitors have twice the risk of UTI than those treated with non-SGLT-2 inhibitors with an odds ratio +/- 95% CI of 2.75 (1.73–4.37). [figure 2]

4. DISCUSSION

The results of this study indicated an increase in UTI occurrence in patients who used SGLT2 inhibitors compared to non-SGLT2 inhibitor users. The UTI incidence in patients who used SGLT2 inhibitors was more than 42% compared with 16% in those who used non-SGLT2 inhibitors. In other words, using SGLT2 inhibitors increased the risk of UTI twice fold the risk of UTI than those treated with non-SGLT-2 inhibitors. Moreover, this study's factors associated with UTI were gender and elder age group.

The UTI incidences reported in this study were much higher than in previous studies; the UTI incidences related to SGLT2 inhibitors were usually approximately reported at 3–9% [7, 8,9]. The leading cause of differences in the incidence and odds ratio between this study and the previous studies might be the difference in data collection; the studies mentioned above included only UTIs documented in hospitals, whereas in the current study, all types were

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recorded. In addition, the difference in diagnostic criteria, such as signs, symptoms, self-report, and urine culture, could result in a dissimilar incidence of UTIs [10,11]. The majority of the studies used only urinary laboratory results to diagnose the events of UTI, which were different from the current study, which analyzed UTI based on broader criteria, including inside (i.e., urinary analysis results) and outside the hospital setting (i.e., patient symptoms and diagnosis in medical clinics or pharmacy stores). Therefore, These event collection methods resulted in higher reported incidences of UTI than other studies.

5. CONCLUSION

This study investigated the high incidence of UTI in patients treated with SGLT-2 inhibitors. Among patients on SGLT2 inhibitor therapy, the incidence of UTI was 42%, compared with 16% in patients without SGLT2 inhibitor treatment. Female and older patients treated with SGLT-2 inhibitors should be closely monitored for UTI events—prospective studies with standardized follow-up periods and assessment methods. To clarify the pattern in infection rates over time, long-term follow-ups are necessary. Considering the possible differences in the glucose control of the subjects, concomitant use of SGLT2 inhibitors and other oral hypoglycemics (i.e., SUR and insulin) in increasing the risk of genitourinary infections should be further explored.

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