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Incidence and risk factors for genitourinary infection in individuals with type 2 diabetes using SGLT2 inhibitors: A retrospective study

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***Abstract*---**Aim: To assess the frequency and risk factors for genitourinary infections in people with type 2 diabetes who are using SGLT2 inhibitors. Study design: A retrospective study. Place and Duration: Jinnah Hospital Lahore from March 2021 to March 2022. Methodology: This study included 57 people with type 2 diabetes who were using SGLT2 inhibitors.The parameters linked to genitourinary

infections were observed via the use of multiple logistic regression analyses. This study utilized patients' medical records for observation and analysis. At the beginning of SGLT2 inhibitor therapy, data on the patient's age, gender, height, weight, duration of diabetes, menopausal status, HbA1c, and creatinine levels were collected. Two independent teams of scientists looked through the results of the investigation before concluding the final hypothesis. Results: Genitourinary infection occurred at a rate of 2.37 percent in the first month and 21.78 percent in the second month of the therapy. Genitourinary infections are more likely in individuals with HbA1c values between 7.0 and 8.0% (OR=3.45, p=0.001), 8.0% to 9.0% (OR=8.56, p=0.0001), and 9.0% (OR=11.45, p=0.0001), as well as diabetes medications such as SUR (OR=4.13, p0.001) and insulin (OR=3.81, p0.001). It was also shown that individuals who were overweight or obese (OR=2.42; p=0.039) and had diabetes for more than 10 years (OR=1.98; p=0.026) had an independent effect on the risk of genital infection alone. A high HbA1c (OR=3.18; p=0.002), a low eGFR (OR=2.48; p=0.008), were all shown to be associated with an increased risk of UTI. Conclusion: Within the first four months of therapy with SGLT2 inhibitors, genitourinary infections were prevalent. Gender-specific risk factors for genitourinary infections included having HbA1c above 7% and using insulin or SUR concurrently. All the same characteristics were connected to genital infection, as well as diabetes for a duration of more than ten years and a BMI above 30. HbA1c levels over 7.0 and eGFR below 60 milliliters per minute (ml/min) have been linked to urinary tract infections (UTIs).

***Keywords*---**SGLT2 inhibitors, type 2 diabetes, women, genital infections, urinary infections.

Introduction

It is the role of SGLT2 inhibitors to reduce the quantity of glucose reabsorbed by the kidneys [1]. The most common adverse effects of SGLT2 inhibitors are urinary tract and vaginal fungal infections. As far as we can conclude from various studies and case reports, vaginal fungal infections are the most prevalent [2]. Despite this, the research on urinary tract infections (UTIs) shows a mixture of different results [3]. Studies showed that individuals using an SGLT2 inhibitor were at an increased risk of genital and urinary tract infections. During the study period the incidence of urinary and genital tract infections was determined, and this was compared to the participants' ages, gender, BMIs, diabetes duration, HbA1c, and renal function tests (eGFR) at the time of treatment initiation, concurrent oral hypoglycemic agents, and menopausal status (in females).

Methodology

When conducting this study, we adhered to the Medical Association of Pakistan's (MAP) 2017 Confession of Pakistan and the National Ethical Guidelines for Health

and Health-Related Research [4]. Preliminary permission to do this was given by the ethical review committee of the institute. The frequency and risk factors for genitourinary infections were examined using a retrospective cohort method. Patients included were above the age of 40 years and diagnosed with Type 2 Diabetes Mellitus determined through the ADA criteria and the following SGLT2 inhibitors had been used during the previous four months: Which included can dapagliflozin, and empagliflozin. Patients were routinely tested after therapy commencement as well as testing was conducted for patients who requested it. Individuals with symptoms of the genital or lower urinary tract, such as frequent or painful urination, burning or itching, or a white discharge, were eligible for this research.

Participant selection was based on an intentional sampling method. In establishing the representative sample, EpiInfo 7 StatCalc was utilized. Specifying a 6.33 percent prevalence of genitourinary infection among patients on SGLT2 inhibitors, a maximal tolerable error of 5 percent, as well as alpha equal to 5 percent, a minimum of 31 individuals were required. To guarantee that there are never more than 10 occurrences per variable, the rule of ten happenings per factor [5] was used (1996). Counting the number of occurrences of each variable in a simulated logistic regression analysis a total of 20 patients were required to achieve the sample size requirements for a predictive model using multiple logistic regression analysis with at least 11 components.

Only medical records were obtained in this investigation. At the beginning of SGLT2 inhibitor therapy, data on the patient's age, gender, height, weight, duration of diabetes, menopausal status, HbA1c, and creatinine levels were collected. Two independent teams of scientists looked through the results of the investigation before deciding on the final conclusions. Once a vaginal infection was diagnosed, blood and urine samples were taken. The patients also experienced vaginal tract infections (dysuria (frequency/urgency), hesitation/urgency, nocturia and bleeding, back pain and fever and erythema) which were also documented. A positive urine test with bacteria and pus cells prompted the study of any symptoms that may indicate a UTI or vaginal infection. To gather and analyze the data, Stata MP Version 6 was utilised. It was found that multivariate logistic regression analysis was used to study the risk of infection in the first five months of therapy with an SGLT2 inhibitor. A statistically significant difference was defined as one with a P-value of 0.05 or below. Odds ratios were utilised in a number of ways to compare outcomes across factors.

Results

A total of 57 diabetic patients on SGLT2 inhibitors participated in the study. SGLT2 inhibitors were successful in 55.73 percent of patients with genitourinary infections in the first 4.5 months after commencing treatment. The median (IQR: 3.096.15) time between the development of the first genital infection is 4.05 months. Gluteal infections occurred in 2.37 percent of those on SGLT2 inhibitors for three months, whereas the rate was 21.78 percent in those taking a placebo (95 percent CI: 17.18-27.40 percent). Infections of the urinary tract occurred in 23 (41%) patients, whereas vaginal infections occurred in 22 (42%) patients.

Within 4.5 months of starting SGLT2 inhibitor therapy, 15 patients (or 25 percent) developed urinary and vaginal tract infections. Cases with recurrent infections at six months were seen in four patients (2%). There was a 6.09-month median period from the first urine infection. It took the patients an average 4.05 months took to get their first genital infection which included both genders.

Separate studies were conducted for urinary infections and genital infections. For the 2-month and 4-month periods, the prevalence of urinary infection was 1.98 per cent and 13.57 per cent, respectively (95 per cent CI: 0.1–4.69 per cent). In the meanwhile, genital infection rates at two and four months were 2.37 percent (95 percent confidence interval [CI]: 1.07-5.20 percent) and 16.95 percent (CI]: 12.82-22.24 percent). Of the 57 patients, 50% were taking dapagliflozin, 46% were taking empagliflozin, and just 5% were using canagliflozin. There were 1.67 percent of genital infections in empagliflozin and 3.25 percent in dapagliflozin at month 3. There were 19.18 percent and 26.10 percent, respectively, of genitourinary infections at month four in empagliflozin and dapagliflozin. First genitourinary infection occurred on empagliflozin at 4.09 months (IQR: 3.16–6.15), and on dapagliflozin at 6.05 months (IQR: 3.09–6.11).

Patients treated with empagliflozin or dapagliflozin had the same chance of developing a genitourinary infection, according to a pairwise study (p=0.4784). On average, diabetics with genitourinary infections had diabetes for more time than diabetics who didn't. Patients with HbA1c levels of 8.0 percent (64 mmol/mol) or above were shown to be substantially more prevalent when compared to those without a genitourinary infection. Infection patients with eGFR levels of 60 ml/min were more likely to initiate treatment. Additionally, those with infection were more likely than those without infection to be using sulfonyl-urea (SUR) and insulin. Genitourinary infection was related with age (p=0.042), diabetes duration of more than ten years (p=0.010), and HbA1c values of more than seven (53 mmol/mol). eGFR of 30–60 ml/min (p=0.045), contemporaneous SUR usage (p0.0001), and concomitant insulin use (p0.0001)

A multivariate logistic regression analysis found that genitourinary infection was highly associated with just three variables (As shown in Table 1). For example, patients with HbA1c levels of less than or equal to 8 percent (53 mmol/mol) had a 3.5-fold increased risk of infection, while those with HbA1c levels between 6 and 8 percent (64 mmol/mol) had an 8- to 11-fold increased risk of infection. Those with HbA1c levels between 8 and 9 percent (75 mmol/mol) had an 11.5-fold increased risk of infection. Patients who took both SUR and insulin concurrently showed a four-fold increased risk of infection compared to those who did not take either of these medications. Insulin users had four times the risk of infection as individuals who did not take the drug.

Analysis of urine and vaginal infections was done in Table 2. At the time of SGLT2 inhibitor introduction, higher HbA1c and eGFR 60 ml/min have been linked to urinary infection. With obese/overweight BMI, HbA1c of more over 7.0 percent (53 mmol/mol) at treatment commencement, diabetes duration of more than ten years, and concurrent SUR and insulin usage are all related with vaginal infection. Finally, sub-analyses by sex were carried out to identify the factors related with genitourinary infection (As shown in Table 3). Only women with

raised HbA1c and eGFR below 60 ml/min were shown to be at increased risk of developing diabetes. Genitourinary infection was observed to be related with HbA1c of 8.0 (64 mmol/L) in men and the concurrent use of SUR and insulin

Table1: Results of the multivariate logistic regression study of factors related with genitourinary infections within 6 months of SGLT2 inhibitor start

	Adjusted OR	P Value
HbA1c level		
< 7.0	reference	reference
≥ 7 to < 8	3.62	0.001
≥ 8 to < 9	8.61	<0.0001
≥ 9	11.34	<0.0001
Use of SUR		
No	reference	reference
Yes	4.21	0.001
Use of Insulin		
Yes	3.95	0.001
No	reference	reference

Table2: Outcomes of the logistic regression analysis for urinary tract infection and genital infection following six months of SGLT2 inhibitor start.

	Adjusted OR	Value of P
HBalc Level		
< 7.0	Reference	reference
≥ 8 to < 9	3.24	<0.0002
≥ 9	2.51	<0.0008
eGFR		
>60	Reference	reference
30 to 60	3.1	0.003
Use of SUR		
No	Reference	reference
Yes	2.95	0.027
Use of Insulin		
Yes	3.21	0.001
No	Reference	reference
Factors impacting Genital Infection		
BMI		
Obese	2.6	0.029

Table3: Results of a multivariate logistic regression study on factors related with genitourinary infection in women (n=27) and men (n=30) within six months of starting an SGLT2 inhibitor

	Female		Male	
	Adjusted OR (95% CI)	P value	Adjusted OR(95% CI)	P value

Hba1c level (in %)				
<7.0 (53)	6.37 (2.28–17.78)	*Ref*	*Ref*	*Ref*
≥ 7.0 (53) to <8.0	22.05 (6.24–77.87)	<0.0001	-	-
≥8.0 (64) to <9.0 (75)	22.05 (6.24–77.87)	<0.0001	4.26 (1.01–16.93)	0.040
eGFR (ml/min)	113.85 (13.10-989.11)	<0.0001	3.82 (1.15–12.72)	0.029
>60	*Ref*	*Ref*	-	-
30–60	5.75 (1.72–19.19)	0.004	-	-
SUR use				
No	-	-	*Ref*	*Ref*
Yes	-	-	4.25 (1.35–13.37)	0.014
Insulin use	-	-		
No	-	-	*Ref*	*Ref*
Yes	-	-	6.61 (2.09–20.94)	0.001

Discussion

SGLT2 inhibitors may increase the incidence of genitourinary infections in diabetes individuals [6], according to certain studies(1-3). Clinicians can better identify patients at risk for genitourinary infection if they are aware of the circumstances that set them up for infection in the first place(4, 5). Within 6.5 months of starting an SGLT2 inhibitor, 55.73 percent of the study group had a genitourinary infection. Infections in the urinary tract (41%) and the genital tract (40%) were found to have occurred independently. A quarter of individuals experienced infections of the urine and genitalia after starting the therapy. Arakaki et al. (2016) found that only 2.7–13.4 percent of patients treated with SGLT2 inhibitors had vaginal infection, while urinary infection (i.e., UTI) occurred in 4.9–15.6 percent of patients (4). The location of the research might have had a role in the discrepancy between the two figures. A higher frequency of urinary tract infections (UTIs) might be a result of heat exhaustion and dehydration especially in countries with warmer climates (6). It's also conceivable that the

follow-up period was too short. Most studies only reported incidence rates during the first 18 to 24 weeks of therapy in the current investigation, which lasted for 4.5 months or 18 weeks of follow-up [7,8].

Contrary to prior research, data suggests that genitourinary infection incidence increased even after six months of medication(7). Johnsson et al. (2013) showed infection rates decreasing after 24 weeks of treatment. Most infections occurred 18 to 22 weeks after starting medication, according to studies. More than half of genital infections occurred within three months or 18 weeks following therapy. SGLT2 inhibitors may reduce genitourinary infections in the first three months of treatment due to polyuria. Increased urinary flow may lower urine bacterial load, avoiding hazardous bacterial and fungal development (8). Recent studies demonstrate increased urine volume may remain for up to 12 weeks after starting an SGLT2 inhibitor (8). The initial diuresis reduces with time, according to the same study. This attenuation may explain why longer-term studies found an increased risk of genitourinary infection similar to the results obtained from the study. Regular urine testing at an interval of 3 to 6 months may help detect and treat genitourinary infections early; only 4% had recurring infections within 4.5 months [9,10,11].

SGLT2 inhibitors vary in safety [12]. A recent meta-analysis found that dapagliflozin increases UTI risk but not empagliflozin. In a 100-day study, 8% and 7% of patients had urinary and vaginal infections due to dapagliflozin (9). Dapagliflozin patients had a 3.25 percent 3-month urinary and vaginal infection incidence. Vaginal and UTIs occurred despite a modest prevalence in early treatment. A rise in infection rates was seen after six months, with a 17.73 percent increase in urine infection and a 20.74 percent increase in genital infection. Empagliflozin, on the other hand, had a lower genitourinary infection rate than dapagliflozin, although the 6-month incidence was still significant. In this research, 10.46% of patients had an infection of the urinary tract, whereas 14.52% had an infection of the genital tract. Emagliflozin's pooled safety analysis estimated 14.04 percent UTI and 5.67 percent genital infection(7)

SGLT2 inhibitors have been associated to an increased risk of genitourinary infection in individuals with glucosuria, a side effect of the medication(10, 11). Glucose in the urine feeds bacteria and fungi, making it simpler for them to spread. Results showed that HbA1c levels at the time of therapy initiation were shown to be highly associated to genitourinary infections. Uremic glucose excretion, on the other hand, depends on the average glucose concentrations (8). To reduce blood glucose levels, SGLT2 inhibitors increase the amount of glucose excreted in the urine. As a consequence, it's likely that those with high glucose levels at the start of the study were more vulnerable to genitourinary infections. In contrast, McGovern's study revealed no link between high levels of HbA1c and genital infection (12). UTI and vaginal infection are not linked to high levels of blood sugar, according to a meta-analysis [13].

Risk factors also differed across genders. Higher HbA1c levels were shown to be linked with both male and female genitourinary infections, although lower eGFR was only found to be related with female genitourinary infections [14]. Patients with renal insufficiency are more likely to get community-acquired infections

including UTIs, according to observational research. These discrepancies, on the other hand, might be explained by the small numbers of patients in each of the several subgroups. There was no difference in the risk of genitourinary infection between women who were menopausal and those who were not [15]. In our research, we found that using SUR and/or insulin at the same time increased the chance of genitourinary infection. SGLT2 inhibitors may worsen glycemic control if insulin and/or SUR are used together. They had HbA1c values over 8% (64 mmol/mol) in our study, contrary to popular belief. According to a study the combination use of insulin and dapaglifozin led to an increased incidence of vaginal infection and urinary tract infection (UTI) [16]. Consequently, it is necessary to study the mechanism by which the concurrent use of these oral hypoglycemic drugs increases the risk of genitourinary infections [17].

The 16-week follow-up period is one of the study's advantages. Shorter follow-up intervals were used in most research, reducing the amount of data that could be collected. Since earlier studies have shown that infections may lead to treatment discontinuation (12) and poor glucose control as a result, patients should continue to be monitored for at least another four months. In addition, urinary and vaginal infections were examined separately. Genital infections, on the other hand, are more often caused by fungus rather than bacteria [18]. Differences in treatment and causative organisms are found between the two types of sickness. The menopausal status of the female must be taken into account since post-menopausal women are more prone to genitourinary infection(6).

There are some limitations to the study as well. It is possible that the greater incidence of genitourinary infection is due to its tropical climate, which has been shown to be a risk factor for the development of UTIs in another research [19]. Because the research was conducted at an institution that caters to educated and wealthy families, the study participants may have a reduced risk of infection than those in government hospitals. Second, the study's limitations prevented it from gathering information on additional variables that could have contributed to the genitourinary infection. Glucosuria and past urinary/genital infection, according to another research (3, 9), may also play an important role in the development of genitourinary infections in diabetics. Medical records are a third factor in making the accurate diagnosis of these types of infections. In contrast to prospective trials, in which patients were obligated to tell researchers as soon as symptoms suggestive of genitourinary infection appeared, researchers in this retrospective analysis had no say over when patients were assessed. Because genital infection is often detected clinically (4), the absence of systematic testing might have brought information bias into our investigation, leading to underreporting of genital infection. When it comes to diagnosing urinary tract infections, laboratory testing is the most common method [20].

Conclusion

People who took SGLT2 inhibitors often get a urinary tract infection within 6 months of starting treatment. Genitourinary infections can be caused by different things depending on the person's sex, such as having HbA1c of more than 7% or using insulin and/or SUR at the same time, both of which are signs of poorly controlled diabetes. Diabetes that has been around for more than 10 years, and

an overweight or obese BMI were also linked to genital infections. A UTI on its own is linked to a high HbA1c and an eGFR of less than 60 ml/min.

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None

Permission
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