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Occurence of urinary tract infections in type 2 diabetes mellitus patients taking Sodium-Glucose Co-Transporter-2 (SGLT-2) inhibitors to regulate their blood sugar levels

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***Abstract*---**Background and Aim: The occurrence of urinary tract infection (UTI) in type 2 diabetes (T2DM) administered with sodium glucose co-transporter-2 (SGLT2) inhibitors are still debatable. The present study aimed to assess the occurrence of UTI in T2DM patients taking SGLT-2 inhibitors to regulate their blood sugar levels. Patients and Methods: This cross-sectional study was carried out on 369 T2DM patients investigated in the Nephrology division of Khyber Teaching Hospital, Peshawar from January 2022 to December 2022. Dapagliflozin and empagliflozin were SGLT-2 inhibitors drugs given to

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each individual. Patient's detailed history and genitourinary infections were noted from medical records. Pain during micturition, micturition urgency, redness, abdominal pain, vomiting, and frequency of micturition, fever, soreness, and diarrhea were recorded using questionnaire based proforma. Results: Of the total 369 patients, the frequency of patients administered with dapagliflozin and empagliflozin was 178 (48.2%) and 191 (51.8%) respectively. Among 178 patients, there were 112 (62.9%) male and 66 (37.1%) females. Among 191 patients, there were 136 (71.2%) male and 55 (28.8%) females. The occurrence of UTIs in patients using dapagliflozin and empagliflozin was 18 (10.1%) and 28 (14.7%) respectively. Likewise, the genital tract infections were found in 20 (11.2%) dapagliflozin users and 26 (13.6%) empagliflozin users. In both dapagliflozin and empagliflozin users, females were more prone to urinary and genital tract infections. There was significant association of uncontrolled diabetes with female gender with a 3% and 1% level of significance. Conclusion: The present study reported that the prevalence of genitourinary infections was significantly higher in diabetic patients than healthy individuals. Additionally, the genitourinary infection is significantly associated with SGLT-2 inhibitors intake among diabetic patients.

***Keywords*---**Urinary tract infections, type 2 diabetes mellitus, sodium glucose co-transporter-2 (SGLT2) inhibitors.

Introduction

Sodium glucose co-transporter 2 (SGLT2) inhibitors are a new family of oral antihyperglycemic medicines used to treat type 2 diabetes. The working principle of SGLT2 inhibitor is the kidney glucose reabsorption leading to blood glucose levels reduction and increased excretion of glucose in diabetic individuals [1]. Because of the abundant data supporting their efficacy in managing hyperglycemia, sodium-glucose cotransporter-2 (SGLT2) inhibitors are routinely prescribed anti-hyperglycemic medicines globally. They also offer additional metabolic advantages, including as weight loss and blood pressure decrease in type 2 diabetic patients [2]. Furthermore, findings from major cardiovascular, renal, and heart failure studies demonstrated that SGLT2 inhibitors were linked with a substantial reduction in heart failure hospitalizations and progression of kidney disease in individuals with and without diabetes [3-5].

Diabetes mellitus is a global disease, and Pakistan ranks seventh among nations with the greatest number of people with diabetes people, according to World Health Organization (WHO) surveys [6]. If necessary steps are not implemented in a timely manner, this burden will skyrocket. One of the primary causes of this rise in burden is a lack of resources in Pakistan's healthcare system [7]. Seven medication classes are mostly employed to regulate an optimal range of blood sugar levels in diabetic patients. SGLT-2 inhibitors are regarded as an innovative and effective pharmacological class among them. The pharmaceuticals in this class are used both alone and in combination with other medications

[8]. Diabetes mellitus can be treated with dapagliflozin, canagliflozin, empagliflozin, and ertugliflozin [9]. These medications have demonstrated great tolerance and safety, with no danger of reducing blood sugar levels below the optimal threshold [10]. SGLT-2 inhibitors have been proven to be effective in decreasing and maintaining blood glucose levels, lipid profiles, blood pressure, body weight, and HbA1C [11]. Another remarkable aspect of this medication class is that it is cardio-protective since it improves endothelial tissue function [12].

SGLT-2 inhibitors work by preventing glucose reabsorption from the kidney's proximal convoluted tubule [13]. It is disputed if genitourinary infections in diabetics who use SGLT-2 inhibitors are caused by the medication [14]. Diabetes patients are more likely than normal people to get a genitourinary infection, which occurs owing to diabetes patients' impaired immune [15]. Similarly, diabetic people are more likely to develop vaginitis [16]. The current investigation is being carried out to determine the incidence of these infections in diabetic individuals and their relationship with SGLT-2 inhibitors.

Methodology

This cross-sectional study was carried out on 369 T2DM patients who were investigated in the Nephrology division of Khyber Teaching Hospital, Peshawar from January 2022 to December 2022. Dapagliflozin and empagliflozin were SGLT-2 inhibitors drugs given to each individual. Patients with diabetes mellitus type 1, gestational diabetes mellitus, and no diabetes at all were excluded. All research participants were asked to provide a detailed personal and clinical background. After taking the history, the clinical assistants completed a specifically developed pro-forma and questionnaire. The pro-forma also contained information about the participants' symptoms of genital tract infections and urinary tract infections while using SGLT-2 inhibitors. After obtaining a full history of the patients, laboratory data such as blood sugar level, lipid profile, HbA1C, and urine complete examination were done. Patients who displayed infection signs such as dysuria, discomfort, fever, sepsis, urgency, and frequency of urination were also subjected to urine culture testing. Patients with positive urine culture results were diagnosed with genitourinary infections. Patient’s detailed history and genitourinary infections were noted from medical records. Pain during micturition, micturition urgency, redness, abdominal pain, vomiting, and frequency of micturition, fever, soreness, and diarrhea were recorded using questionnaire based pro-forma.

SPSS version 27 was used for descriptive statistics. Numerical variables were expressed as mean and standard deviation whereas categorical variables were described as frequency and percentages. The chi-square test was used to evaluate the association between several categories.

Results

Of the total 369 patients, the frequency of patients administered with dapagliflozin and empagliflozin was 178 (48.2%) and 191 (51.8%) respectively. Among 178 patients, there were 112 (62.9%) male and 66 (37.1%) females. Among 191 patients, there were 136 (71.2%) male and 55 (28.8%) females. The

occurrence of UTIs in patients using dapagliflozin and empagliflozin was 18 (10.1%) and 28 (14.7%) respectively. Likewise, the genital tract infections were found in 20 (11.2%) dapagliflozin users and 26 (13.6%) empagliflozin users. In both dapagliflozin and empagliflozin users, females were more prone to urinary and genital tract infections. There was significant association of uncontrolled diabetes with female gender with a 3% and 1% level of significance. The demographic details and baseline characteristics are shown in Table-I. Incidence of infections based on the gender distribution are presented in Table-II. The association of various variables with genitourinary infections are represented in Table-III.

Table-I Baseline characteristics of patients

Parameters	Value (Mean ± SD)
Age (years)	38.4±10.92
Gender N (%) Male Female	 248 (67.2%) 121 (32.8%)
BMI (kg/m^2)	27.9±4.8
Diabetes mean duration (years)	5.9±2.5
UTI prior history	25 (6.8%)
HbA1c mean level	7.6±2.3

Table-II Incidence of infections based on the gender distribution

Infections	Dapagliflozin users (N=178)	Empagliflozin users (N=191)
UTIs N (%) Male Female Total	 8 (4.5) 10 (5.6) 18 (10.1)	 9 (4.7) 19 (9.9) 28 (14.6)
Genital infections N (%) Male Female Total	 14 (7.9) 6 (3.4) 20 (11.3)	 15 (7.9) 11 (5.8) 26 (13.7)

Table-III association of various variables with genitourinary infections

Parameters	GTIs (n=46)	P-value
Female gender	19 (41.3)	0.001
Diabetes duration (>5 years)	7 (15.2)	0.159
BMI (>30 Kg/m^2)	8 (17.4)	0.229
HbA1c (>8.5%)	32 (69.6)	0.002
GTIs prior history	6 (13)	0.459

Discussion

The present study mainly focused on the occurrence of UTIs among T2DM patients taking SGL-2 inhibitors and found that diabetes patients are more likely than healthy people to get genitourinary infections. Patients on SGLT-2 inhibitors

have a greater risk of contracting genitourinary infections. Female patients using SGLT-2 inhibitors and individuals with uncontrolled diabetes had a higher prevalence. The study found that the association is not significant; nonetheless, female diabetes patients are more likely to get infections than male diabetic patients. In diabetic patients, genitourinary infections are more prevalent than in healthy people. Johnston et al. [17] studied the association of UTI with T2DM and their study has a sample size of 350 people. All of the individuals had type 2 diabetes. In those individuals, the total prevalence of UTI was over 47%. They concluded that diabetic people are more likely to get a UTI.

Liu et al. carried out their investigation on 400 diabetic individuals by administration of 5 mg and 10 mg dapagliflozin. Blood and urine samples were collected to test for genitourinary infections. 5.3% of the individuals were found to have urinary tract infections. They came to the conclusion that the infections were mild to severe. The infection was not serious enough to warrant withdrawal of the treatment [18].

SGLT-2 is an anti-hyperglycemic medications associated with increased prevalence of UTIs [19]. Dapagliflozin increases the glucose concentration leading to bacterial growth and colonization in urine in turn causes UTIs [20]. Whereas the results of the present investigation reported that SGLT-2 use from lower to moderate severity increased the risk of UTIs.

A larger dose of dapagliflozin increases glucose excretion in the urine, which presumably thrive the bacteria favorable environment by increasing the risk of UTIs [21]. However, we did not find this in our trial since UTIs were not significantly linked with dapagliflozin dosage strength ($p = 0.95$). These findings are consistent with previous investigation, which found that increasing the SGLT2i dosage increased glycosuria but had no effect on the incidence of UTIs [22].

Dapagliflozin lowers blood glucose levels by blocking reabsorption in the kidneys [23]. The research on the connection between UTIs and dapagliflozin dosage size is contradictory [24, 25]. In various research, including ours, it is critical to detect confounding factors. Rauf et al. did a research comparable to this one. Their investigation, however, was retrospective. They carefully examined the medical records of 57 individuals who were on SGLT-2 inhibitors to treat their diabetes. According to their findings, individuals who had been using the medicine for four months had a greater rate of UTIs. They also observed that the link between UTIs and female gender was strong [26].

In multiple investigations, dapagliflozin, has been shown to increase the incidence of UTI. Hsia et al. [27] showed a substantial rise in UTI comparable to another study. This investigation discovered that individuals using dapagliflozin had a significantly greater risk of UTI. Furthermore, a substantial increase in UTI occurrences in empagliflozin-treated individuals, although earlier meta-analysis studies reported no significance [28].

Conclusion

The present study reported that the prevalence of genitourinary infections was significantly higher in diabetic patients than healthy individuals. Additionally, the genitourinary infections is significantly associated with SGLT-2 inhibitors intake among diabetic patients. Patients on SGLT-2 inhibitors have a greater risk of contracting genitourinary infections. Female patients using SGLT-2 inhibitors and individuals with uncontrolled diabetes had a higher prevalence.

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