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ASSESSMENT OF GENITAL AND URINARY TRACT INFECTIONS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS TREATED WITH DAPAGLIFLOZIN

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Several studies have shown that pharmacologically induced glucosuria with dapagliflozin increases the risk of developing urinary and genital tract infections (UTIs). The aim of this study is to assess the incidence of urinary and genital infections and to investigate risk factors in T2DM patients treated with dapagliflozin 5 and 10 mg. The study included 108 patients with type 2 diabetes, aged between 40-70 years, randomly selected from the outpatient of the Endocrinology Department at Tishreen University Hospital in Syria. 52 patients received once daily dapagliflozin (5 or 10 mg) as add-on therapy to oral antihyperglycemic drugs, and 56 patients treated with antihyperglycemic agents for ٢٤ weeks. We compared patients with well-controlled diabetes to deny the effect of HbA1c on the incidence of urinary and genital infections.

We observed that treatment with dapagliflozin is associated with an increased risk of developing genital infections. There was no statistically significant increase in the incidence of urinary infections in patients treated with dapagliflozin. We identified gender and a previous history of genital infection as risk factors for genital infection. Long-term studies are still needed to determine association of dapagliflozin with an increased risk of UTIs.

***Keywords**: Type 2 diabetes mellitus, Dapagliflozin, Urinary tract infections, Genital infections, Risk factors.*

INTRODUCTION

Diabetes mellitus is one of the most common chronic diseases in the twenty-first century, and is considered one of the most alarming health emergencies. According to the General Diabetes Federation, the prevalence of diabetes has reached 463 million people in 2019. In Syria, the prevalence of diagnosed diabetes reached 13.5% in the same year [1].

Type 2 diabetes (T2DM) is the most prevalent form of diabetes globally. It accounts for greater than 90% of diabetes cases[1&2].

T2DM is associated with an increased risk of urinary and genital infections, which is due to a combination of factors: the presence of glycosuria, greater adherence of pathogens to the uroepithelium, and weakened cellular and humoral immune responses[3&4].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are effective glucose-lowering drugs that were developed to overcome the problems of traditional antidiabetic drugs. These drugs act by blocking the reabsorption of glucose through SGLT2 channels in the proximal tubule and also by lowering the renal threshold for glucose excretion, which in turn causes glucosuria[5]. Therefore, it is logical to expect that SGLT2 inhibitors might increase the risk of urinary and genital infections.

Dapagliflozin is the first new SGLT2 inhibitor that was marketed in Syria. It is

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commonly used as a second or third-line treatment for type 2 diabetes mellitus. It has been studied in patients in placebo-controlled clinical studies as monotherapy, as add-on therapy to other standard antidiabetic treatments, and as first-line combination therapy with metformin[6-8]. In most studies, the incidence of urinary and genital infections (such as vulvovaginitis and balanitis) increased in patients treated with dapagliflozin compared to placebo and other hypoglycemic drugs[8-12] . Gender (women) and previous history of urinary and genital infections were identified as risk factors[9&10&13], while relationship between HbA1c values and the incidence of infections in many studies was not clear [11&13].

The studies show conflicting results regarding the effects of dapagliflozin dose on the incidence of both urinary and genital infections. K.M. Johnsson et al did not demonstrate a dose-dependent relationship with the incidence of urinary tract infections (UTIs) ,vulvovaginitis and balanitis[9&10]. This contrasts with the dose-response relationship documented between dapagliflozin and glucosuria[14].

Therefore, our aim in this study was to evaluate the incidence of urinary and genital infections and risk factors associated with in T2DM patients treated with dapagliflozin 5 and 10 mg.

MATERIALS AND METHODS

Patients selection

The study included 115 patients with type 2 diabetes of both genders. The patients' ages ranged between 40 - 70 years. Type 2 diabetes was diagnosed according to the American Diabetes Association guidelines, from less than 1 year to 13 years ago.

They were randomly selected from the outpatient of the Endocrinology Department at Tishreen University Hospital in Syria. The patients were divided into two groups:

The first group included 56 patients with type 2 diabetes who were prescribed dapagliflozin (5 mg or 10 mg) once daily as an add-on therapy to oral antihyperglycemic agents (Metformin, Sulfonylureas and Gliptins).

The second group (Conrtol) includes 59 patients with type 2 diabetes treated with oral antihyperglycemic agents (Metformin, Sulfonylureas and Gliptins).

Patients were followed up for 24 weeks.

Seven people did not continue the study for several reasons (3 patients changed the medication after a short period, 4 patients did not comeback for follow-up evaluation).

52 patients in dapagliflozin group and 56 patients in control group completed the study.

To deny the effect of HbA1c on the incidence of urinary and genital infections, we also compared between patients with controlled diabetes in both study groups.

We designed a questionnaire to record patients' information (age, weight and height to calculate body mass index (BMI), current and previous diseases, duration of diabetes, medications, history of urinary and genital infections, history of urinary incontinence and nocturia, etc.). An informed written consent was taken from each participant in the study. The study protocol was approved by the local ethical committee.

The exclusion criteria were as follows:

- Pregnancy and breast-feeding
- Kidney stones
- Benign prostatic hyperplasia
- Recent use of urinary catheters
- Use of contraceptives such as spermicides and condoms
- Insulin therapy

Biochemical evaluation

Venous blood samples were taken in the morning after fasting for at least 8 hours overnight.

Laboratory assessments included:

1- Fasting plasma glucose levels which were measured by colorimetric method using an automated analyzer (BS-380, Mindary) normal range: 70-110 mg/dL

2- Glycosylated hemoglobin HbA1c was measured by fluorescent immunoassay technology (Diabetes> 6.5%) by an automated analyzer (Finecare, Wondfo)

Morning urine samples were collected in sterile urine collection containers. Macroscopic and chemical examinations of urine was conducted to determine the pH of urine, the presence of glucose and nitrite in the urine, then 10 ml of the urine sample was centrifuged at a speed of 4000 revolutions per minute within 3 minutes. Then the precipitate was examined on a slide vitreous under the

microscope to determine the presence and enumeration of the following:

Leukocytes (WBC), Erythrocytes (RBC), Crystais, Casts, Epithelial Cells, Mucus, Bacteria and Candida.

Urinary tract infections were diagnosed based on clinical symptoms including: dysuria, a feeling of needing to urinate (urgency), a burning sensation when urinating, an increase in the frequency of urination, and pain in the lower abdomen or lower back. In addition to the macroscopic, microscopic and chemical examination of morning urine samples.

Genital infections were diagnosed by clinical symptoms that included itching, pain when urinating, vaginal discharge, redness, burning and soreness in the genital area.

Statistical analysis

The nature of the distribution of the data was tested using the Kolmogorov-Smirnov test. To analyze the relationships between qualitative variables we used the Chi-Square test or Fisher exact test. The level of significance was set at $p < 0.05$.

RESULTS AND DISCUSSION

Results

The mean age of patients was 54.80 ± 7.7 years. 47(43.5%) of them were males and 61 (56.5%) were females.

The baseline mean HbA1c was 7.60 ± 1.3%. More than 67% of patients treated with dapagliflozin had HbA1c> 7.

Patients had a baseline mean BMI of 28.42±4.1 kg/m^2 (65.7% had a BMI < 30 kg/m^2 and 34.3% had a BMI≥ 30 kg/m^2). The majority of patients treated with dapagliflozin had a diabetes duration of 3-7 years.

The study groups were generally balanced with respect to a previous history of urinary and gential infections.

Table 1 shows the demographic and baseline characteristics of patients.

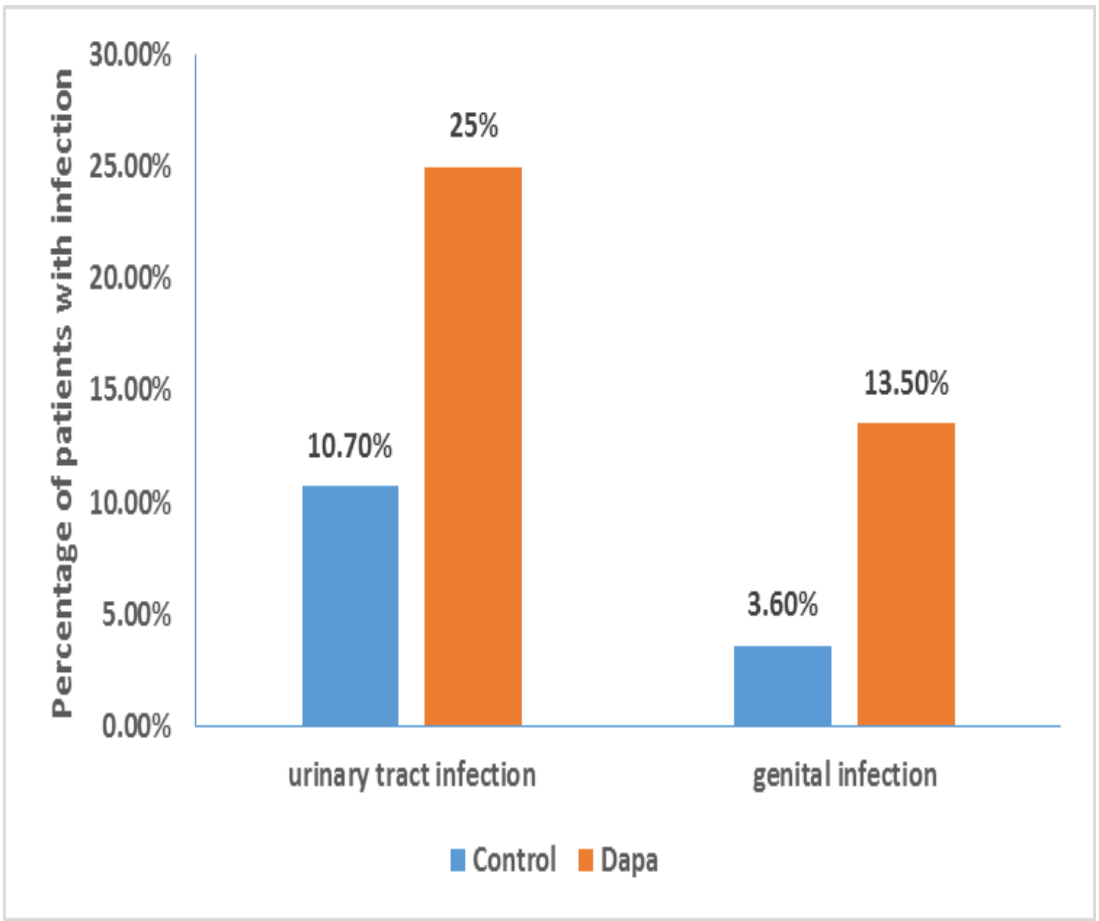

Fig.1: Percentage of patients with urinary and genital tract infection between the two study groups.

Table 1: Demographic and Baseline Characteristics of Patients.

Characteristic	Control n = 56	Dapagliflozin n = 52	P.value
Age, n (%) 40-49 50-59 ≥ 60	 16 (28.6%) 28 (50%) 12 (21.4%)	 13(25%) 21 (40.4%) 18 (34.6%)	 0.3
Sex, n (%) Women Men	 30 (53.6%) 26 (46.4%)	 31 (59.6%) 21 (40.4%)	 0.5
Body mass index, n (%) < 30 kg/m^2 ≥ 30 kg/m^2	 39 (69.6%) 17 (30.4%)	 32(61.5%) 20 (38.5%)	 0.3
HbA1c, n (%) < 7 % ≥ 7 %	 28 (50%) 28 (50%)	 17 (32.7%) 35 (67.3%)	 0.06
Diabetes duration, n (%) < 3 years 3-7 years > 7 years	 29 (51.8%) 16 (28.6%) 11 (19.6%)	 10 (29.2%) 39 (75%) 3 (5.8%)	 < 0.0001*
Previous urinary tract infection, n (%)	9 (16.1%)	9 (17.3%)	0.8
Previous genital tract infection, n (%)	4 (7.1%)	7 (13.5%)	0.2
History of urinary incontinence, n (%)	2 (3.6%)	2 (3.8%)	0.9
History of nocturia, n (%)	3 (5.4%)	3 (5.8%)	0.9
n = 108. The data was analyzed using Chi-Square test or Fisher exact test. *p value ≤ 0.05			

Urinary tract infections

After 24 weeks of follow-up the overall proportion of patients reporting on UTI events was 13 patients in dapagliflozin 5 mg and 10 mg groups (11.5% and 38.5%, respectively) compared with 6 patients in control group (10.7%). (Fig.2)

Most events were mild to moderate and responded well to antibiotic therapy.

Baseline characteristics and their association with urinary infections among 52 patients treated with dapagliflozin are shown in (Table 3).

To understand the potential risk factors for UTI, incidence rates were determined based on various subgroups, including categories of baseline HbA1c (<7 % and ≥ 7 %), age (40-49, 50-59 and ≥60 years). Body mass index (<30 and ≥ 30), Diabetes duration (<3 , 3-7 and >7 years), gender, history of UTI, urinary incontinence and nocturia.

Urinary tract infections were more common among women (92.3%) compared with men (7.7%) (P value =0.006)

More than 53% of dapagliflozin-treated patients with prior history of UTI reported an infection versus 5.1% who did not (P< 0.0001).

Patients who had BMI ≥ 30 kg/m2 were also more likely to have infection after treatment with dapagliflozin compared with patients who had BMI < 30 kg/m2 (69.2% vs 30.8%).

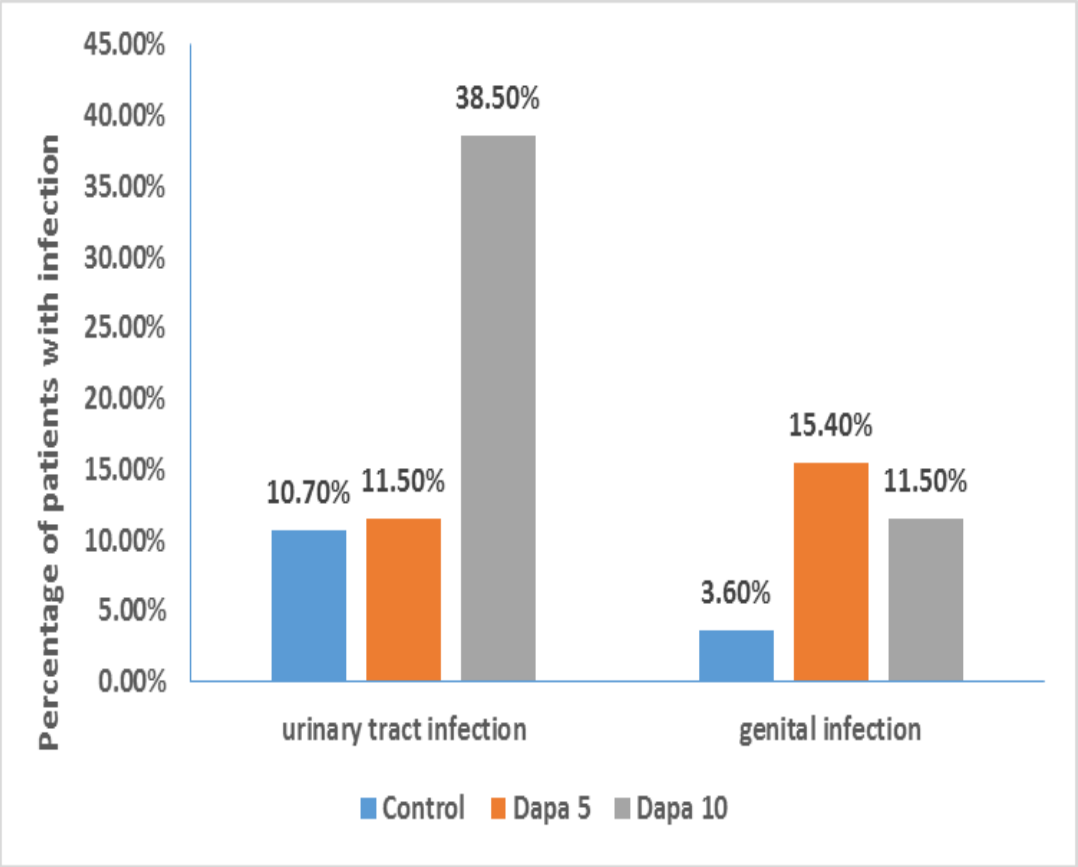

Fig.2: Percentage of patients who reported urinary and genital tract infection between pratients treated with dapagliflozin 5 mg, 10 mg and control group patient.

Table 2: Distribution differences according to the presence of urinary and genital infections between the two groups of patients.

	Control	Dapagliflozin	P.value
Urinary tract infections, n (%)	6 (10.7%)	13 (25%)	0.05*
Genital tract infections, n (%)	2 (3.6%)	7 (13.5%)	0.06

The data was analyzed using Chi-Square test or Fisher exact test. *p value ≤ 0.05.

In addition, 2 out of 3 patients with nocturia reported urinary tract infections (p= 0.04). There was no significant difference in the incidence of urinary infections between the three age categories.

In 53.8% of the urinary infection cases, the HbA1c was greater than 7 but there was no statistically significant difference in the incidence of urinary tract infection according to the HbA1c value or diabetes duration. The incidence of urinary infections was higher in patients treated by dapagliflozin 10 mg than in patients who received dapagliflozin at 5 mg (76.9% vs. 23.1%, p= 0.02) (Table 3**)**.

Among the patients with controlled diabetes, six patients (35.3%) treated by dapagliflozin reported urinary infections compared to 4 patients (14.3%) in the control group (P= 0.1). (Fig.3)

Table 3: Baseline characteristics (categorical variables) and their association with urinary infections among patients treated with dapagliflozin.

	Urinary Tract Infection		P-value
	Yes	No	
Sex, n (%) Female Male	 12 (92.3%) 1 (7.7%)	 19(48.7%) 20 (51.3%)	0.006*
Age, n (%) 40-49 50-59 ≥ 60	 4 (30.8%) 5 (38.5%) 4 (30.8%)	 9 (23.1%) 16 (41%) 14 (35.9%)	0.8
Body mass index, n (%) < 30 kg/m^2 ≥ 30 kg/m^2	 4 (30.8%) 9 (69.2%)	 28 (71.8%) 11 (28.2%)	0.008*
HbA1c, n (%) < 7 % ≥ 7 %	 6 (46.2%) 7 (53.8%)	 11(28.2%) 28 (71.8%)	0.2
Diabetes duration, n (%) < 3 years 3-7 years > 7 years	 2 (15.4%) 11 (84.6%) 0 (0%)	 8 (20.5%) 28 (71.8%) 3 (7.7%)	0.5
Dapagliflozin Dose, n (%) 5 mg 10 mg	 3 (23.1%) 10 (76.9%)	 23 (59%) 16 (41%)	0.02*
Previous urinary tract infection	7 (53.8%)	2 (5.1%)	< 0.0001*
History of urinary incontinence	1 (7.7%)	1 (2.6%)	0.4
History of nocturia	2 (15.4%)	1 (2.6%)	0.04*

The data was analyzed using Chi-Square test or Fisher exact test. *p value ≤ 0.05.

In addition, 2 out of 3 patients with nocturia reported urinary tract infections (p= 0.04). There was no significant difference in the incidence of urinary infections between the three age categories.

In 53.8% of the urinary infection cases, the HbA1c was greater than 7 but there was no statistically significant difference in the incidence of urinary tract infection according to the HbA1c value or diabetes duration. The incidence of urinary infections was higher in patients treated by dapagliflozin 10 mg than in patients who received dapagliflozin at 5 mg (76.9% vs. 23.1%, p= 0.02) (Table 3).

Among the patients with controlled diabetes, six patients (35.3%) treated by dapagliflozin reported urinary infections compared to 4 patients (14.3%) in the control group (P= 0.1). (Fig.3)

Gential Infections

Seven patients in the dapagliflozin group reported genital infections versus two patients in the control group (13.5% vs. 3.6%, respectively). (Table 2)

The number of genital infections events in patients treated with dapagliflozin 5 mg and 10 mg was close (15.4% and 11.5%, respectively) of all patients included in the study. (Fig.2)

Most cases were mild to moderate and responded well to antibiotic therapy.

All events occurred in females, while no genital infection was reported in men (P= 0.01).

Baseline characteristics and their association with genital infections among patients treated with dapagliflozin are shown in (Table 4).

When examining the risk factors for genital infection in patients treated with dapagliflozin, the incidence of genital infections was significantly higher in patients who reported a history of genital infections compared to patients who did not report a history of genital infection (71.4% vs 28.6%, P = 0.0001)

Patients with BMI ≥ 30 kg/m2 were also more likely to have infection after dapagliflozin treatment compared with patients who had BMI < 30 kg/m2 (71.4% vs 28.6%, respectively).

There were no statistically significant differences regarding the rate of genital infections in patients treated with dapagliflozin based on age, HbA1c values, and duration of diabetes.

Among controlled diabetes patients, four patients (23.5%) treated with dapagliflozin reported genital infections, while none of the patients in the control group reported genital infections (P= 0.007). (Fig.3)

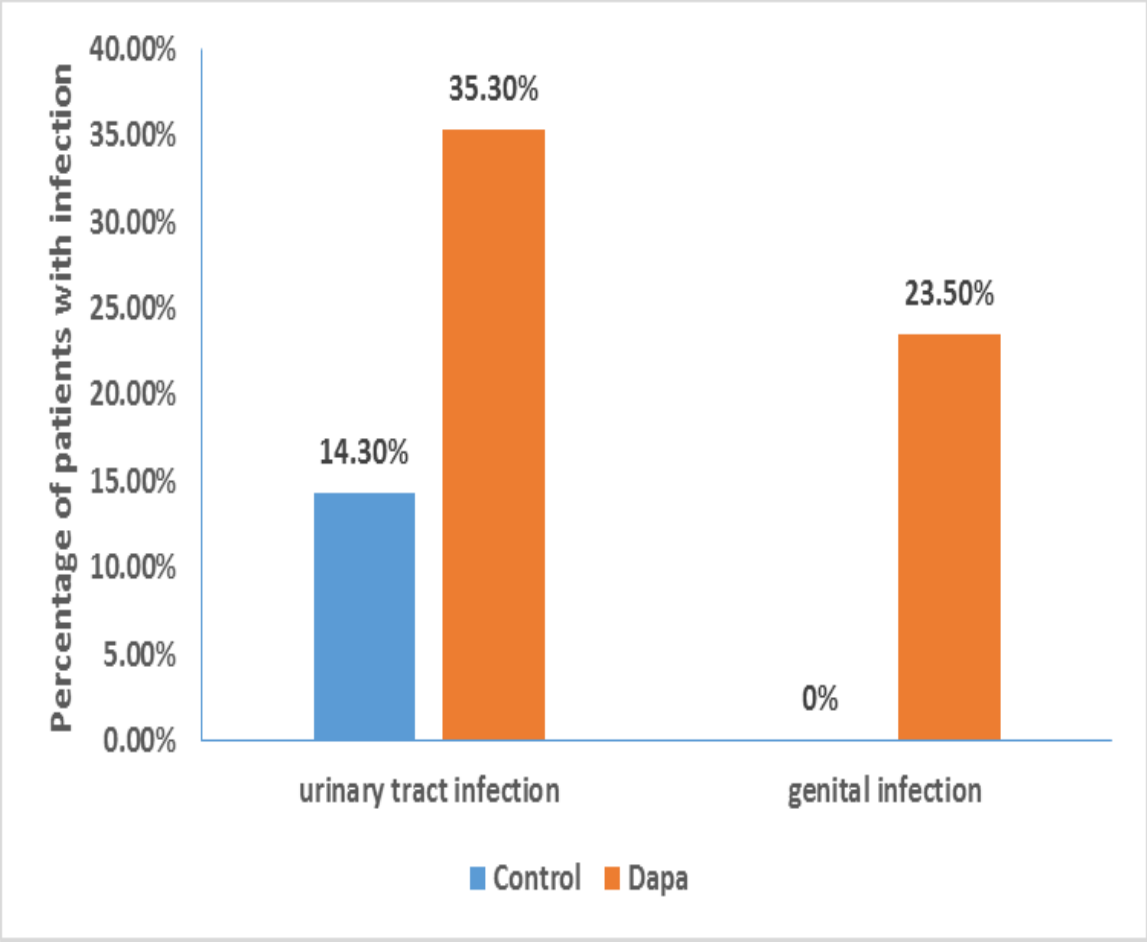

Fig.3: Percentage of patients who reported urinary and genital tract infection between controlled diabetes patients**.**

Table 4: Baseline characteristics (categorical variables) and their association with genital infections among patients treated with dapagliflozin.

	Genital Tract Infection		P-value
	Yes	NO	
Sex, n (%) Female Male	 7 (100%) 0 (0%)	 24 (53.3%) 21 (46.7%)	 0.01*
Age, n (%) 40-49 50-59 ≥ 60	 3 (42.9%) 3 (42.9%) 1 (14.3%)	 10 (22.2%) 18 (40%) 17 (37.8%)	 0.3
Body mass index, n (%) < 30 kg/m^2 ≥ 30 kg/m^2	 2 (28.6%) 5 (71.4%)	 30 (66.7%) 15 (33.3%)	 0.05*
HbA1c, n (%) < 7 % ≥ 7 %	 4 (57.1%) 3 (42.9%)	 13 (28.9%) 32 (71.1%)	 0.1
Diabetes duration, n (%) < 3 years 3-7 years > 7 years	 2 (28.6%) 5 (71.4%) 0 (0%)	 8 (17.8%) 34 (75.6%) 3 (6.7%)	 0.6
Dapagliflozin Dose, n (%) 5 mg 10 mg	 4 (57.1%) 3 (42.9%)	 22 (48.9%) 23 (51.1%)	 0.6
Previous genital tract infection	5 (71.4%)	2 (4.4%)	< 0.0001*
History of urinary incontinence	0 (0%)	2 (4.4%)	0.5
History of nocturia	0 (0%)	3 (6.7%)	0.4

The data was analyzed using Chi-Square test or Fisher exact test.
*p value ≤ 0.05.

Discussion

Early phase 2-3 studies have shown that SGLT2 inhibitors increase the risk of developing UTIs[15]. SGLT2 inhibitors such as dapagliflozin lower blood glucose concentrations by preventing glucose reabsorption through SGLT2 channels in the kidneys, thereby increasing urinary glucose excretion, providing an ideal environment for colonization and growth of bacteria and fungi[16].

However, current research has not supported an increased risk of UTIs with SGLT2 inhibitors. Only dapagliflozin was associated with a slight increase in UTIs and this mainly occurred with the dose of 10 mg[12&17].

In contrast with UTIs, mycotic genital infections were consistently shown to be more frequent in patients treated with SGLT2 is including dapagliflozin compared with placebo or other GLAs[12].

Our study aimed to determine the prevalence of urinary and genital infections induced by dapagliflozin in our region and to examine the risk factors associated with. This study is the first study to be conducted in our region.

In our study, the incidence of genital and urinary infections was higher in patients treated with dapagliflozin compared to patients in the control group. But the difference was not statistically significant. After excluding patients with uncontrolled diabetes in both study groups (dapagliflozin and

control group), the difference was statistically significant between the two groups regarding the incidence of genital infections. This result was not similar for urinary infections, indicating that dapagliflozin was associated with a significantly higher risk of genital infections than other oral antihyperglycemic drugs. This result is in agreement with previous and current studies[10&13].

When we examined the risk factors in patients treated with dapagliflozin, we identified sex as a risk factor for developing urinary and genital fungal infections with dapagliflozin treatment, in our study all genital infections were in women and only one man reported a UTI event in the dapagliflozin group. Women are more prone to urinary tract infections than men due to the anatomical structure of their lower urinary tract. The short urethra allows bacterial penetration, Also it opens into the vulvar vestibule[18]. Hormonal changes shortly before menstruation and during pregnancy lead to a change in the acidity of the vagina. Also decreased estrogen levels after menopause make vaginal tissues thinner, drier and more fragile, which increases the growth of pathogens such as Candida and bacteria in women.

We also identified a previous history of urinary and genital infections as a risk factor for the development of infections, a similar finding noted by Johnsson et al [9&10].

Several studies have shown that urinary and genital infections increase with age[19]. In our study, most of the patients treated with dapagliflozin were aged between 40 and 60 years (about 34% of them were over 60) so, there was no statistically significant difference in the percentage of infections between the three age categories.

Since patients with Type 2 diabetes are at greater risk for genital and urinary tract infections, and obesity is a risk factor for infection, obese patients with Type 2 diabetes could be more susceptible to urinary and genital infections when treated with dapagliflozin. In our study, we identified obesity as a risk factor for the development of UTIs. For genital infections the P-value was a cut-off. Thus, there is a need to increase the number of patients to confirm this finding, this result is on line with some previous studies[19&20], but not all studies [21].

We did not find an effect of diabetes duration on developing genital and urinary infection, However 75% of patients treated with dapagliflozin had diabetes duration between 3 and 7 years, so most cases were in this category of patients.

Baseline HbA1c was not a risk factor, a similar result obsrved by Johnsson et al [9&10] and Thong et al[13].

We observed a statistically significant difference in the incidence of urinary infections in patients with a history of nocturia, possibly due to that these patients are female and have a previous history of urinary infections. We did not identify other risk factors for developing genital and urinary infection with dapagliflozin treatment.

In several studies, glucose excretion was shown to be progressively greater with increased doses of dapagliflozin[22-24], and the data suggest that glucosuria is a risk factor for the development of UTI[3].

In our study, the incidence of UTI was statistically significantly higher with dapagliflozin 10 mg vs the 5 mg.

Since our results indicate that dapagliflozin is not associated with an increase in the incidence of UTI in well-controlled diabetes patients. It is possible that the increase in UTIs with dapagliflozin 10 mg due to other potential risk factors, such as gender and a previous history of UTIs (90% of them were female and 50% had a history of UTIs), or many other risk factors that we didn't address in our study, such as bowel function and water intake[25].

There was no clear dose–response relationship between dapagliflozin and the incidence of genital infections in our study. This contrasts with the dose–response relationship documented between glucosuria and dapagliflozin. It is likely that the higher frequency reported for the dapagliflozin 5 mg dose

is due to chance or small number of patients.

Recent literature does not support increased UTI risk with SGLT2 inhibitors.

M Fralick et al explained the expected absence of this adverse event is that the diuretic effect of SGLT2 inhibitors which may reduce bacterial loads and/or prevent ascension of bacteria up the urinary tracts[26].

Recent studies suggest that the increased urine volume caused by SGLT2 inhibitors does reduce over time[27].

This attenuation over time may explain why some clinical trials of SGLT2 inhibitors with a follow-up period of ≥ 1 year did detect an increased risk of UTI with SGLT2 inhibitors [28]. Dapagliflozin was associated with an increased risk of UTI compared to other SGLT2 inhibitors in some short-term studies[9] now it remains unclear why dapagliflozin is associated with an increased risk of UTI, possibly it is due to pharmacodynamic or pharmacokinetic effect (e.g., faster attenuation of diuretic effect).

Our study has several potential limitations. First, the small number of patients. Second, short follow-up time.

Conclusion

Our data strengthen the previous findings that treatment with dapagliflozin is associated with an increased risk of genital infections in patients with type 2 diabetes. Women and patients with previous genital and urinary tract infections are risk factors of developing urinary and genital infections with dapagliflozin treatment. Long-term studies are still needed to determine the association of dapagliflozin with urinary infections.

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تقييم الإنتانات التناسلية والبولية لدى مرضى السكري من النمط الثاني المعالجين بالداباجليفلوزين

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أظهرت العديد من الدر اسات أن البيلة السكرية المحدثة دوائياً بالاداباجليفلوزين تزيد من خطر الإصابة بعدوى المسالك البولية والتناسلية. كان الهدف من هذا البحث هو تقييم حدوث إنتانات المسالك البولية والتناسلية وتحديد عوامل الخطورة المرتبطة بها لدى مرضى T2DM الذين عولجوا بداباجليفلوزين ٥ و١٠مجم . شملت الدراسة ١٠٨ مريضاً مشخصاً بالسكري من النمط الثاني، تتراوح أعمارهم بين ٤٠-٧٠ سنة، تم اختيارهم عشوائياً من العيادات الخارجية لقسم الغدد الصماء في مستشفى تشرين الجامعي في سوريا. تلقى ٥٢ مريضاً داباجليفلوزين مرة واحدة يومياً (٥ أو ١٠ مجم) كعلاج إضافي للأدوية الفموية الخافضة لسكر الدم، و٥٦ مريضاً عولجوا بعوامل خافضة لفرط سكر الدم لمدة ٢٤ أسبوعاً. قمنا أيضاً باستبعاد المرضى الذين لديهم سكري غير مضبوط بشكل جيد لنفي تأثير الخضاب الجلوكوزي على حدوث الإنتانات، ومن ثم المقارنة بين المرضى ذوي السكري المضبوط.

لاحظنا أن العلاج بداباجليفلوزين يرتبط بزيادة خطر الإصابة بإنتانات الأعضاء التناسلية. لم تكن هناك زيادة ذات دلالة إحصائية في حدوث إنتانات المسالك البولية لدى المرضى الذين عولجوا بداباجليفلوزين. حددنا الجنس والتاريخ السابق للعدوى التناسلية والبدانة كعوامل خطورة لتطوير الإنتانات التناسلية. لا تزال هناك حاجة لدراسات طويلة الأمد لتحديد العلاقة بين العلاج بالداباجليفلوزين وزيادة خطورة الإصابة بعدوى المسالك البولية.