EFFECT OF SGLT2 INHIBITORS ON THE INCIDENCE OF URINARY TRACT INFECTIONS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Background

The incidence of urinary tract infection (UTI) among patients with type 2 diabetes mellitus (T2DM) who received Sodium Glucose Cotransporter-2 (SGLT-2)inhibitors is disputable. Therefore, we performed this study.

Objectives

To investigate the effect of SGLT-2 inhibitors on the incidence of UTI among patients with T2DM and to find out the factors related to high risk of UTI.

Materials and Methods

This is a prospective cohort study that included 200 patients with T2DM attended private medical clinics in Sulaimanyah city, Kurdistan region, Iraq between 1st October 2022 and 30th April 2023. The participants were split into Non-SGLT-2 inhibitors & SGLT-2 inhibitors groups to collate the incidence of UTI.

Results

The incidence rate of UTI in the SGLT-2 inhibitors group was 17%, while it was 3% in the Non-SGLT-2 inhibitors group. Although the incidence rates of UTI were different between Empagliflozin and Dapagliflozin treatment (70.6% and 29.4% respectively) statistically it was near significant (P value 0.06). Patients who received SGLT-2 inhibitors had a 5.67-fold higher risk of UTI in comparison to those who were on Non-SGLT-2 inhibitors (95% CI 1.71-18.73). Furthermore, the only significant risk factor for UTI found in this research was a high level of glycosylated Haemoglobin (HbA1c).

Conclusion

This study showed higher UTI incidence in patients with T2DM using Empagliflozin and Dapagliflozin compared with Non-SGLT-2 inhibitors. Furthermore, patients with high HbA1c >9% had a compelling higher risk of UTI when receiving SGLT-2 inhibitors.

Keywords: *SGLT-2 inhibitors*, *UTI*, *incidence*, *risk factors*, *type 2 diabetes mellitus.*

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INTRODUCTION

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycaemia. DM is classified based on the pathogenic process leading to hyperglycaemia. Type 2 diabetes mellitus is a heterogeneous group of disorders distinguished by varying degrees of the insulin resistance, impaired insulin secretion, and increased hepatic glucose production [(1)].

Sodium Glucose Cotransporter-2 (SGLT-2) inhibitors are derived from apple tree bark and were first licensed for T2DM in March 2013 in the USA after the approval by FDA. The best-known drugs in the class are Empagliflozin, Dapagliflozin and Canagliflozin. The mechanism by which they lower blood glucose exploits the handling of glucose in the kidneys. Glucose is filtered freely in the glomerulus and then completely reabsorbed in the proximal tubules with sodium (mainly via SGLT-2). SGLT-2 inhibitors act by lowering the renal threshold for glucose excretion, such that typically 25% of filtered glucose is not reabsorbed. SGLT-2 inhibitors reduce the rates of major adverse cardiovascular outcomes, particularly heart failure, and also have a reno-protective effect, i.e. reducing rates of death, dialysis and transplantation. The main adverse effect (5-10% of those who take these agents) is genital mycotic (fungal) infections usually with Candida albicans, i.e. vaginal 'thrush' and balanitis. Urine infection is also common and, very rarely severe genital infection (Fournier's gangrene) can occur [(2)].

Susceptibility to genital infections and UTIs in T2DM result from certain factors such as glucosuria, adherence of bacteria to the uroepithelium and immune dysfunction. The propensity to develop these infections could be even higher in those with T2DM treated with emerging class of SGLT-2 inhibitors [(3)].

Up to this date, no local data exists that looked into the effect of SGLT-2 inhibitors on the prevalence of UTIs in T2DM who are treated with these agents. For that reason we conducted this study amid patients with T2DM who received SGLT-2 inhibitors and we determined the incidence of urinary tract infections and assessed whether age, gender, duration of DM, body mass index (BMI), HbA1c, estimated Glomerular Filtration Rate (eGFR) and menopausal status (in females) were linked with incidence of urinary tract infections within these groups of patients. We compared this group with another group of Type 2 diabetic patients with similar characteristic to the first group in the same period but they were on other anti-diabetic medications other than SGLT-2 inhibitors according to the diabetes management guidelines.

PATIENTS AND METHODS

Study design and setting

A prospective cohort study was performed on 200 patients with T2DM who were managed in private clinics in Sulaimanyah city, Kurdistan region, Iraq from October 1st 2022 to 30th April 2023. The participants were split into two groups, one group was started on one of SGLT-2 inhibitors specifically Empagliflozin 10 mg daily orally or Dapagliflozin 10mg daily orally. The second group was on anti-diabetic medications other than SGLT-2 inhibitors like Metformin, Sulfonylureas, Thiazoilidinediones (TZDs) and Dipeptidyl Peptidase IV Inhibitors (DPP4) inhibitors. Our aim was to find out the effect of SGLT-2 inhibitors on the prevalence of UTI among those patients, also to find out factors linked with higher risk of UTIs.

Method of data collection

Those patients were diagnosed with T2DM according to ADA guidelines. One group was started on SGLT-2 inhibitors according to up to date diabetes management guidelines i.e. with chronic kidney disease (CKD) and cardiovascular disease (CVD) risks. The second group was on other agents other than SGLT-2 inhibitors like Metformin, Sulfonylureas, TZDs and DPP4 inhibitors.

The following baseline data were collected at the first visit: age, sex, BMI, menopausal status if female, baseline urine exam, baseline HbA1c and baseline creatinine. Both groups were reviewed at 3 and 6 months from the beginning of presentation. Every patient was asked to call back if he or she develops symptoms of UTI like suprapubic pain, loin pain, fever, dysuria, frequency, hesitancy, urgency and haematuria. All participants were assessed for UTI by routine general Urine Exam (positive bacteria and pus cells) at three and six months follow – up visits.

Inclusion criteria

Adult patients $\geq$40 years old, diagnosed with T2DM according to ADA guideline criteria, newly started on one SGLT-2 inhibitors: either Empagliflozin 10 mg daily or Dapagliflozin 10 mg daily.

Exclusion criteria

Patients with T1DM or Latent Autoimmune Diabetes

in Adulthood (LADA), patients with Gestational DM, patients recently diagnosed with T2DM, diabetic patients on insulin injections (poorly controlled T2DM), patients with previous or current UTI at the time of initiation of SGLT2 inhibitors and in the other group who were not initiated on SGLT-2 inhibitors.

Measuring the outcome

The first aftermath of this research was the occurrence of UTI in patients who received SGLT-2 inhibitors. The episode of UTI in this study was recognized if a patient had UTI symptoms like dysuria, frequency, urgency, hesitancy, haematuria, loin pain, suprapubic pain and fever. Regarding asymptomatic bacteriurea does not require treatment regardless if the patient is diabetic or not. The patients were assessed by a doctor and found to have a positive General Urine Examination i.e. positive for bacteria and pus cells.

The other outcome was the UTI risk factors looked into the characteristics of patients and applicable laboratory data including age, sex, duration, Body Mass Index (BMI), serum creatinine and HbA1c.

STATISTICAL ANALYSIS

Data entry performed via using an Excel Spreadsheet then the statistical analysis was performed by SPSS program, version 24.0 (IBM SPSS). Kolmogorov-Smirnov and Shapiro - Wilk test were used to test the data normality.

Chi-square tests were used to collate the categorical data between these two groups of patients (cases and controls) in respect to different variables.

Independent t-test used to collate the dissimilarity between two groups, while paired t-test used for comparing mean of certain variable within a group in two occasions (basal and last).

Non parametric tests like Mann-Whitney test and Wilcoxon – sign rank test were used for non-normally distributed quantitative variables. P values of ≤ 0.05 were used for significance of statistical tests.

Ethical Consideration

This research was approved by the committee of ethics at the College of Medicine, Sulaimani University. The research was explained to each patient and a verbal consent attained from each patient and documented in the patient's medical note. Confidentiality and anonymity of data were ensured.

RESULTS

Patients Characteristics

Table 1 shows the baseline characteristic of both participants' groups. In the group of SGLT-2 inhibitors, out of 100 patients 69 (69%) cases were female and 31(31%) were male, with a mean (SD) age 56.45 ± 9.28. In the Non-SGLT-2 group, out of 100 patients 57 (57%) were female and 43 (43%) were male, with a mean (SD) age 55.80±9.63. Regarding the menopause in females in the group of SGLT2 inhibitors, out of 69 patients 50 females were in menopause which was similar to those in Non-SGLT-2 inhibitors group, with 46 female patients (Table1).

The UTI Incidence

100 patients who were provided with SGLT-2 inhibitors, 17 patients (17%) developed UTI. In the Non-SGLT-2 inhibitors group only 3 patients (3%) among patients on the medications other than SGLT-2 inhibitors developed UTI (Figure 1). The rate of UTI in participants who were on SGLT-2 inhibitors was substantially greater than those who used Non-SGLT-2 inhibitors (P value < 0.001). Patients receiving SGLT-2 inhibitors had 5.67 times higher risk of UTI (95% CI 1.71-18.73) (Table 2). All UTI events were lower UTIs. There were not any cases with upper UTI (pyelonephritis).

Among the group of SGLT-2 inhibitors, twelve (70.6%) participants having Emapgliflozin developed UTI, whereas five (29.4%) participants on Dapagliflozin developed UTI (Figure2). Although participants taking Empagliflozin developed UTI nearly 2.5 times more than those patients were taking Dapagliflozin but statistically was nearly significant (P: 0.06).

Among the Non SGLT-2 inhibitors group, those who developed UTI, all of them were on Metformin and 2 of them were on sulfonylurea. All of the patients in the group were on metformin, 62 patients were on sulfonylurea and 76 patients were on DPP4 inhibitors. Only 2 patients in the group were on TZDs (Table3).

The factors correlated with the UTI

Uncontrolled DM was correlated with UTI (Table4). 13 out of 17 patients who developed UTI among the group of SGLT2 inhibitors had an HbA1c level of >9% which is statistically significant with a P value of 0.04.

Regarding the gender, although 15 out of 17 patients who developed UTI among the group of SGLT2 inhibitors were female but this was not statistically significant (P: 0.06).

The remaining factors were not correlated with the UTI episodes, including Age, Menopause, BMI, Duration of DM and eGFR.

Table1. Demographic features of participants issued with SGLT-2 inhibitors and Non-SGLT-2 inhibitors

Participant characteristics	Groups		Total	P value
	SGLT-2i	Non- SGLT-2i		
Age				
Mean ± SD	56.45 ± 9.28	55.80 ± 9.63	56.13 ± 9.44	**0.63**
Median (IQR)	55.0 (14)	56 (15)	55.5 (14)	**0.71**
40 - 54 Years	48	48	96	**0.93**
55 - 64	30	28	58	
≥ 65 Years	22	24	46	
Gender				
Male	31	43	74	**0.08**
Female	69	57	126	
Menopause				
Yes	50	46	96	**0.28**
No	19	11	30	
BMI groups				
< 30 Kg / m2	42	69	111	**0.001**
≥ 30	58	31	89	
DM duration				
1 - 5 Years	26	28	54	**0.94**
6 - 10	36	36	72	
11 Years and more	38	36	74	
eGFR				
30-60	11	6	17	**0.21**
> 60	89	94	183	
Baseline HBA1c % Mean ± SD	9.30 ± 0.87	8.92 ± 0.82	8.96 ± 0.83	**0.11 ***
Total	100	100	200	

*** performed by independent t- test**

Table2. The UTI incidence among the study group.

Groups	UTI Incidence	Relative risk (95% Confidence interval)	P value
SGLT-2 inhibitors group	17.0 %	5.67 (1.71 – 18.73)	**< 0.001**
Non – SGLT-2 group	3.0 %	1*	

*** Reference group**

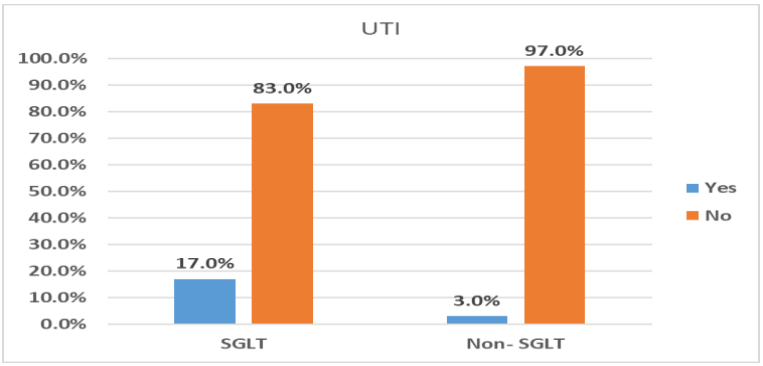

Figure1. The UTI incidence rate comparing SGLT-2 inhibitors and Non- SGLT-2 inhibitors.

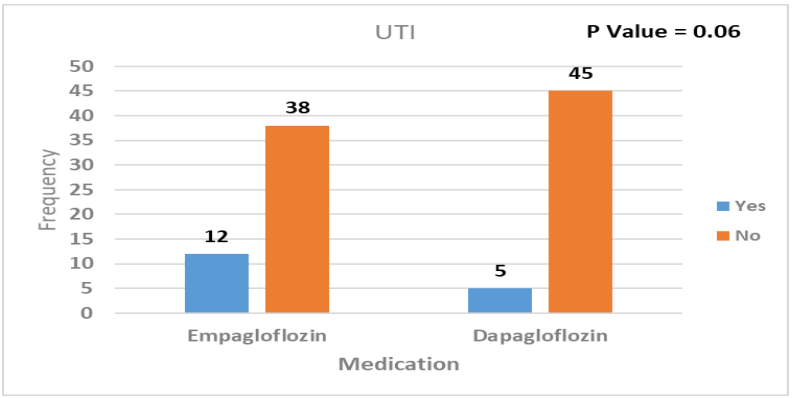

Figure2. Comparison between Empagliflozin and Dapagliflozin regarding the UTI incidence.

Table3. Type of medications among Non-SGLT-2 inhibitors group

Medications	UTI	
	Yes	No
Metformin	3	97
Sulfonylurea	2	60
DPP4 inhibitors	0	76
Thiazolidinediones (TZDs)	0	2

Table4. The factors linked with UTI in participants who were issued SGLT-2 inhibitors.

SGLT2i characteristics' / UTI	UTI				Total		P value
	Yes		No				
Age							
30 - 44 Years	3	17.6%	7	8.4%	10	10.0%	0.50
45 - 64	11	64.7%	57	68.7%	68	68.0%	
65 - 84 Years	3	17.6%	19	22.9%	22	22.0%	
Gender							
Male	2	11.8%	29	34.9%	31	31.0%	0.06
Female	15	88.2%	54	65.1%	69	69.0%	
Duration							
1 - 5 Years	4	24%	22	27%	26	26%	0.89
6 - 10	7	41%	29	35%	36	36%	
11 years and More	6	35%	32	39%	38	38%	
Menopause							
Yes	4	23.5%	14	16.9%	18	18.0%	0.98
No	11	64.7%	38	45.8%	49	49.0%	
BMI groups							
< 30 Kg / m2	6	35.3%	36	43.4%	42	42.0%	0.54
≥ 30	11	64.7%	47	56.6%	58	58.0%	
HbA1c %							
7 - 7.99	3	17.6%	6	7.2%	9	9.0%	0.04
8 - 8.99	1	5.9%	29	34.9%	30	30.0%	
≥ 9.00	13	76.5%	48	57.8%	61	61.0%	
eGFR							
30 -60	2	11.8%	8	9.6%	10	10.0%	0.79
> 60	15	88.2%	75	90.4%	90	90.0%	
Drug class							
Empagloflozin	12	70.6%	38	45.8%	50	50.0%	0.06
Dapagloflozin	5	29.4%	45	54.2%	50	50.0%	
Total	**17**	**100.0%**	**83**	**100.0%**	**100**	**100.0%**	

Table5. The Effect of BMI on the UTI incidence amid SGLT-2 inhibitors and Non-SGLT-2 inhibitors' group.

		UTI				Total		P value
		Yes		No				
< 30 Kg / m2	**SGLT2i group**	6	14.3%	36	85.7%	42	100.0%	0.02
	Non- SGLT group	2	2.9%	67	97.1%	69	100.0%	
Total		8	7.2%	103	92.8%	111	100.0%	
≥ 30 Kg / m2	**SGLT2i group**	11	19.0%	47	81.0%	58	100.0%	0.04
	Non- SGLT group	1	3.2%	30	96.8%	31	100.0%	
Total		12	13.5%	77	86.5%	89	100.0%	

Table5. The Effect of BMI on the UTI incidence amid SGLT-2 inhibitors and Non-SGLT-2 inhibitors' group.

		UTI				Total		P value
		Yes		No				
< 30 Kg / m2	**SGLT2i group**	6	14.3%	36	85.7%	42	100.0%	**0.02**
	Non- SGLT group	2	2.9%	67	97.1%	69	100.0%	
Total		8	7.2%	103	92.8%	111	100.0%	
≥ 30 Kg / m2	**SGLT2i group**	11	19.0%	47	81.0%	58	100.0%	**0.04**
	Non- SGLT group	1	3.2%	30	96.8%	31	100.0%	
Total		12	13.5%	77	86.5%	89	100.0%	

DISCUSSION

The result of this study revealed a rise in the UTI incidence in patients who utilized SGLT-2 inhibitors, i.e. Empagliflozin and Dapagliflozin. The incidence in participants who used SGLT-2 inhibitors was 17% compared with 3% in participants who used Non – SGLT-2 inhibitors. The use of SGLT-2 inhibitors increased the likelihood of UTI 5.67 times greater than using Non - SGLT2 inhibitors. Furthermore, the only factor linked with UTI in this paper was HbA1c.

The UTI incidence outlined in this research was lower than in numerous past researches, the UTI incidences in relation to SGLT-2 inhibitors were between 30-41% [4, 5]. However, the prevalence of UTI in this research was higher than other past papers; the UTI incidences linked to SGLT-2 inhibitors were reported at 3-9% [6, 7].

Concentrating on individual SGLT-2i, Empagliflozin has shown more increased risk (70.6%) in comparison to Dapagliflozin (29.4%) but statistically was not significant, with a P value of 0.06. This result was going with a study done by Yang et al [8], who noticed that the difference was not significant. Also supported by a study performed by Caro MKC et al revealed that, pairwise analysis showed no remarkable dissimilarity in the probability of UTI amongst participants who issued with Empagliflozin and dapagliflozin [5]. In several studies, they found significant increase in the UTI risk in patients having dapagliflozin [4, 9, 10].

Among the mechanisms associated with the more risk of genito-urinary infection in patients who were on SGLT-2 inhibitors is the drug class induced glucosuria [11]. The presence of glucose in the urine provide environment for fungi and bacteria to cause infection.

The cause of dissimilarity in the UTI incidence amidst this research and the previous researches is possibly the difference in the collection of data. In the above mentioned studies some of them included UTIs recorded by hospitals and others documented all variants of the UTIs. In our study we recorded only those patients with proven UTI clinically and by Urinalysis together. Most of those studies depended on electronic data search for UTIs events [6], but in our study we depended on patient's direct contact with the health provider. The lion's share of previous researches was using UTI symptoms alone for the diagnosis [12]. This was not matching the current study that diagnosed UTI based on broad standard like patient's signs and symptoms and urinalysis results. These helped to find the UTI cases more accurately and precisely, leading to a higher percentage of UTI incidences than other researches [6, 7]. Another reason why we got higher UTI rate in this paper is longer duration of follow up. One study with a short follow-up time (100 days) showed using SGLT-2 inhibitors led to UTI in about 8% of patients [13].

The elements influence the events of UTI have been broadly looked for in this research. In this study, HbA1c at the time of treatment initiation was significantly linked with UTI events. SGLT-2 inhibitors reduce glucose concentration in the blood by increasing excretion of glucose in the urine; however the urinary excretion of glucose is also dependent on the mean plasma glucose levels (14). It is, therefore, possible that high concentration of glucose at baseline could have predisposed patients to an increased UTI risk in the current research. This result is similar to a study done by Caro MKC et al and Aswani et al [5, 15]. In contrast, a meta-analysis by Li et al stated that HbA1c is not a UTI risk factor [16].

In accordance to this study's results, other elements

were not linked with increased UTI incidences, including age, sex, BMI, duration, menopause and eGFR. However, in contrast to the current research, there were records of increase in the events of UTI of some of those factors. For example gender in our research, although 15 out of 17 patients with UTI were female among those who received SGLT-2 inhibitors but it was not statistically significant with a P Value of 0.06. This result was in contrast to other studies that showed ladies had higher events of UTI and had a substantial proneness to developing symptomatic UTI and recurring complications than male population [17, 18]. The reason could be the small size of sample in our research.

Regarding BMI, there was a notable dissimilarity in both SGLT-2 inhibitors and Non- SGLT-2 inhibitors group, with 58% of patients had a BMI ≥ 30 kg/m² in the group of SGLT-2 inhibitors and 31% of patients had a BMI ≥ 30 kg/m² (Table1). We were comparing both groups of patients regarding the rate of UTI for each group of BMI separately. We can note in either group, the UTI rate in between SGLT-2 inhibitors group was greater so SGLT-2 inhibitors will have a relation with UTI irrespective to BMI status (Table5). In our study elevated BMI is not linked with increased UTI incidences and this was in contrast to a study done in The Saudi Arabia by Al-et al Rubeaan who found that BMI, particularly greater than 30 kg/m², was linked with an increased UTI incidence due to the inability to apply sufficient pressure to empty the urinary bladder [19].

In the current research we found several limitations that need to be mentioned. First, the small size of the sample in our research (200 patients) that may affect some outcomes of this paper and the reason was the short duration of the study (6 months) and depending on one source for the patients which is the private medical clinic. The second constraint was the basis for the UTI diagnosis in this research that were dissimilar from those used in the previous researches [12, 16], and therefore could result in a higher reported incidence of UTI. Thirdly, our study did not adjust for other factors like urinary glucose and personal hygiene of the patients because of incomplete data in patient medical record. Fourth limitation is the study site which is a private institution that catered for middle and high income patients, thus the characteristics of the patients in the study might put them at lower risk of infection compared to low-income patents attending government hospitals.

A strong point of our research is longer follow up period of 6 months. Most studies had shorter follow-up duration, thereby limiting assessment. Monitoring patients beyond 6 months is still essential since previous studies showed that infections might lead to discontinuation of the drug [20], and subsequently, poor glycaemic control. All participants (17%) who developed UTI after they were started on SGLT-2 inhibitors were treated properly for their UTI and they continue taking SGLT-2 inhibitors. In another word, UTI did not lead to discontinuation of the SGLT-2 inhibitors.

ThispapershowedthatallUTIeventswerelowerUTIsand there weren't any cases with upper UTIs (pyelonephritis).

CONCLUSION

The UTI incidence in patients who issued with SGLT-2 inhibitors was 17%, compared with 3% in patients issued with non-SGLT-2 inhibitor. Although Empagliflozin was causing more UTI in comparison to Dapagliflozin but statistically was not significant. Patients with high level of HbA1c > 9% should be closely observed for UTI events.

Recommendations

Monitoring patients beyond six months is essential since previous studies showed that infections might lead to drug discontinuation.

Modification for other elements like glucose in the urine in future studies.

Clinicians should closely monitor for signs of UTIs, especially those with the known predisposing factors identified in this research. Untimely diagnosis of patients with UTI can expedite earlier treatment and reduce the possibility of drug discontinuation among patients who developed these adverse effects.

Conflict of Interest

The author declares no fund has been received from any company or entity.

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